Role of Diet and Lifestyle Factors in the Primary and Secondary Prevention of GI Cancers

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New Haven, CT
Presenter Disclosure Information

The following relationships exist related to this presentation:

Dr. Fuchs has no relationships to disclose.

Off-Label/Investigational Discussion

In accordance with Harvard Medical School CME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
Diet and Lifestyle and CRC Incidence

• In U.S.: 136,830 new cases and 50,310 deaths annually

• Geographic variation in colorectal cancer incidence
  – Incidence highest in Western countries
  – 40-fold difference between US and Africa

• Emigration studies
  – Migrants from low-incidence areas to high-incidence areas assume the incidence of the host country within one generation
Ongoing Prospective Cohort Studies

**Health Professionals Follow-up Study (N = 52,000)**

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<td>DIET</td>
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**Nurses’ Health Study (N = 121,700)**

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<tbody>
<tr>
<td>OC’s</td>
<td>Diet</td>
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<tr>
<td>Smoking</td>
<td>Diet</td>
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<tr>
<td>Weight/Ht</td>
<td>Diet</td>
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<tr>
<td>Med. Hist.</td>
<td>Diet</td>
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</tbody>
</table>

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YaleNewHavenHealth
Smilow Cancer Hospital
## Red Meat Intake and the Risk of Colon Cancer in Women

<table>
<thead>
<tr>
<th>Servings of Beef, Pork, or Lamb</th>
<th>&lt; 1/ Month</th>
<th>1-4/ Month</th>
<th>2-4/ Week</th>
<th>5-6/ Week</th>
<th>&gt; 1/ Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>14</td>
<td>42</td>
<td>57</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.0</td>
<td>1.39</td>
<td>1.50</td>
<td>1.84</td>
<td>2.75</td>
</tr>
<tr>
<td></td>
<td>(0.75-2.56)</td>
<td>(0.84-2.70)</td>
<td>(0.90-3.75)</td>
<td>(1.24-5.03)</td>
<td></td>
</tr>
</tbody>
</table>
### Relative Risk of Colon Cancer by Physical Activity

<table>
<thead>
<tr>
<th>MET – Hours Per Week</th>
<th>Cases</th>
<th>Multi, RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>47</td>
<td>1.0</td>
</tr>
<tr>
<td>2-4</td>
<td>26</td>
<td>0.71</td>
</tr>
<tr>
<td>5-10</td>
<td>36</td>
<td>0.78</td>
</tr>
<tr>
<td>11-21</td>
<td>29</td>
<td>0.67</td>
</tr>
<tr>
<td>&gt; 21</td>
<td>23</td>
<td>0.54</td>
</tr>
</tbody>
</table>

**P, Trend**

0.03

(95% CI)

(0.44-1.15) (0.50-1.20) (0.42-1.07) (0.33-0.90)
Waist-to-Hip Ratio and Risk of Colorectal Adenoma and Cancer: HPFS

<table>
<thead>
<tr>
<th>Waist-to-Hip Ratio</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.90</td>
<td>2.63</td>
</tr>
<tr>
<td>0.90-0.92</td>
<td>2.68</td>
</tr>
<tr>
<td>0.93-0.94</td>
<td>2.09</td>
</tr>
<tr>
<td>0.95-0.98</td>
<td>2.04</td>
</tr>
<tr>
<td>≥ 0.99</td>
<td>3.41</td>
</tr>
</tbody>
</table>

Large Adenoma:
- 0.90-0.92: 2.86
- 0.93-0.94: 2.98
- ≥ 0.99: 3.42

Cancer:
- < 0.90: 3.41
- 0.90-0.92: 3.42
- 0.93-0.94: 2.04
- ≥ 0.99: 2.04
Aspirin and Risk of Colorectal Cancer: NHS

82,911 Women in the Nurses’ Health Study 1980-2000

## Randomized Trials of Aspirin and Adenoma Recurrence

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Duration</th>
<th>Dose</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandler, 2003</td>
<td>635</td>
<td>3 years</td>
<td>325 mg</td>
<td>0.65 (0.46-0.91)</td>
</tr>
<tr>
<td>Baron, 2003</td>
<td>1121</td>
<td>3 years</td>
<td>81 mg, 325 mg</td>
<td>0.83 (0.70-0.98), 0.96 (0.81-1.13)</td>
</tr>
<tr>
<td>Benamouzig, 2003</td>
<td>272</td>
<td>1 year</td>
<td>160 mg, 300 mg</td>
<td>0.85 (0.57-1.26), 0.61 (0.37-0.99)</td>
</tr>
<tr>
<td>Logan, 2008</td>
<td>945</td>
<td>3 years</td>
<td>300 mg</td>
<td>0.79 (0.63-0.99)</td>
</tr>
</tbody>
</table>
Randomized Trial of Aspirin and Risk of Colorectal Cancer: British Doctors Aspirin Trial

Flossman et al. Lancet 2007

7,588 subjects followed for > 20 Years:

- Aspirin
  - ≥ 300 mg per day
- Placebo

- Regular aspirin use = 29% reduction in colorectal cancer risk
  - HR = 0.74 (95% CI, 0.56-0.97)
Randomized Trials of Celebrex and Vioxx for Adenoma Recurrence

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Agent</th>
<th>Dose per day</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertagnolli, 2006</td>
<td>2,035</td>
<td>Celebrex</td>
<td>400 mg, 800 mg</td>
<td>0.67 (0.59-0.77), 0.55 (0.48-0.64)</td>
</tr>
<tr>
<td>Arber, 2006</td>
<td>1,561</td>
<td>Celebrex</td>
<td>400 mg</td>
<td>0.64 (0.56-0.75)</td>
</tr>
<tr>
<td>Baron, 2006</td>
<td>2,587</td>
<td>Vioxx</td>
<td>25 mg</td>
<td>0.76 (0.69-0.83)</td>
</tr>
</tbody>
</table>
Aspirin Use and Risk of Colorectal Cancer According to Circulating Inflammatory Markers

sTNFR-2 Quartile 4 v 1 1.67 (1.05-2.68; P,trend = 0.03)

Effect of Regular Aspirin Use According to Baseline Levels

sTNFR-2 (≥ median) 0.39 (0.18-0.86)

sTNFR-2 (< median) 0.86 (0.41-1.79)
Prospective Study of Plasma Vitamin D and Colorectal Cancer Risk

Plasma 25(OH) Vitamin D and Colorectal Cancer Nurses’ Health Study

Highest 25(OH) conferred a 47% reduction in mortality
Meta-analysis of plasma 25(OH)D levels and risk of colorectal cancer

<table>
<thead>
<tr>
<th>Studies Examining Blood 25(OH)D Levels</th>
<th>Range (ng/mL)</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jenab et al19</td>
<td>8.0</td>
<td>0.77</td>
<td>0.56 to 1.06</td>
</tr>
<tr>
<td>Woolcott et al20</td>
<td>16.0</td>
<td>0.60</td>
<td>0.33 to 1.07</td>
</tr>
<tr>
<td>Wu et al21</td>
<td>21.0</td>
<td>0.66</td>
<td>0.42 to 1.05</td>
</tr>
<tr>
<td>Otani et al30 (M)</td>
<td>9.2</td>
<td>0.73</td>
<td>0.35 to 1.50</td>
</tr>
<tr>
<td>Otani et al30 (F)</td>
<td>8.3</td>
<td>1.10</td>
<td>0.50 to 2.30</td>
</tr>
<tr>
<td>Wactawski-Wende et al31</td>
<td>11.0</td>
<td>0.75</td>
<td>0.39 to 1.48</td>
</tr>
<tr>
<td>Feskanich et al32</td>
<td>20.4</td>
<td>0.53</td>
<td>0.27 to 1.04</td>
</tr>
<tr>
<td>Tangrea et al32</td>
<td>9.5</td>
<td>0.60</td>
<td>0.30 to 1.10</td>
</tr>
<tr>
<td>Braun et al33</td>
<td>12.9</td>
<td>0.40</td>
<td>0.10 to 0.40</td>
</tr>
<tr>
<td>Garland et al35</td>
<td>23.0</td>
<td>0.73</td>
<td>0.20 to 2.66</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.67</td>
<td>0.54 to 0.80</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $Q = 3.637$; $P = .934$; $I^2 = 0.0\%$
## Lifestyle Risk Factors for Colorectal Cancer

<table>
<thead>
<tr>
<th>Decrease Risk</th>
<th>Increase Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Exercise</td>
<td>• Obesity</td>
</tr>
<tr>
<td>• Aspirin</td>
<td>• Red meat</td>
</tr>
<tr>
<td>• Calcium, vitamin D</td>
<td>• High glycemic diet</td>
</tr>
<tr>
<td>• Post-menopausal estrogen</td>
<td>• Alcohol</td>
</tr>
<tr>
<td>• Screening</td>
<td>• Smoking</td>
</tr>
</tbody>
</table>
Proportion of Colon Cancer Preventable in Middle-Aged Men: HPFS

- BMI ≤ 25 kg/m²
- Physical activity ≥ 15 MET-hours/week
- Daily multivitamin
- Alcohol < 15 g/day
- Non-smoker
- Red meat ≤ 2 servings/week

  - 3.1% of all men

- **Eliminate 71% of all colorectal cancer**
  (95% CI, 33-92%)

What is the role of diet and lifestyle among patients with established colorectal cancer?
## Adjuvant Irinotecan + 5-FU/LV for Stage III Colon Cancer: CALGB 89803

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Patients (n)</th>
<th>Chemotherapy Protocol</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>630</td>
<td>CPT-11: 125 mg/m², LV: 20 mg/m², 5-FU: 500 mg/m²</td>
<td>Weekly x 4 wk q6wk x 5 cycles (30 weeks of therapy)</td>
</tr>
<tr>
<td>2</td>
<td>630</td>
<td>LV: 500 mg/m², 5-FU: 500 mg/m²</td>
<td>Weekly x 6 wk q8wk x 4 cycles (32 weeks of therapy)</td>
</tr>
</tbody>
</table>

CALGB 89803: Diet, Lifestyle, Medication Use Study

Completion of 1st questionnaire*

2 months

0
Study Enrollment

Completion of 2nd questionnaire*

12-14 months

8 months: Completion of adjuvant therapy

Follow-up

*Questionnaire: Diet, physical activity, height, weight, medication use, family history, smoking.
CALGB 89803: Survival by Physical Activity

Hazard Ratio for Death

Walking ≥ 6 hours per week: 47% improvement in DFS

P, trend = .01
Analysis of Dietary Patterns in Stage III Colon Cancer: CALGB 89803

- Factor analysis – 2 major patterns
- Western: higher red meat, sweets, desserts, French fries, refined grains
- Prudent: higher fruits, vegetables, legumes, fish, poultry, whole grains

Western and prudent pattern diets predictive of heart disease, diabetes, and colon cancer risk

CALGB 89803: DFS According to Dietary Pattern

5-Year Survival

Non-diabetics 66%
Diabetics 57%

Hazard Ratio = 1.42 (1.22-1.67)

INT-0089 Adjuvant Colon Study
Overall Survival - Diabetics vs NonDiabetics

log rank p < 0.0001

Meyerhardt et al. JCO 2003;21:433-440
5-Year Recurrence-Free Survival
Non-diabetics 64%
Diabetics 56%
Hazard Ratio = 1.21 (1.00-1.46)

Meyerhardt et al. JCO 2003;21:433-440
CALGB 89803: DFS According to Glycemic Load

Glycemic Index: Measure of food-induced rise in plasma glucose

Glycemic Load: Total dietary intake

Plasma C-peptide and IGFBP-1 and Survival Among Colorectal Cancer Patients

373 participants with stage I-III CRC:

<table>
<thead>
<tr>
<th>Quartiles of Plasma Marker</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-peptide</td>
<td>1.0</td>
<td>1.69</td>
<td>1.79</td>
<td>2.11</td>
</tr>
<tr>
<td>HR for death (95% CI)</td>
<td>1.0</td>
<td>(0.89-3.22)</td>
<td>(0.93-3.44)</td>
<td>(1.06-4.21)</td>
</tr>
<tr>
<td>IGFBP-1</td>
<td>1.0</td>
<td>0.86</td>
<td>0.75</td>
<td>0.44</td>
</tr>
<tr>
<td>HR for death (95% CI)</td>
<td>1.0</td>
<td>(0.48-1.55)</td>
<td>(0.43-1.31)</td>
<td>(0.24-0.81)</td>
</tr>
</tbody>
</table>

Risk Factors for Diabetes and Colon Cancer Survival

**Dietary Risk Factors for Type II Diabetes:**

- **Sugar-Sweetened Beverages**
  - Increased risk of type 2 diabetes, obesity, and heart disease

- **Coffee Intake**
  - Reduced risk of type 2 diabetes and coronary heart disease
  - Increased sensitivity to insulin

- **Nut Intake**
  - Reduced risk of type 2 diabetes, coronary heart disease, and mortality
  - Biochemical studies suggest reduced insulin resistance
Sugar-sweetened beverages linked to diabetes, obesity, heart disease

P = 0.02

P = 0.03, after controlling for BMI, diet, glycemic load

Risk of Cancer Recurrence or Death

<2/month 2/month-2/week 3-6/week 1-<2/day ≥2/day

0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8
CALGB 89803: Coffee Intake and DFS in Stage III Colon Cancer

Guercio et al, J Clin Oncol 2015

Risk of Recurrence or Death

Total Coffee Intake (8 oz cups per day)

P = 0.002
CALGB 89803: Nut Intake and DFS in Stage III Colon Cancer

Risk of Recurrence or Death vs. Nut Intake

Never < 1/wk 1/wk ≥2 /wk

Risk of Recurrence or Death

P = 0.04
CALGB 89803: Aspirin Use and DFS in Stage III Colon Cancer

Consistent aspirin users vs. Non-consistent users

54% improvement in disease-free survival

Log rank, $P = 0.03$

Ng et al, J Natl Cancer Inst. 2014
CALGB 89803: Rofecoxib or Celecoxib Use and DFS

- Rofecoxib or celecoxib use ≥ 3 times per week
- Non-regular use

56% improvement in disease-free survival

Ng et al, J Natl Cancer Inst. 2014
COX-2 Expression in Colorectal Neoplasia

COX-2 upregulated in 75% of adenomas/cancers

Aspirin/NSAIDs may inhibit colon carcinogenesis via COX-2 inhibition

Does aspirin preferentially improve survival in patients with COX-2 overexpressing tumors?
### Effect of Post-Diagnosis Aspirin Use by COX-2 Expression

<table>
<thead>
<tr>
<th></th>
<th>Non-user Post-diagnosis</th>
<th>Regular user Post-diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All participants (n=1,279)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Events / No. at Risk</td>
<td>141 / 730</td>
<td>81 / 549</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>0.71 (0.53-0.95)</td>
</tr>
<tr>
<td><strong>COX-2 negative primary cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Events / No. at Risk</td>
<td>7 / 84</td>
<td>7 / 61</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>1.22 (0.36-4.18)</td>
</tr>
<tr>
<td><strong>COX-2 positive primary cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Events / No. at Risk</td>
<td>38 / 182</td>
<td>13 / 132</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>0.39 (0.20-0.76)</td>
</tr>
</tbody>
</table>
Aspirin Use, PIK3CA Mutations, and Colorectal Cancer Survival

- Inflammatory and energy balance pathways interact
- PI3K/AKT key pathway for energy balance
- Does the survival effect associated with post-diagnosis aspirin use differ according to PIK3CA mutational status?
- Assess 964 colorectal cancer patients
- PIK3CA mutations (17%)

Liao et al. NEJM 2012
CRC Mortality According to Aspirin Use and PIK3CA Mutation Status

Liao et al. NEJM 2012

**A** Colorectal Cancer–Specific Mortality, Mutant PIK3CA

- No aspirin use
- Aspirin use
- \( P < 0.001 \) by log-rank test

**C** Overall Mortality, Mutant PIK3CA

- No aspirin use
- Aspirin use
- \( P = 0.01 \) by log-rank test
CALGB/SWOG 80702: Phase III Trial in Stage III Colon Cancer

**Resected Stage III Colon Cancer**

N = 2,500

Celecoxib starts concurrently with FOLFOX and continue for 3 years
Statin Use and CRC Risk and Survival

• Among 131,922 health professionals in the NHS and HPFS, statin use was associated with colorectal cancer risk

• Among 842 stage III colon cancer patients in CALGB 89803, statin use was not associated risk of recurrence or survival
  – Ng et al. J Natl Cancer Inst. 2011;103:1540-51
Vitamin D in Colorectal Cancer

- Vitamin D receptors present on colorectal cancer cells.
- Vitamin D inhibits cellular proliferation and angiogenesis.
- Diet accounts for only 20% of vitamin D in humans.
CALGB/SWOG 80405

mCRC 1st-line

KRAS wild type (codons 12, 13)

Strata:
- FOLFOX/FOLFIRI
- Prior adjuvant chemo
- Prior XRT

FOLFIRI or FOLFOX

MD choice

Chemo + Cetuximab

Chemo + Bevacizumab

n = 1140

1° Endpoint: Overall Survival

Presented by: Kimmie Ng, MD, MPH

Presented at the Gastrointestinal Cancers Symposium

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Multivariate Analysis: Overall Survival

Presented by: Kimmie Ng, MD, MPH

Hazard Ratio for Death

- Plasma 25(OH)D (ng/mL)
  - 19.3 – 24.0: 0.79 [0.63 – 1.00]
  - 16.5 – 19.2: 0.81 [0.65 – 1.02]
  - 10.9 – 15.4: 0.83 [0.66 – 1.03]
  - 2.2 – 10.8: 1.0
  - > 24.1: 0.65 [0.51 – 0.83]

$P$ trend = 0.001

Presented at the Gastrointestinal Cancers Symposium

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Presented by: Kimmie Ng, MD, MPH
Multivariate Analysis: PFS

Presented by: Kimmie Ng, MD, MPH

Hazard Ratio for Progression or Death

Plasma 25(OH)D (ng/mL)

P trend = 0.01
Phase II Trial of Chemotherapy and Supplemental Vitamin D in Previously Untreated Metastatic Colorectal Cancer

120 patients with stage IV colorectal cancer:

- mFOLFOX6/bevacizumab plus Vitamin D 400 IU/day
- mFOLFOX6/bevacizumab plus Vitamin D 8,000 IU/day X 14 days then 4,000 IU/day

Primary endpoint: Progression-free survival
Colorectal Cancer: Reducing Incidence & Mortality

<table>
<thead>
<tr>
<th>Decrease Risk of Developing CRC:</th>
<th>Improve CRC Patient Survival:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• BMI ≤ 25 kg/m²</td>
<td>• BMI ≤ 25 kg/m²</td>
</tr>
<tr>
<td>• Physical activity ≥ 15 MET-hours/week</td>
<td>• Physical activity ≥ 15 MET-hours/week</td>
</tr>
<tr>
<td>• Alcohol &lt; 15 g/day</td>
<td>• Avoid high glycemic load diet</td>
</tr>
<tr>
<td>• Don’t smoke</td>
<td>• Avoid excessive “Western” diet</td>
</tr>
<tr>
<td>• Red meat ≤ 2 servings/week</td>
<td>• Vitamin D 1000 IU/day</td>
</tr>
<tr>
<td>• Vitamin D 1000 IU/day</td>
<td>• Consider ASA</td>
</tr>
<tr>
<td>• Consider ASA</td>
<td></td>
</tr>
</tbody>
</table>