Physical activity, Obesity, Diet and Colorectal Cancer Prognosis

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Colorectal Cancer Incidence

- Approximately 148,000 cases in the US annually and ~50,000 deaths.
- 1 in 16 people in the United States will be diagnosed with colorectal cancer over their lifetime.
- 6% of Americans will develop colorectal cancer at some point.
## Colorectal Cancer: Risk Factors Overview

<table>
<thead>
<tr>
<th>Decrease Risk</th>
<th>Increase Risk</th>
<th>Uncertain Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Family history</td>
<td>Statins</td>
</tr>
<tr>
<td>Exercise</td>
<td>IBD</td>
<td>Fiber</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Diabetes</td>
<td>Glycemic load/index</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Obesity</td>
<td>Fruits/Vegetables</td>
</tr>
<tr>
<td>Post-menopausal estrogen</td>
<td>Red meat</td>
<td>Folic Acid</td>
</tr>
<tr>
<td>Calcium</td>
<td>Western diet</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td></td>
</tr>
</tbody>
</table>
Doc, what should I eat?
Should I exercise?
What else can I do?
Colorectal Cancer: Diet and Lifestyle Impact on Cancer Patients

- Many studies on diet / lifestyle and risk of developing colorectal cancer

- Few studies show whether these factors affect patients with colorectal cancer
  - Disease recurrence
  - Survival
  - Tolerance to chemotherapy
Energy Balance and Recurrence

- **Emerging Data**
  - Decrease risk of recurrence
    - Physical activity
    - Avoidance of Western pattern diet
    - Avoidance of class III obesity (BMI > 35 kg/m²)
    - Higher vitamin D levels
    - Aspirin or COX-2 inhibitor
  - No association with recurrence
    - Weight change (gain or loss)
    - Obesity < 35 kg/m²
Physical Activity and Colorectal Cancer Outcomes
Physical Activity and Colorectal Cancer

• Many studies have looked at physical activity and quality of life during treatment or beyond treatment for colorectal cancer patients
  – Most observational
  – Few intervention (single arm or different ways of intervening)
  – Only 1 RCT of exercise intervention v control – contamination of control limits conclusions

• This talk will focus on recurrences and survival (for exercises and other host factors)
Physical Activity and Colorectal Cancer

- Cohort study from Australia of 526 colorectal cancer patients with pre-diagnosis physical activity assessment
CALGB 89803

- NCI-sponsored adjuvant therapy trial for stage III colon cancer
- Patients randomized to Roswell Park 5-FU/LV or IFL (bolus 5-FU/LV/Irinotecan)
- 1264 enrolled between 1999 and 2001

CALGB 89803

**Proportion Surviving**

**Time From Study Entry (years)**

- **FU/LV**
  - N: 629
  - Events: 171
  - \( P \) (stratified) = .74 (1-sided)

- **CPT-11/FU/LV**
  - N: 635
  - Events: 181
89803 and Exercise: Disease-Free Survival in Stage III Colon Cancer Survivors

Hazard Ratio Recurrence or Death

- Regular Physical Activity (met-hours per week)
  - <3
  - 3-8.9
  - 9-17.9
  - 18.26.9
  - >27

89803 and Exercise: Disease Free Survival

89803 and Exercise: Stratification

Nurses Health Study

- Ongoing observational study of 121,700 female registered nurses initiated in 1976
- Every 2 year questionnaires to update exposures and capture diseases
- Dietary exposures every 4 years
- Leisure-time physical activity first surveyed in 1986. Updated every 2 years
NHS and Post-diagnosis Physical Activity

### NHS and Pre-diagnosis Physical Activity

#### Colorectal Cancer-Specific Mortality

<table>
<thead>
<tr>
<th>Prediagnosis Activity (MET-hours per week; n = 573)</th>
<th>No. of Events</th>
<th>No. of Patients at Risk</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>&lt; 3</td>
<td>22</td>
<td>142</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>3-8.9</td>
<td>22</td>
<td>152</td>
<td>0.92</td>
<td>0.51 to 1.65</td>
</tr>
<tr>
<td>9-17.9</td>
<td>19</td>
<td>118</td>
<td>1.02</td>
<td>0.55 to 1.88</td>
</tr>
<tr>
<td>≥ 18</td>
<td>17</td>
<td>161</td>
<td>0.70</td>
<td>0.37 to 1.31</td>
</tr>
<tr>
<td>P for trend</td>
<td>.26</td>
<td></td>
<td>.81</td>
<td></td>
</tr>
</tbody>
</table>

NHS and Change in Physical Activity

Health Professionals
Follow Up Study

• Ongoing observational study of 51,500 male health care professionals started in 1986
• Similar questionnaires at Nurses’ Health Study
• Disease capture every 2 years
• Physical activity every 2 years
• Diet every 4 years
HPFS and Physical Activity

Colorectal cancer specific mortality

Overall mortality

CHALLENGE: Colon Health and Life-Long Exercise Change trial

High risk Stage II or stage III colon cancer - completed adjuvant chemotherapy within 2-6 months

REGISTRATION

Baseline Testing

STRATIFICATION

Disease stage high risk III; centre; BMI ≤ 27.5 vs. > 27.5;
ECOG PS 0 vs. 1

RANDOMIZATION

ARM 1
Physical Activity Program + General Good Health Education Material (Intervention Arm)

ARM 2
General Health Education Materials (Control Arm)

Assessment of disease-free survival every 6 months for first 3 years and annually from years 4-10

## CHALLENGE: Colon Health and Life-Long Exercise Change trial – Intervention Arm

<table>
<thead>
<tr>
<th>Content</th>
<th>Baseline to 6 mo.</th>
<th>6-12mo.</th>
<th>12-36 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior support sessions</td>
<td>12 mandatory face-to-face sessions held biweekly</td>
<td>12 Mandatory sessions held biweekly, with option for face-to-face or telephone delivery</td>
<td>Mandatory monthly sessions, with option for face-to-face or telephone delivery</td>
</tr>
<tr>
<td>Supervised physical activity sessions</td>
<td>12 Mandatory sessions combined with the mandatory behavior support sessions</td>
<td>12 sessions recommended; can be combined with the biweekly behavior support sessions for those who choose face-to-face sessions</td>
<td>Monthly sessions recommended; can be combined with the monthly behavior support sessions for those who choose face-to-face sessions</td>
</tr>
<tr>
<td></td>
<td>12 Additional supervised physical activity sessions on alternate weeks strongly recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity goal</td>
<td>Gradually increase recreational physical activity by 10 metabolic equivalent tast (MET)- hours weekly over baseline (to 10-19 MET-hours weekly)</td>
<td>Individualized (based on phase I results) to a maximum increase of 20 MET-hours weekly (to a total of 20-27 MET-hours weekly)</td>
<td>Individualized (based on phase II results) to a maximum total of 27 MET-hours weekly</td>
</tr>
</tbody>
</table>

Diet and Colorectal Cancer Outcomes
Dietary Patterns

• Western and prudent pattern diets predictive of heart disease, diabetes
• Prudent pattern: high intakes of vegetables, fruit, legumes, whole grains, fish, and poultry
• Western pattern: high intakes of red meat, processed meat, refined grains, sweets and dessert, French fries, and high-fat dairy products
CALGB 89803: DFS By Dietary Pattern

Hazard Ratio for Cancer Recurrence or Death

Western diet
- Hazard Ratio: 1.2, 2, 2.2, 3.9
- P, trend < 0.001

Prudent diet
- Hazard Ratio: 1.1, 1.1, 0.7, 1.3

# CALGB 89803: Dietary Pattern

<table>
<thead>
<tr>
<th></th>
<th>1 (n = 201)</th>
<th>2 (n = 202)</th>
<th>3 (n = 202)</th>
<th>4 (n = 202)</th>
<th>5 (n = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red meat, servings/wk</td>
<td>2.3 (1.5)</td>
<td>3.1 (1.8)</td>
<td>3.7 (2.1)</td>
<td>4.7 (2.5)</td>
<td>6.1 (3.0)</td>
</tr>
<tr>
<td>Processed meats, servings/wk</td>
<td>1.8 (1.7)</td>
<td>2.3 (1.8)</td>
<td>3.0 (2.6)</td>
<td>4.2 (2.9)</td>
<td>5.6 (4.1)</td>
</tr>
<tr>
<td>Refined grains, servings/d</td>
<td>2.0 (1.3)</td>
<td>2.8 (1.6)</td>
<td>3.5 (1.8)</td>
<td>4.2 (2.2)</td>
<td>5.8 (2.7)</td>
</tr>
<tr>
<td>Dessert, servings/d</td>
<td>0.7 (0.6)</td>
<td>1.1 (0.8)</td>
<td>1.3 (0.9)</td>
<td>1.6 (1.0)</td>
<td>2.5 (1.6)</td>
</tr>
<tr>
<td>Total fat, g/d</td>
<td>69 (15)</td>
<td>72 (18)</td>
<td>73 (13)</td>
<td>77 (15)</td>
<td>80 (13)</td>
</tr>
</tbody>
</table>

*Values are rounded to nearest 0.5. The median total servings of poultry and fish were similar across each quintile (approximately 2 servings per week of poultry and 1.5 servings per week of fish).*
Obesity and Colorectal Cancer Outcomes
Obesity and Colon Cancer Outcomes

- Most studies limited to single measurement at time of diagnosis / time of initiation of chemotherapy

- Literature limited to body mass index - ? if best measure
<table>
<thead>
<tr>
<th>Author</th>
<th>Years</th>
<th>N</th>
<th>Outcome</th>
<th>Hazard Ratio (95% CI) or P value (compared to normal weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tartter</td>
<td>1976-1979</td>
<td>279</td>
<td>Recur Rate</td>
<td>P = 0.003 for above median weight</td>
</tr>
<tr>
<td>Meyerhardt</td>
<td>1988-1992</td>
<td>3759</td>
<td>DFS</td>
<td>1.11 (0.94-1.30) BMI ≥ 30 kg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OS</td>
</tr>
<tr>
<td>Meyerhardt</td>
<td>1990-1992</td>
<td>1792 rectal</td>
<td>DFS</td>
<td>1.10 (0.91-1.32) BMI ≥ 30 kg/m²</td>
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<td></td>
<td>OS</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Local Recur</td>
</tr>
<tr>
<td>Dignam</td>
<td>1989-1994</td>
<td>4288</td>
<td>DFS</td>
<td>1.06 (0.93-1.21) BMI 30-34.9 kg/m²</td>
</tr>
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<td></td>
</tr>
<tr>
<td>Meyerhardt</td>
<td>1999-2001</td>
<td>1053</td>
<td>DFS</td>
<td>1.00 (0.72-1.40) BMI 30-34.9 kg/m²</td>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td>OS</td>
<td>0.90 (0.61-1.34) BMI 30-34.9 kg/m²</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hines</td>
<td>1981-2001</td>
<td>496</td>
<td>OS</td>
<td>0.77 (0.61-0.97) BMI ≥ 25 all stages</td>
</tr>
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</tbody>
</table>
Disease-free and overall survival by body mass index (BMI) category in 4288 patients from National Surgical Adjuvant Breast and Bowel Project randomized clinical trials for Dukes B and C colon cancer

89803 and Body Mass Index

![Graph showing disease-free survival (proportion) over time (years) for different BMI categories.](Meyerhardt J Clin Oncol. 2008 Sep 1;26(25):4109-15.)

- BMI categories: 
  - < 21 kg/m²
  - 21-24 kg/m²
  - 25-29.9 kg/m²
  - 30-34.9 kg/m²
  - ≥ 35 kg/m²

Log-rank $P = .38$
## Body Mass Index in Colon Cancer Patients over Past Decade

<table>
<thead>
<tr>
<th></th>
<th>&lt; 21</th>
<th>21-24.9</th>
<th>25-29.9</th>
<th>30-34.9</th>
<th>≥ 35</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INT-0089</strong></td>
<td>14 %</td>
<td>34 %</td>
<td>34 %</td>
<td>13 %</td>
<td>5 %</td>
</tr>
<tr>
<td>(1988-92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>89803</strong></td>
<td>8 %</td>
<td>26 %</td>
<td>36 %</td>
<td>20 %</td>
<td>10 %</td>
</tr>
<tr>
<td>(1999-2001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% change in a decade</td>
<td>- 43%</td>
<td>- 24%</td>
<td>+ 6%</td>
<td>+ 54%</td>
<td>+ 100%</td>
</tr>
</tbody>
</table>
89803 and Change in Weight

Adjusted Hazard ratio (95% CI)

\[
\begin{array}{ll}
> 5 \text{ kg weight loss} & 1.39 (0.69 - 2.79) \\
2.1 - 5 \text{ kg weight loss} & 1.15 (0.54 - 2.44) \\
+/- 2 \text{ kg change} & \text{Referent} \\
2 - 4.9 \text{ kg weight gain} & 1.11 (0.66 - 2.06) \\
> 5 \text{ kg weight gain} & 1.19 (0.73 - 1.94) \\
\end{array}
\]

\[P_{trend} = 0.13\]
\[P_{trend} = 0.90\]

Vitamin D and Colorectal Cancer Outcomes
Plasma Vitamin D and Survival in Colorectal Cancer Patients: NHS/HPFS (N = 304)

Hazard Ratio for Death

People with highest level of vitamin D have 50% improvement in outcome

Ng et al J Clin Oncol. 2008 Jun 20;26(18):2984-91
Predicted Vitamin D Level* & Survival in Colorectal Cancer Patients: NHS/HPFS (N=1017)

CRC Specific Mortality

Overall Mortality

* Based on race, geography, exercise, BMI, dietary vitamin D, supplement vitamin D

Ng et al Br J Cancer. 2009 101: 916-23.
Aspirin/NSAIDs and Colorectal Cancer Outcomes
Survival According to Aspirin Use After Diagnosis: NHS

Aspirin and COX-2 Use in Stage III Colon Cancer Survivors: Findings from CALGB 89803

<table>
<thead>
<tr>
<th>Drug Use</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent aspirin use</td>
<td>0.45</td>
<td>(0.21-0.97)</td>
</tr>
<tr>
<td>Celecoxib or Rofecoxib use</td>
<td>0.56</td>
<td>(0.21-1.54)</td>
</tr>
</tbody>
</table>

Fuchs ASCO 2005
CALGB/SWOG 80702 for Stage III Colon Cancer

Resected Stage III Colon Cancer

N = 2,500

6 treatments of mFOLFOX6

12 treatments of mFOLFOX6

Celecoxib 400 mg daily

Placebo

Celecoxib 400 mg daily

Placebo

Celecoxib starts concurrently with FOLFOX and continue for 3 years
Conclusions

• Colorectal cancer has the most consistent data for certain modifiable factors impacting risk of developing disease

• Increasing evidence that some of these factors may impact outcomes of patients with disease
Where do we go from here

• Are these data sufficient to make recommendations?

• Are there intermediaries to use in studies to hasten progress, reduce sample size?

• Physical activity questions
  – How much activity required?
  – How long to sustain exercise program to impact on recurrence?
  – If people are already modestly active, will increasing help?
  – If we do an RCT and it is negative, what’s the message?
Where do we go from here

• Diet questions
  – What’s the right diet?
  – Which components of diet are most important to process?
  – The preliminary data suggests avoidance of certain foods rather than increasing – is that harder to study?

• Obesity questions
  – Class II and III obesity may have increased risk of recurrence but does weight loss in those patients impact recurrences?

• Vitamin D questions
  – Will supplementation for deficient and insufficient levels impact on outcomes?
  – Is supplementation after diagnosis too late?