Leveraging Prospective Cohort Studies to Advance Colorectal Cancer Prevention, Treatment and Biology

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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

Nurses’ Health Study (N = 121,700)

Health Professionals Follow-up Study (N = 52,000)
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>
<tr>
<td>MET – Hours Per Week</td>
<td>&lt; 2</td>
<td>2-4</td>
<td>5-10</td>
<td>11-21</td>
<td>&gt; 21</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----</td>
<td>-----</td>
<td>------</td>
<td>------</td>
<td>-----</td>
</tr>
<tr>
<td>Cases</td>
<td>47</td>
<td>26</td>
<td>36</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>Multi, RR (95% CI)</td>
<td>1.0</td>
<td>0.71</td>
<td>0.78</td>
<td>0.67</td>
<td>0.54</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.44-1.15)</td>
<td>(0.50-1.20)</td>
<td>(0.42-1.07)</td>
<td>(0.33-0.90)</td>
<td></td>
</tr>
</tbody>
</table>
Waist-to-Hip Ratio and Risk of Colorectal Adenoma and Cancer: HPFS

<table>
<thead>
<tr>
<th>Waist-to-Hip Ratio</th>
<th>Large Adenoma</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.90</td>
<td>2.63</td>
<td>2.68</td>
</tr>
<tr>
<td>0.90-0.92</td>
<td>2.86</td>
<td>2.09</td>
</tr>
<tr>
<td>0.93-0.94</td>
<td>2.98</td>
<td></td>
</tr>
<tr>
<td>0.95-0.98</td>
<td>3.41</td>
<td>2.04</td>
</tr>
<tr>
<td>≥ 0.99</td>
<td>3.42</td>
<td></td>
</tr>
</tbody>
</table>
Aspirin and Risk of Colorectal Cancer: NHS

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

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

P trend = .02
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>
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

n = 630

CPT-11: 125 mg/m²
LV: 20 mg/m²
5-FU: 500 mg/m²
Weekly x 4 wk q6wk x 5 cycles
(30 weeks of therapy)

n = 630

LV: 500 mg/m²
5-FU: 500 mg/m²
Weekly x 6 wk q8wk x 4 cycles
(32 weeks of therapy)

CALGB 89803: Diet, Lifestyle, Medication Use Study

Completion of 1st questionnaire*

2 months

0
Study Enrollment

8 months:
Completion of adjuvant therapy

Completion of 2nd questionnaire*

12-14 months

Follow-up

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

Hazard Ratio for Death

Physical Activity, MET-hours per week

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

Hazard Ratio for Cancer Recurrence or Death

Prudent diet

Western diet

P, trend < .001

Overconsumption

GH

Abdominal Obesity

Physical Activity

Insulin Resistance

Western Pattern Diet
High Glycemic Diet

Fasting Hyperinsulinemia

Competent b-cells

Post-prandial Hyperinsulinemia
CALGB 89803: DFS According to Glycemic Load

Meyerhardt JA, et al.

JNCI, 2012.

Risk of Cancer Recurrence or Death

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><strong>C-peptide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR for death (95% CI)</td>
<td>1.0</td>
<td>1.69</td>
<td>1.79</td>
<td>2.11</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.89-3.22)</td>
<td>(0.93-3.44)</td>
<td>(1.06-4.21)</td>
<td></td>
</tr>
<tr>
<td><strong>IGFBP-1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR for death (95% CI)</td>
<td>1.0</td>
<td>0.86</td>
<td>0.75</td>
<td>0.44</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.48-1.55)</td>
<td>(0.43-1.31)</td>
<td>(0.24-0.81)</td>
<td></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

Risk of Cancer Recurrence or Death

P = 0.02

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

Sugar-sweetened beverage intake

<2/mon 2/mon-2/wk 3-6/wk 1-<2/day ≥2/day
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 decreases with increasing nut intake. The risk of recurrence or death decreases from 1.0 to 0.8 to 0.68 to 0.59.

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

54% 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/NSAID(s) 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>All participants (n=1,279)</th>
<th>Non-user Post-diagnosis</th>
<th>Regular user Post-diagnosis</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COX-2 negative primary cancer</th>
<th>Non-user Post-diagnosis</th>
<th>Regular user Post-diagnosis</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COX-2 positive primary cancer</th>
<th>Non-user Post-diagnosis</th>
<th>Regular user Post-diagnosis</th>
</tr>
</thead>
<tbody>
<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

N = 2,500

Resected Stage III Colon Cancer

Celecoxib starts concurrently with FOLFOX and continue for 3 years

6 treatments of mFOLFOX6

12 treatments of mFOLFOX6

Celecoxib 400 mg daily

Placebo

Celecoxib 400 mg daily

Placebo
Baseline Plasma 25-OH-Vitamin D and Survival in Stage IV Colorectal Cancer Patients n = 1,140

Presented by: Kimmie Ng, MD, MPH

$P$ trend $= 0.001$
Previously Untreated Metastatic CRC
n=139

April 2012–November 2016

Randomization 1:1

FOLFOX-bevacizumab + Vitamin D3 8,000 IU/day x 2 weeks (loading dose), followed by Vitamin D3 4,000 IU/day (maintenance dose)

FOLFOX-bevacizumab + Vitamin D3 400 IU/day

Progression or Unacceptable toxicity or Withdrawal of consent

Data lock April 25, 2017
High-Dose Vitamin D Resulted in Improved PFS

Log rank $P = 0.04$

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median PFS (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Dose</td>
<td>13.1</td>
<td>10.1-14.7</td>
</tr>
<tr>
<td>Control</td>
<td>11.2</td>
<td>9.5-14.2</td>
</tr>
</tbody>
</table>

Unadjusted HR 0.69 (95% CI, 0.46-1.02)

Data lock April 25, 2017

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

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>HR</th>
<th>95% CI</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose vitamin D3</td>
<td>0.67</td>
<td>0.45 – 0.99</td>
<td>0.02</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.01</td>
<td>0.99 – 1.03</td>
<td>0.17</td>
</tr>
<tr>
<td>Female (vs. male)</td>
<td>1.04</td>
<td>0.70 – 1.56</td>
<td>0.42</td>
</tr>
<tr>
<td>White (vs. non-white)</td>
<td>1.11</td>
<td>0.69 – 1.79</td>
<td>0.33</td>
</tr>
<tr>
<td>ECOG PS 1 (vs. 0)</td>
<td>1.28</td>
<td>0.87 – 1.88</td>
<td>0.10</td>
</tr>
<tr>
<td>No. metastatic sites</td>
<td>0.95</td>
<td>0.76 – 1.18</td>
<td>0.31</td>
</tr>
</tbody>
</table>

* One-sided P-value
Molecular Characterization of Colorectal Cancer

- 1,000 colorectal cancer patients
- Whole exome sequencing
- RNA-seq
- Assess the immune infiltrate
- Assess the microbiome
- Define unique subtypes of colorectal cancer.
- Identify new therapeutic targets for both treatment and prevention.
Lymphocytic reaction to colorectal cancer and patient survival

Fusobacterium nucleatum in CRC: NHS & HPFS

The amount of *Fusobacterium nucleatum* DNA

- Blue: Negative
- Green: Low
- Red: High

Log-rank test for trend

\[ p = 0.023 \]

Survival probability vs. colorectal cancer-specific survival (years)

Relative T cell infiltrate (OR)

- Negative: 1.0
- Low: 0.63
- High: 0.47

Tumoral *Fusobacterium Nucleatum* Levels

\[ P \text{ for Trend } = 0.006 \]
## Colorectal Cancer: Reducing Incidence & Mortality

### Decrease Risk of Developing CRC:
- BMI \( \leq 25 \text{ kg/m}^2 \)
- Physical activity \( \geq 15 \text{ MET-hours/week} \)
- Alcohol < 15 g/day
- Don’t smoke
- Red meat \( \leq 2 \text{ servings/week} \)
- Vitamin D 1000 IU/day
- Consider ASA

### Improve CRC Patient Survival:
- BMI \( \leq 25 \text{ kg/m}^2 \)
- Physical activity \( \geq 15 \text{ MET-hours/week} \)
- Avoid high glycemic load diet
- Avoid excessive “Western” diet
- Vitamin D supplementation
- Consider ASA