Nutrition and Cancer: What We Know, What We Don’t Know

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Animal Fat and Breast Cancer Mortality

Breast Cancer Deaths / 100,000 pop

Animal Fat Intake (g/day)

Carroll, 1975
Relative Risk of Breast Cancer for 25 gm of Fat per Day

Case-Control

Prospective

*p, Heterogeneity < 0.001

**p, Heterogeneity = 0.24

Study

0.215
Dietary Total Fat and Breast Cancer in Pooling Project of Diet and Cancer
(8 cohorts with 7,329 cases)

Multivariate RR

Quintiles of Total Fat

(Smith-Warner S et al. Int J Cancer, 2001)

1.086
Deattenuated Spearman correlation coefficients (and lower bound of the 95% CI) between diet assessed by FFQ’s, 24-hour recalls, and 1-week diet records and biomarkers of diet (n = 627 U.S. female nurses aged 45-80 years)

De-attenuated r and lower bound of the 95% CI

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Single ASA24</th>
<th>Averaged ASA24</th>
<th>SFFQ2</th>
<th>SFFQ1&amp;2</th>
<th>Single 7DDR</th>
<th>Averaged 7DDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (% energy)</td>
<td>0.37</td>
<td>0.46</td>
<td>0.54</td>
<td>0.52</td>
<td>0.67</td>
<td>0.59</td>
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<tr>
<td>Potassium (mg/1,000 kcal)</td>
<td>0.41</td>
<td>0.52</td>
<td>0.49</td>
<td>0.49</td>
<td>0.59</td>
<td>0.64</td>
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<tr>
<td>Long Chain N-3* (% total fat)</td>
<td>0.23</td>
<td>0.36</td>
<td>0.58</td>
<td>0.53</td>
<td>0.64</td>
<td>0.64</td>
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<tr>
<td>Beta carotene*</td>
<td>0.24</td>
<td>0.36</td>
<td>0.47</td>
<td>0.50</td>
<td>0.50</td>
<td>0.58</td>
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</table>

*Subgroups of women who didn’t take supplements for this nutrient (N= 363 for long-chain N-3 fatty acids, and 335 for beta-carotene)

(Yuan C et al. unpublished)
Breast Cancer Incidence in WHI

HR, 0.91 (95% CI, 0.83-1.01)

P=0.09

Prentice RL et al. JAMA 2006; 295(6):629-42
Change in Dietary Fat, HDL, Triglycerides in the WHI

<table>
<thead>
<tr>
<th>Fat Intake (%E)</th>
<th>Baseline</th>
<th>Year 6</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>38.8%</td>
<td>38.1%</td>
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<tr>
<td>Intervention</td>
<td>38.8%</td>
<td>29.8%</td>
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</table>

<table>
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<tr>
<th>HDL (mg/dl)</th>
<th>Year 3</th>
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<td>Control</td>
<td>56.4</td>
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<tr>
<td>Intervention</td>
<td>58.1</td>
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<tr>
<th>Triglyceride (mg/dl)</th>
<th>Year 3</th>
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<tr>
<td>Control</td>
<td>141.1</td>
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<tr>
<td>Intervention</td>
<td>138.6</td>
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</tbody>
</table>

Randomized trial of dietary intervention for breast cancer prevention

Cohort analysis

All invasive breast cancer

HR$^*$ = 1.19 (95% CI$^+$: 0.91–1.55)

Cumulative hazard

Year

Intervention

Comparison

(Martin LJ, et al. 2011)
Fat & Postmenopausal Breast Cancer in NHS, 1980-2000 (3537 cases)

RR of Breast Cancer

Cumulative Average Fat Intake (%E)

\( P, \text{ trend test } 0.11 \)

(Kim et al. 2006)
Major takeaways for 2015 DGAC report

- Focus on dietary patterns rather than individual nutrients – one size doesn’t fit all
- **Remove restriction on total fat**: types of fat are more important
- **Retain 10% upper limit on saturated fat**
- **Remove restriction on dietary cholesterol**: eggs (moderate amount) are Okay
- **Consider environment**: reduce red meat for both health & planet
- **Set a 10% calorie upper limit on added sugars**
- **Retain 2300 mg/day sodium limit**, but not 1500 mg/day
- **Coffee consumption** as part of a healthy diet/lifestyle
- **Farm-raised and wild-caught seafood** are equally nutritious
- **Promote “Culture of health”**: Accessible, affordable, and normative
<table>
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<tr>
<th>Sufficient Evidence</th>
<th>Limited Evidence</th>
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<tr>
<td>Colon</td>
<td>Fatal prostate cancer</td>
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<td>Esophagus (Adeno Ca)</td>
<td>Large B-cell lymphoma</td>
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<td>Kidney</td>
<td>Male breast</td>
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<td>Breast (postmenopausal)</td>
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<td>Uterine (corpus)</td>
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<td>Gastric (Cardia)</td>
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<td>Liver</td>
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<td>Gall bladder</td>
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<td>Pancreas</td>
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<td>Ovary</td>
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<tr>
<td>Thyroid</td>
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<td>Multiple myeloma</td>
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<tr>
<td>Meningioma</td>
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</tbody>
</table>
BMI and cancer mortality in pooled data from 1.46 million adults

(Berrington de Gonzalez et al. NEJM 2010)
Cardiovascular Disease

P-value, test for trend < 0.001

Cancer
P-value, test for trend = 0.77

Cardiovascular Disease
P-value, test for trend < 0.001

Hsin-Chia Hung, 2004
Intake of fruits and vegetables and risk of total cancer in EPIC cohort

$P_{trend} = < .001$

(Boffeta P et al., 2010)
Vegetable intake and RR of breast cancer by hormone receptor status (19,869 cases in 1 million women)

Relative Risk

P-trend, 0.06
P-trend, <.001

(Jung S et al., JNCI 2013)
Plasma β-carotene and risk of breast cancer in pooled cohorts (ER+ vs ER-)

(Eliassen AH et al. JNCI 2012)
Intakes of fruits and vegetables (per 3 servings/week) and risk of pancreatic cancer in pooled analysis of 14 cohort studies

(Koushik A et al. AJE, 2012)
Number of new colon and rectum cancer cases and deaths per 100,000, from 2008-2013

Cumulative Alcohol Consumption & Risk of Breast Cancer in the NHS, 1980-2004

(P for trend, <0.0001)

(relative risk)

(Chen WY et al. JAMA 2011)
Processed meat and colorectal cancer; cohort studies

Relative risk (95% CI)

Goldbohm 1994: 1.69 (1.10–2.58)
Pietinen 1999: 0.99 (0.79–1.24)
Chao 2005 Men: 1.40 (1.04–1.88)
Chao 2005 Women: 1.14 (0.64–2.05)
Norat 2005: 1.30 (0.93–1.80)
Larsson 2005 Women: 1.13 (0.85–1.51)
Summary estimate: 1.21 (1.04–1.42)
Potential Relationships Needing Further Examination:

- Milk and fatal prostate cancer (+)
- Calcium and colorectal cancer (-)
- Soy and breast and prostate cancer (-)
- Lycopene and prostate cancer (-)
- Vitamin D and colorectal cancer (-)
Western & Prudent Diet and CRC

(24 to 32 years of follow-up in NHS/HPFS, N = 3,209 cases)

(Mehta RS et al., unpublished data)
Greater Height Is Associated with Higher Risk of Breast Cancer

*(Van den Brandt et al 2000)*

**Pooled Analysis of 8 Cohort Studies**

![Graph showing incidence rate ratio (IRR) vs. height in cm](image)

**FIGURE 1.** Nonparametric regression curve for the relation between height and breast cancer, the Pooling Project of Diet and Cancer.
Adolescent Meat Intake and Premenopausal Breast Cancer

NHSII (n=44,231)

P, trend = 0.007

(Farvid MS et al., Int J Cancer 2014)
**Premenopausal fiber intake and risk of breast cancer in NHSII (1991-2011)**

- Multivariate RRs
- Quintiles (Farvid M et al., preliminary data)

\[ P_{\text{trend}} = 0.002 \]
Intake of vegetable fat and RRs for prostate cancer-specific and overall survival among 4577 men with prostate cancer

Relative Risk

Prostate-cancer specific mortality

$P_{\text{trend}} = .06$

Overall mortality

$P_{\text{trend}} = <.001$

(Richman E et al. JAMA Intern Med 2013)
Multivariate RRs of Type 2 Diabetes

A. Cereal-Fiber Intake

B. Ratio of Polyunsaturated-Fat Intake to Saturated-Fat Intake

C. Trans-Fat Intake

D. Glycemic Load

(Hu et al. 2001)
Conclusions: Methodological

- All types of studies have limitations; case-control studies are prone to serious bias
- Current methods to assess diet are sufficient to detect most important associations; specificity among correlated nutrients will always be challenging
- Large randomized trials of diet and cancer incidence may fail due to poor adherence and limited duration
- The best evidence will probably come from replicated cohort studies in combination with short-term trials with intermediate biomarkers
- Integration of genomics, metabolomics, epigenetics and molecular characterization of tumors is likely to be useful in establishing causality
CONCLUSIONS

1. Estimate of 30-35% of cancer due to nutritional factors is still reasonable, but much of this is related to overweight & inactivity.

2. Alcohol consumption does increase risks of breast & other cancers.

3. Low folate intake likely contributes to colon, breast, and possibly other cancers.

4. Considerable evidence supports a role of low intakes of calcium, folate, lycopene, and vitamin D in human cancer.

5. We still have much to learn. Studies of maternal diet, diet during childhood, & long follow-ups will be important.
### Relationship of dietary factors with risk of selected individual cancer sites (WCRF/AICR, Willett & McCullough, 2016)

#### Macronutrients/energy balance

<table>
<thead>
<tr>
<th>Dietary Factor</th>
<th>Colorectum</th>
<th>Breast</th>
<th>Prostate</th>
<th>Lung</th>
<th>Stomach</th>
<th>Esophagus</th>
<th>Pancreas</th>
<th>Liver</th>
<th>Ovary</th>
<th>Endometrium</th>
<th>All cancers</th>
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<tbody>
<tr>
<td>Obesity</td>
<td>↑↑</td>
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<td>Abdominal fatness</td>
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<td>Carbohydrates/sugars</td>
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<td>Glycemic Load</td>
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#### Nutrients

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<th>Esophagus</th>
<th>Pancreas</th>
<th>Liver</th>
<th>Ovary</th>
<th>Endometrium</th>
<th>All cancers</th>
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<tr>
<td>Vitamin D</td>
<td>↓</td>
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<td>Non-linear</td>
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<td>Calcium</td>
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<td>Fiber (foods)</td>
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<td>Carotenoids</td>
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<td>Lycopene</td>
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<td>↓(foods)</td>
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<td>β-carotene supplements</td>
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<td>Vitamin E supplements</td>
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<td>Selenium supplements</td>
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<td>Antioxidant (combin -ation) supplements</td>
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<td>Salt preservation</td>
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#### Foods

<table>
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<th>Dietary Factor</th>
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<th>Breast</th>
<th>Prostate</th>
<th>Lung</th>
<th>Stomach</th>
<th>Esophagus</th>
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<th>Liver</th>
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<td>Fruits</td>
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<td>Vegetables</td>
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<td>Red meat</td>
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<td>Processed meat</td>
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<td>Other protein sources, fish, poultry, nuts</td>
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<td>Whole grains</td>
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<td>Dairy or milk</td>
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<td>Soy</td>
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<td>Coffee</td>
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Hazard ratios for breast cancer by quintile of saturated-fat intake according to the FFQ and food diary.

Quintile estimates and smoothed data for every quintile rise of fat are shown as saturated fat adjusted for non-fat energy intake. p value for trend (smoothed) relative risk.

(Bingham et al. 2003)
Associations between total fat intake (% energy) and breast cancer risk (n=657 cases)

Food Diaries -- $P_{trend} = 0.37$

FFQs -- $P_{trend} = 0.50$

(Key TJ et al. AJCN 2011)
Percent of Energy from Fat and Plasma Triglyceride Level

Mean TG Level

% of Energy from Fat by FFQ

0.195

NHS (n=185)

HPFS (n=269)
Folate deficiency (<3.0 ng/mL)

MTHFR genotype

- ala/ala: 1.00
- ala/val: 1.49
- val/val: 1.33

Odds Ratio

(Ma, J. et al. 1997)