The Dietary Inflammatory Index and Risk of Colorectal and Breast Cancers in the Women’s Health Initiative

Susan Steck, PhD, MPH, RD
Epidemiology and Biostatistics
Cancer Prevention and Control Program
Arnold School of Public Health
University of South Carolina
Presentation Outline

- Background
  - Development of the dietary inflammatory index (DII)

- Results (and list of approved WHI manuscript proposals):
  - Baseline DII:
    - MS1421: Construct validation of the DII
    - MS1419: The DII and colorectal cancer
    - MS1420: The DII and breast cancer
  - Repeated measures DII:
    - MS2094: Longitudinal changes in DII over time
    - MS2095: The DII and breast cancer
    - MS2096: The DII and colorectal cancer

- Acknowledgements and list of presentations, abstracts, and manuscripts in preparation
Inflammation and Cancer

- Inflammation plays an important role in cancer causation and/or progression

- Many cancers arise at sites of chronic inflammation and chronic inflammation increases cancer risk

- Long-term use of non-steroidal anti-inflammatory drugs reduces risk of some cancers
Diet and Chronic Inflammation

- Many dietary factors affect inflammation
  - **Anti-inflammatory, e.g.:**
    - Phytochemicals and micronutrients commonly found in vegetables and fruits
    - Whole grains/fiber
    - Certain spices and seasonings
  - **Pro-inflammatory, e.g.:**
    - Saturated fat
    - Trans fats

- Adherence to the healthy diet patterns, such as Mediterranean diet, reduces concentrations of pro-inflammatory biomarkers
Development of the DII

Goal: to characterize an individual’s usual diet with regard to its inflammatory potential
Development of the DII

- **Earlier DII version (no longer in use):**

- **Updated DII (population-based):**
1) 1943 articles on 45 food parameters identified and scored

2) Weight articles by study design and calculate pro- and anti-inflammation fractions

3) Adjust scores if total weighted articles is <236

4) Inflammatory effect score calculated from 2) and 3)

5) World composite database for 45 food parameters based on data from 11 countries - Calculate world mean and standard deviation for each of the 45 food parameters.

6) Based on available dietary intake data calculate z-scores and centered percentiles for each of the food parameters for each individual in the study, based on the world average and standard deviation.

7) Multiply centered percentile by the inflammatory effect score to obtain “component-specific DII score.”

8) Sum all of the “component specific DII scores” to create the “overall DII score” for an individual.

Shivappa et al, 2014
Literature Search Strategy

- List of terms was compiled to search for articles on inflammation: IL-1β, IL-4, IL-6, IL-10, TNF-α, CRP
- Variations in the names of food parameters were used to ensure full representation
- Each food parameter was individually combined with the list of inflammatory terms
- A total of 1943 articles published through 2010 qualified and were indexed and scored
Scoring Strategy

One of three possible values was assigned to each article based on the effect of the particular food parameter on each inflammatory biomarker:

+1 if pro-inflammatory
0 if produced no change in inflammatory marker
-1 if anti-inflammatory
Articles were weighted by study design

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Study Design</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Experimental</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Prospective Cohort</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Case-Control</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional</td>
<td>6</td>
</tr>
<tr>
<td>Animal</td>
<td>Experimental</td>
<td>5</td>
</tr>
<tr>
<td>Cell Culture</td>
<td>Experimental</td>
<td>3</td>
</tr>
</tbody>
</table>
Using these weighted values, a score for each food parameter was calculated. The following steps were used to calculate the score:

- **Step 1**: Divide the weighted pro- and anti-inflammatory articles by total weighted number of articles.

- **Step 2**: Subtract the pro-inflammatory fraction from the anti-inflammatory fraction.
### Example of saturated fat

<table>
<thead>
<tr>
<th>Effect</th>
<th>Study design</th>
<th>Number of articles</th>
<th>Weighted number of articles</th>
<th>Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory</td>
<td>Clinical</td>
<td>0</td>
<td>0</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>Cohort</td>
<td>0</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Case-Control</td>
<td>0</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional</td>
<td>1 x 6 =</td>
<td>6</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>0</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Cell</td>
<td>1 x 3 =</td>
<td>3</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>2</td>
<td>9</td>
<td>0.000</td>
</tr>
<tr>
<td>Pro-inflammatory</td>
<td>Clinical</td>
<td>3 x 10 =</td>
<td>30</td>
<td>0.473</td>
</tr>
<tr>
<td></td>
<td>Cohort</td>
<td>0</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Case-Control</td>
<td>1 x 7 =</td>
<td>7</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional</td>
<td>4 x 6 =</td>
<td>24</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>3 x 5 =</td>
<td>15</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Cell</td>
<td>7 x 3 =</td>
<td>21</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>18</td>
<td>97</td>
<td>0.000</td>
</tr>
<tr>
<td>No Effect</td>
<td>Clinical</td>
<td>3 x 10 =</td>
<td>30</td>
<td>0.473</td>
</tr>
<tr>
<td></td>
<td>Cohort</td>
<td>0</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Case-Control</td>
<td>0</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional</td>
<td>9 x 6 =</td>
<td>54</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>3 x 5 =</td>
<td>15</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Cell</td>
<td>0</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>15</td>
<td>99</td>
<td>0.000</td>
</tr>
<tr>
<td>Overall Total</td>
<td></td>
<td>35</td>
<td>205</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Score = 0.473 - 0.044 = 0.429

Shivappa et al, 2014
Weighting by the Size of the Literature Base

- Foods parameters with a weighted number of articles less than 236 (the median value of weighted number of articles for each of the 45 food parameters) were adjusted as follows:
  1) Number of weighted articles was divided by 236.
  2) The fraction was then multiplied by the score for that food parameter, which resulted in the new adjusted score for each food parameter.
### Example of saturated fat (continued)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Study design</th>
<th>Number of articles</th>
<th>Weighted number of articles</th>
<th>Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-inflammatory</strong></td>
<td>Clinical</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cohort</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Case-Control</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional</td>
<td>1 x 6 = 6</td>
<td>6</td>
<td>9/205 = 0.044</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cell</td>
<td>1 x 3 = 3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>2</td>
<td>9</td>
<td>9/205 = 0.044</td>
</tr>
<tr>
<td><strong>Pro-inflammatory</strong></td>
<td>Clinical</td>
<td>3 x 10 = 30</td>
<td>30</td>
<td>97/205 = 0.473</td>
</tr>
<tr>
<td></td>
<td>Cohort</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Case-Control</td>
<td>1 x 7 = 7</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional</td>
<td>4 x 6 = 24</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>3 x 5 = 15</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cell</td>
<td>7 x 3 = 21</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>18</td>
<td>97</td>
<td>97/205 = 0.473</td>
</tr>
<tr>
<td><strong>No Effect</strong></td>
<td>Clinical</td>
<td>3 x 10 = 30</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cohort</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Case-Control</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional</td>
<td>9 x 6 = 54</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>3 x 5 = 15</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cell</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>15</td>
<td>90</td>
<td>99/205 = 0.475</td>
</tr>
<tr>
<td><strong>Overall Total</strong></td>
<td></td>
<td>35</td>
<td>205</td>
<td>0.473 - 0.044 = 0.429</td>
</tr>
</tbody>
</table>

\[
\text{Score} = \frac{0.429 \times 205}{236} = 0.373 \text{ (new adjusted score)}
\]

Shivappa et al, 2014
## Development of the DII

Table 2: Food parameters included in the dietary inflammatory index, inflammatory effect scores, and intake values from the global composite data set; Dietary Inflammatory Index Development Study, Columbia, SC, USA, 2011–2012

<table>
<thead>
<tr>
<th>Food parameter</th>
<th>Weighted number of articles</th>
<th>Raw inflammatory effect score*</th>
<th>Overall inflammatory effect score†</th>
<th>Global daily mean intake‡ (units/d)</th>
<th>sd‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (g)</td>
<td>417</td>
<td>-0.278</td>
<td>-0.278</td>
<td>13.98</td>
<td>3.72</td>
</tr>
<tr>
<td>Vitamin B₁₂ (µg)</td>
<td>122</td>
<td>0.205</td>
<td>0.106</td>
<td>5.15</td>
<td>2.70</td>
</tr>
<tr>
<td>Vitamin B₆ (mg)</td>
<td>227</td>
<td>-0.379</td>
<td>-0.365</td>
<td>1.47</td>
<td>0.74</td>
</tr>
<tr>
<td>β-Carotene (µg)</td>
<td>401</td>
<td>-0.584</td>
<td>-0.584</td>
<td>3718</td>
<td>1720</td>
</tr>
<tr>
<td>Caffeine (g)</td>
<td>209</td>
<td>-0.124</td>
<td>-0.110</td>
<td>8.05</td>
<td>6.67</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>211</td>
<td>0.109</td>
<td>0.097</td>
<td>272.2</td>
<td>40.0</td>
</tr>
<tr>
<td>Cholesterol (mg)</td>
<td>75</td>
<td>0.347</td>
<td>0.110</td>
<td>279.4</td>
<td>51.2</td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>245</td>
<td>0.180</td>
<td>0.180</td>
<td>2056</td>
<td>338</td>
</tr>
<tr>
<td>Eugenol (mg)</td>
<td>38</td>
<td>-0.868</td>
<td>-0.140</td>
<td>0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Total fat (g)</td>
<td>443</td>
<td>0.298</td>
<td>0.298</td>
<td>71.4</td>
<td>19.4</td>
</tr>
<tr>
<td>Fibre (g)</td>
<td>261</td>
<td>-0.663</td>
<td>-0.663</td>
<td>18.8</td>
<td>4.9</td>
</tr>
<tr>
<td>Folic acid (µg)</td>
<td>217</td>
<td>-0.207</td>
<td>-0.190</td>
<td>273.0</td>
<td>70.7</td>
</tr>
<tr>
<td>Garlic (g)</td>
<td>277</td>
<td>-0.412</td>
<td>-0.412</td>
<td>4.35</td>
<td>2.90</td>
</tr>
<tr>
<td>Ginger (g)</td>
<td>182</td>
<td>-0.588</td>
<td>-0.453</td>
<td>59.0</td>
<td>63.2</td>
</tr>
<tr>
<td>Fe (mg)</td>
<td>619</td>
<td>-0.032</td>
<td>-0.032</td>
<td>13.35</td>
<td>3.71</td>
</tr>
<tr>
<td>Mg (mg)</td>
<td>351</td>
<td>-0.484</td>
<td>-0.484</td>
<td>310.1</td>
<td>139.4</td>
</tr>
<tr>
<td>MUFA (g)</td>
<td>106</td>
<td>-0.019</td>
<td>-0.009</td>
<td>27.0</td>
<td>6.1</td>
</tr>
<tr>
<td>Niacin (mg)</td>
<td>58</td>
<td>-1.000</td>
<td>-0.246</td>
<td>25.90</td>
<td>11.77</td>
</tr>
<tr>
<td>n-3 Fatty acids (g)</td>
<td>2588</td>
<td>-0.436</td>
<td>-0.436</td>
<td>1.06</td>
<td>1.06</td>
</tr>
<tr>
<td>n-6 Fatty acids (g)</td>
<td>924</td>
<td>-0.159</td>
<td>-0.159</td>
<td>10.80</td>
<td>7.50</td>
</tr>
<tr>
<td>Onion (g)</td>
<td>145</td>
<td>-0.490</td>
<td>-0.301</td>
<td>35.9</td>
<td>18.4</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>102</td>
<td>0.049</td>
<td>0.021</td>
<td>79.4</td>
<td>13.9</td>
</tr>
<tr>
<td>PUFA (g)</td>
<td>4002</td>
<td>-0.337</td>
<td>-0.337</td>
<td>13.88</td>
<td>3.76</td>
</tr>
<tr>
<td>Riboflavin (mg)</td>
<td>22</td>
<td>-0.727</td>
<td>-0.068</td>
<td>1.70</td>
<td>0.79</td>
</tr>
<tr>
<td>Saffron (g)</td>
<td>53</td>
<td>-1.000</td>
<td>-0.140</td>
<td>0.37</td>
<td>1.78</td>
</tr>
<tr>
<td>Saturated fat (g)</td>
<td>205</td>
<td>0.429</td>
<td>0.373</td>
<td>28.6</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Shivappa et al, 2014
Development of the DII

1) 1943 articles on 45 food parameters identified and scored

2) Weight articles by study design and calculate pro- and anti-inflammatory fractions

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7) Multiply centered percentile by the inflammatory effect score to obtain “component-specific DII score.”

8) Sum all of the “component specific DII scores” to create the “overall DII score” for an individual.

Shivappa et al, 2014
Construct Validation of the DII in Postmenopausal Women

- **WHI Ancillary study:**
  - Data from an ancillary study of inflammatory biomarkers in the WHI-OS at baseline (1993-1998)
  - The DII was calculated from baseline FFQs (n=~2600)
- **Evaluated association between the DII and inflammatory biomarkers:**
  - IL-6
  - hs-CRP
  - tumor necrosis factor alpha receptor 2 (TNFα-R2)
  - overall inflammatory biomarker score derived from a combination of the three biomarkers
Statistical Analysis: Construct Validation

- DII categorized into quintiles
- hs-CRP and IL-6 were log transformed
- Overall inflammatory biomarker score = z-score (log hs-CRP) + z-score (log IL-6) + z-score (TNFα-R2)
- DII quintiles used to predict concentrations of hs-CRP, IL-6, TNFαR2 and the overall inflammatory biomarker
- Four separate multivariable linear regression models
- hs-CRP dichotomized at 3 mg/L – logistic model
Results – Construct Validation

Table 1. Association between quintiles of the FFQ-derived DII and biomarkers of inflammation

<table>
<thead>
<tr>
<th>Inflammatory biomarker</th>
<th>Q1</th>
<th>Q3</th>
<th>Q5</th>
<th>(P_{\text{trend}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>referent</td>
<td>-0.002 (-0.03, 0.02)</td>
<td>0.05 (0.03, 0.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>hs-CRP (continuous)</td>
<td>referent</td>
<td>-0.01 (-0.04, 0.03)</td>
<td>0.002 (-0.03, 0.03)</td>
<td>0.20</td>
</tr>
<tr>
<td>hs-CRP (dichotomous)</td>
<td>referent</td>
<td>1.28 (0.97, 1.69)</td>
<td>1.34 (1.01, 1.78)</td>
<td>0.22</td>
</tr>
<tr>
<td>TNFα-R2</td>
<td>referent</td>
<td>-11.77 (-71.68, 48.14)</td>
<td>82.75 (20.84, 144.66)</td>
<td>0.002</td>
</tr>
<tr>
<td>Overall inflammatory biomarker</td>
<td>referent</td>
<td>0.11 (-0.02, 0.24)</td>
<td>0.27 (0.14, 0.41)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Models adjusted for age, body mass index, race/ethnicity, educational level, smoking status, physical activity, use of NSAIDs, statins, inflammation-related co-morbidities (history of ulcerative colitis, diabetes, Alzheimer's disease, arthritis, hypertension, cancer, and hypercholesterolemia)
Dietary Inflammatory Index and Risk of Colorectal and Breast Cancers in Postmenopausal Women
Methods

- DII calculated from baseline FFQs (1993-1998)
- Categorized into quintiles or tertiles
- Both OS and CT data used
- Participants followed until incident cancer or September 30, 2010
- Cancer cases ascertained through a centralized physician adjudication process (n=1,922 colorectal cancers, n=7,013 breast cancers)
Excluded from analysis:
- Women who reported previous colorectal cancer or breast cancer at baseline or missing previous cancer status at baseline
- Women with implausible reported total energy intake values (≤600 kcal/d or ≥ 5000 kcal/d) or extreme body mass index (BMI) values (≤15kg/m² or ≥ 50kg/m²)

Multiple covariate-adjusted Cox proportional hazards (PH) regression models used to calculate hazard ratios (HR) for:
- Colorectal cancer
- Colon cancer
  - proximal colon cancer
  - distal colon cancer
- Rectal cancer
- Invasive breast cancer
- Breast cancer by tumor subtypes
Statistical Analysis

- Lowest DII quintile/tertile (most anti-inflammatory diet) was the referent for all models

- Potential effect modification by waist-to-hip ratio, waist circumference, BMI, and NSAID use, investigated by stratifying on these covariates in the Cox PH models

- Tests of linear trend adjusted for covariates, computed by assigning the median value of each quintile/tertile to each participant in the quintile/tertile

- Sensitivity analyses- exclusion of colorectal or breast cancer cases that occurred within 3 years from baseline

- Analyses by stage of cancer at diagnosis (localized, regional and distant)
## Results

### Table 2. Risk of colorectal cancer across quintiles of the DII

<table>
<thead>
<tr>
<th></th>
<th>Q1 (-7.055, &lt;-3.136) (healthiest)</th>
<th>Q3 (-1.995, &lt;-0.300)</th>
<th>Q5 (1.953, 5.636) (least healthy)</th>
<th>P&lt;sub&gt;trend&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer cases, n=1920</td>
<td>365 (19.0%)</td>
<td>359 (18.7%)</td>
<td>435 (22.6%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Colorectal cancer, HR (95%CI)</td>
<td>1.00 (ref)</td>
<td>0.98 (0.84, 1.14)</td>
<td>1.22 (1.05, 1.43)</td>
<td></td>
</tr>
<tr>
<td>Colon cancer cases, n=1559</td>
<td>299 (19.2%)</td>
<td>288 (18.5%)</td>
<td>346 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>Colon cancer, HR (95%CI)</td>
<td>1.00 (ref)</td>
<td>0.98 (0.83, 1.15)</td>
<td>1.23 (1.03, 1.46)</td>
<td>0.02</td>
</tr>
<tr>
<td>Proximal colon cancer cases, n=1034</td>
<td>193 (18.7%)</td>
<td>181 (17.5%)</td>
<td>229 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>Proximal colon cancer, HR (95%CI)</td>
<td>1.00 (ref)</td>
<td>0.98 (0.79, 1.20)</td>
<td>1.35 (1.09, 1.67)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Models adjusted for age, body mass index, race/ethnicity, educational level, smoking status, physical activity, use of NSAIDs, statins, inflammation-related co-morbidities (history of ulcerative colitis, diabetes, Alzheimer's disease, arthritis, hypertension, cancer, and hypercholesterolemia)
## Results

### Table 3. Risk of breast cancer incidence and mortality across DII tertiles

<table>
<thead>
<tr>
<th></th>
<th>T1 (−7.055, ≤−2.366) (healthiest)</th>
<th>T2 (−2.366, &lt;0.468)</th>
<th>T3 (0.468, 5.789) (least healthy)</th>
<th>$P_{\text{trend}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer cases, n=1922</td>
<td>2155</td>
<td>1912</td>
<td>1774</td>
<td>0.89</td>
</tr>
<tr>
<td>Breast cancer, HR (95%CI)$^a$</td>
<td>1.00 (ref)</td>
<td>0.95 (0.89, 1.01)</td>
<td>0.99 (0.92, 1.06)</td>
<td></td>
</tr>
<tr>
<td>HER2+ cases, n=662</td>
<td>215</td>
<td>222</td>
<td>225</td>
<td>0.01</td>
</tr>
<tr>
<td>HER2+ cancer, HR (95%CI)$^a$</td>
<td>1.00 (ref)</td>
<td>1.12 (0.92, 1.35)</td>
<td>1.29 (1.05, 1.59)</td>
<td></td>
</tr>
<tr>
<td>Breast cancer mortality, n=406</td>
<td>117</td>
<td>136</td>
<td>153</td>
<td>0.04</td>
</tr>
<tr>
<td>Breast cancer mortality, HR (95%CI)$^b$</td>
<td>1.00 (ref)</td>
<td>1.06 (0.81, 1.37)</td>
<td>1.30 (0.99, 1.71)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$adjusted for age, race/ethnicity, body mass index, physical activity, education, smoking status, mammography within 2 years of baseline, age at menarche, number of live births, oophorectomy status, hormone therapy use, NSAID use, dietary modification trial arm, hormone therapy trial arm, calcium and vitamin D trial arm, and total energy intake; $^b$adjusted for age, race/ethnicity, body mass index, physical activity, education, smoking status, mammography within 2 years of baseline, hormone therapy use, NSAID use, dietary modification trial arm, hormone therapy trial arm, calcium and vitamin D trial arm, total energy intake, estrogen receptor status, progesterone receptor status, stage and time since diagnosis.
Summary of Results

- A more pro-inflammatory DII score was associated positively with inflammatory biomarkers.

- Having higher DII score was associated with increased risk of colorectal cancer, especially proximal colon cancer.

- The DII was not associated with invasive breast cancer risk
  - Suggestion of increased risk for HER2+ cancers and for breast cancer mortality
Overall Limitations

- Study limited to postmenopausal women
- FFQ measurement error
- Potential residual or unmeasured confounding
- Diet assessment at only one time point (baseline)
Changes in the Dietary Inflammatory Index Over Time and Risk of Colorectal and Breast Cancers in Postmenopausal Women
Results—Observational Study

- Mean (±SD) overall DII decreased slightly
  - Baseline DII: -0.98 (± 2.67)
  - Year 3 DII: -1.33 (± 2.71)

- **BMI**: normal-weight women experienced the largest decrease in DII between baseline and Year 3 compared to obese women

- **Education**: women with at least some college education showed the greatest change in DII compared to women with less than a high school education, whose DII scores were more pro-inflammatory

- **Race/ethnicity**: A/PI experienced the largest decrease in DII followed by EA. AA and HP had more pro-inflammatory DII scores
P-value for the difference in DII scores between intervention and control was 0.62 at baseline, and <0.0001 for each year from year 1 onwards.
Fig. 2: Mean DII over time by BMI status and DMT arm
Fig. 3: Mean DII over time by educational level and DMT arm

- **Intervention arm**
  - Time from baseline (years)
  - Mean DII score
  - <High school, High school/GED, Some college/graduate>

- **Control arm**
  - Time from baseline (years)
  - Mean DII score
  - <High school, High school/GED, Some college/graduate>
Fig. 4: Mean DII over time by race/ethnicity and DMT arm
Associations between repeated measures of the DII and breast and colorectal cancer risk

- **Main exposures:**
  - Cumulative average history of DII
  - Changes in patterns of the inflammatory potential of diet
Models for Cumulative Average DII

- Ten cumulative averages of DII were calculated incrementally starting from the average between baseline and year one DII.
- The cumulative average was then categorized into quintiles. Used in multivariable-adjusted Cox PH models to estimate hazard ratios (HR) for the incidence of colorectal and breast cancers.
- Cancer cases diagnosed prior to the cumulative DII average were excluded.
- Approach repeated until all time points of FFQ data were used.
Models for Patterns of Change in DII

- The DII calculated from baseline and year 3 FFQs in the OS and DMT
- DII categorized at both time points into quintiles (Q)
- Quintiles changes between baseline and Year 3, classified as follows (names given to these categories are qualitative):
  - **Anti-inflammatory stable**: Q1 or Q2 at both time points or change from Q3 to Q2;
  - **Anti-inflammatory change**: changes ≤ -2Q;
  - **Neutral inflammation stable**: changes from Q2 to Q3, Q4 to Q3 or stable at Q3 at both time points;
  - **Pro-inflammatory change**: changes ≥ 2Q;
  - **Pro-inflammatory stable**: Q4 or Q5 at both time points, or change from Q3 to Q4.

- Cox PH models were used to estimate hazard ratios (HR) and 95% confidence intervals (95%CI) for cancer risk, with adjustment for multiple covariates.
Exclusions

Participants were excluded from these analyses based on the following criteria:

- Reported colorectal or breast cancer at baseline or missing cancer status at baseline
- Implausible reported total energy intake values (≤600 kcal/day or ≥5000 kcal/day)
- Extreme BMI values (<15kg/m^2 or > 50kg/m^2)
- Missing data in the covariates
- Single FFQs

**Final sample:**
- 111,741 participants for these analyses (74,051 in OS and 37,690 in DMT)
**Table 4. Cumulative Average DII and Breast Cancer Risk**

<table>
<thead>
<tr>
<th>Quintile 1 (Healthiest)</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5 (Least healthy)</th>
<th>P$_{trend}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referent</td>
<td>HR (95%CI)$^a$</td>
<td>HR (95%CI)</td>
<td>HR (95%CI)</td>
<td>HR (95%CI)</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td>Baseline, year 1, DMT</td>
<td>1.00</td>
<td>0.81 (0.70, 0.93)</td>
<td>0.90 (0.78, 1.04)</td>
<td>1.04 (0.91, 1.20)</td>
<td>0.99 (0.86, 1.15)</td>
</tr>
<tr>
<td>Baseline, years 1-2, DMT</td>
<td>1.00</td>
<td>0.84 (0.73, 0.98)</td>
<td>0.93 (0.80, 1.07)</td>
<td>1.03 (0.89, 1.19)</td>
<td>0.98 (0.84, 1.15)</td>
</tr>
<tr>
<td>Baseline, years 1-3, OS and DMT</td>
<td>1.00</td>
<td>1.00 (0.91, 1.10)</td>
<td>0.98 (0.89, 1.07)</td>
<td>0.99 (0.90, 1.10)</td>
<td>1.02 (0.92, 1.14)</td>
</tr>
<tr>
<td>Baseline, years 1-3: OS</td>
<td>1.00</td>
<td>1.05 (0.94, 1.19)</td>
<td>1.00 (0.89, 1.13)</td>
<td>0.98 (0.86, 1.11)</td>
<td>0.98 (0.86, 1.12)</td>
</tr>
<tr>
<td>Baseline, years 1-3: DMT</td>
<td>1.00</td>
<td>0.91 (0.78, 1.07)</td>
<td>0.93 (0.80, 1.09)</td>
<td>1.05 (0.90, 1.23)</td>
<td>1.02 (0.86, 1.20)</td>
</tr>
<tr>
<td>Baseline, years 1-4, DMT</td>
<td>1.00</td>
<td>0.93 (0.79, 1.09)</td>
<td>0.86 (0.73, 1.02)</td>
<td>1.09 (0.93, 1.28)</td>
<td>0.98 (0.82, 1.17)</td>
</tr>
<tr>
<td>Baseline, years 1-5, DMT</td>
<td>1.00</td>
<td>1.03 (0.86, 1.22)</td>
<td>0.93 (0.78, 1.11)</td>
<td>1.02 (0.86, 1.22)</td>
<td>1.08 (0.89, 1.30)</td>
</tr>
<tr>
<td>Baseline, years 1-6, DMT</td>
<td>1.00</td>
<td>1.00 (0.83, 1.21)</td>
<td>0.97 (0.80, 1.18)</td>
<td>1.03 (0.84, 1.25)</td>
<td>1.07 (0.88, 1.22)</td>
</tr>
<tr>
<td>Baseline, years 1-7, DMT</td>
<td>1.00</td>
<td>1.00 (0.81, 1.23)</td>
<td>0.97 (0.78, 1.20)</td>
<td>1.09 (0.88, 1.36)</td>
<td>1.14 (0.91, 1.43)</td>
</tr>
<tr>
<td>Baseline, years 1-8, DMT</td>
<td>1.00</td>
<td>1.02 (0.81, 1.29)</td>
<td>1.01 (0.80, 1.27)</td>
<td>1.22 (0.96, 1.53)</td>
<td>1.11 (0.86, 1.43)</td>
</tr>
<tr>
<td>Baseline, years 1-9, DMT</td>
<td>1.00</td>
<td>1.03 (0.79, 1.34)</td>
<td>1.11 (0.85, 1.44)</td>
<td>1.20 (0.92, 1.56)</td>
<td>1.19 (0.89, 1.58)</td>
</tr>
<tr>
<td>Baseline, years 1-10, DMT</td>
<td>1.00</td>
<td>1.09 (0.80, 1.49)</td>
<td>1.21 (0.88, 1.65)</td>
<td>1.34 (0.98, 1.83)</td>
<td>1.32 (0.94, 1.84)</td>
</tr>
</tbody>
</table>

$^a$all models were adjusted for age, race/ethnicity, education, smoking status, physical activity, body mass index, NSAID use, category and duration of estrogen use, category and duration of estrogen & progesterone use, and total energy intake.
### Table 5. Patterns of Change in DII and Breast Cancer Risk

<table>
<thead>
<tr>
<th></th>
<th>Patterns of DII quintile changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-inflammatory stable</td>
</tr>
<tr>
<td><strong>Invasive breast cancer</strong></td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td><strong>Triple negative (ER−, PR−, HER2−)</strong></td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td><strong>ER−, PR−, HER2+ subtype</strong></td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td><strong>Luminal A (ER+ and/or PR+, HER2−)</strong></td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td><strong>Luminal B (ER+ and/or PR+, HER2+)</strong></td>
<td>1.00 (ref)</td>
</tr>
</tbody>
</table>

All models were adjusted for age, race/ethnicity, education, smoking status, physical activity, body mass index, NSAID use, category and duration of estrogen use, category and duration of estrogen & progesterone use, and total energy intake.
Figure 5. Cumulative Average DII and Colon Cancer Risk

Multivariable adjusted HR and 95% CI for highest vs. lowest quintile

HR (95% CI) for colon cancer risk

Time from baseline (years)
Table 6. Patterns of Change in DII Quintiles and Colorectal Cancer Risk

<table>
<thead>
<tr>
<th></th>
<th>Anti-inflammatory stable</th>
<th>Anti-inflammatory change</th>
<th>Neutral inflammation stable</th>
<th>Pro-inflammatory change</th>
<th>Pro-inflammatory stable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>1.00 (ref)</td>
<td>1.13 (0.92, 1.39)</td>
<td>1.04 (0.88, 1.24)</td>
<td>1.04 (0.84, 1.29)</td>
<td>1.18 (0.99, 1.41)</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1.00 (ref)</td>
<td>1.06 (0.86, 1.36)</td>
<td>1.04 (0.86, 1.25)</td>
<td>1.01 (0.80, 1.28)</td>
<td>1.11 (0.91, 1.35)</td>
</tr>
<tr>
<td>Proximal colon cancer</td>
<td>1.00 (ref)</td>
<td>1.12 (0.83, 1.51)</td>
<td>1.11 (0.87, 1.42)</td>
<td>1.20 (0.90, 1.62)</td>
<td>1.23 (0.96, 1.59)</td>
</tr>
<tr>
<td>Distal colon cancer</td>
<td>1.00 (ref)</td>
<td>0.93 (0.65, 1.52)</td>
<td>1.10 (0.76, 1.60)</td>
<td>0.89 (0.54, 1.47)</td>
<td>0.99 (0.66, 1.49)</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>1.00 (ref)</td>
<td>1.24 (0.75, 2.04)</td>
<td>1.12 (0.73, 1.72)</td>
<td>1.10 (0.64, 1.88)</td>
<td>1.53 (1.01, 2.32)</td>
</tr>
</tbody>
</table>

All multivariable models were adjusted for age, race/ethnicity, educational level, smoking status, diabetes, hypertension, arthritis, NSAID use, category and duration of estrogen use, category and duration of estrogen & progesterone use, dietary modification trial arm, body mass index, physical activity.
Summary of Results

- DII scores changed over time in the DMT and this was influenced by BMI, education and race/ethnicity

- No substantial association between changes in dietary inflammatory potential over time, and risk of total breast cancer
  - Suggestion of reduced risk for triple negative breast cancer with anti-inflammatory change in diet

- A higher cumulative average score of the DII was associated with an increased risk of colon cancer, but not rectal cancer

- A stable pro-inflammatory diet from baseline to year 3 increased the risk of rectal cancer with suggestion of increased risk of proximal colon cancer.
Limitations

- FFQ data were not available in the OS after Year 3

- Assumption that the random 30% of DMT participants sampled from year 2 until study end was representative of the entire DMT study population

- Percent energy from fat was inclusion criteria for DMT participants
Overall Conclusions

- Consumption of pro-inflammatory diets, both at baseline and when diet persisted over time, was associated with increased risk of colorectal cancer in postmenopausal women.

- The dietary inflammatory index was not associated with breast cancer risk overall, though there was suggestion of associations with specific tumor subtypes and with breast cancer mortality.
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UCLA School of Medicine
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Manuscripts in preparation


Questions?
The WHI began in 1992, and enrolled a total of 161,808 women 50 to 79 years old, in 40 sites in the United States between 1993 and 1998.

WHI study design: multifactorial, with overlapping clinical trial (CT) components
- OS: 93,676 participants
- DMT: 48,835 participants
- HRT: 27,347 participants
- CaD: 36,282 participants

17.5% minority populations (Hispanics, African Americans, Asian & Pacific Islanders, others)
Diet Assessment in the DM

Study Start

Food Frequency Questionnaire All

Year 1

Food Frequency Questionnaire All

4-day food records

4-day food records 4.6% of ppt

Year 2→Close-out

Food Frequency Questionnaire Rotating 1/3 of participants

Year 3, 6, 9

Repeat (x2) 24HR 4.6% of participants

24HR 1% of participants

Adapted from WHI data training slides
Diet Assessment in the OS

Study Start
Food Frequency Questionnaire All

Year 3
Food Frequency Questionnaire All

Note: CT participants not in the DM have only the baseline FFQ

Adapted from WHI data training slides
## Distribution of Food Groups in Quintiles (Q) of the DII

<table>
<thead>
<tr>
<th>Food group (medium servings/day)</th>
<th>Q1 (-7.055, &lt;= 3.136) (healthiest)</th>
<th>Q2 (-3.136, &lt;=-1.995)</th>
<th>Q3 (-1.995, &lt;=-0.300)</th>
<th>Q4 (-0.300, &lt;1.953)</th>
<th>Q5 (1.953, 5.636) (least healthy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruits</td>
<td>2.71</td>
<td>2.04</td>
<td>1.85</td>
<td>1.73</td>
<td>1.73</td>
</tr>
<tr>
<td>Vegetables</td>
<td>3.15</td>
<td>2.30</td>
<td>2.12</td>
<td>2.00</td>
<td>2.00</td>
</tr>
<tr>
<td>Combo Fruit/Veg</td>
<td>5.86</td>
<td>4.34</td>
<td>3.97</td>
<td>3.73</td>
<td>3.73</td>
</tr>
<tr>
<td>Fish</td>
<td>0.07</td>
<td>0.07</td>
<td>0.07</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>Red meat</td>
<td>0.63</td>
<td>0.73</td>
<td>0.74</td>
<td>0.76</td>
<td>0.76</td>
</tr>
<tr>
<td>Poultry</td>
<td>0.44</td>
<td>0.40</td>
<td>0.38</td>
<td>0.38</td>
<td>0.38</td>
</tr>
<tr>
<td>Soy</td>
<td>0.08</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Nuts</td>
<td>0.26</td>
<td>0.20</td>
<td>0.18</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>Combo Nut/soy</td>
<td>0.34</td>
<td>0.22</td>
<td>0.20</td>
<td>0.18</td>
<td>0.18</td>
</tr>
<tr>
<td>Grains</td>
<td>5.89</td>
<td>4.69</td>
<td>4.55</td>
<td>4.47</td>
<td>4.47</td>
</tr>
<tr>
<td>Whole Grain</td>
<td>1.73</td>
<td>1.24</td>
<td>1.17</td>
<td>1.12</td>
<td>1.12</td>
</tr>
<tr>
<td>Milk</td>
<td>0.97</td>
<td>0.88</td>
<td>0.80</td>
<td>0.71</td>
<td>0.71</td>
</tr>
<tr>
<td>Dairy</td>
<td>2.30</td>
<td>2.06</td>
<td>1.92</td>
<td>1.76</td>
<td>1.76</td>
</tr>
</tbody>
</table>

Actual intake data in the WHI CT-OS
Covariates Considered

- Total energy intake
- Age
- BMI
- Race/ethnicity
- Educational level
- Physical activity
- Smoking status
- Family history of cancer
- Diabetes
- Hypertension
- Arthritis
- Cancer screening history
- NSAID use
- Antidepressant use
- Age at menarche
- Age at menopause
- Number of live births
- Oophorectomy status
- Category & duration of estrogen use
- Category & duration of combined estrogen & progesterone use
- DM arm, HRT arm, and CaD arm
MS1419 Additional Results

HRs were strengthened when CRC cases that developed within 3 years from baseline were excluded,

- e.g. HR \textsubscript{Q5vsQ1} for colon cancer: 1.36 (1.11, 1.66), P\textsuperscript{trend}=0.003

HRs for CRC differed by category of NSAID use:

- Non-NSAID users: 1.31 (1.05, 1.65) \textsubscript{Q5vsQ1}, P\textsuperscript{trend}=0.03
- NSAID users: 1.11 (0.89, 1.38) \textsubscript{Q5vsQ1}, P\textsuperscript{trend}=0.61
- Though interaction not significant (p=0.25)

No significant association with:

- Distal colon cancer
- Rectal cancer
- CRC stage at diagnosis
No significant associations with other tumor subtypes or stage at diagnosis

After excluding participants diagnosed within 3 years of baseline, results for incidence did not change. HR for mortality reached marginal statistical significance: HR=1.34 (1.02, 1.77), $p_{\text{trend}}=0.03$