Epidemiology of Lifestyle Factors and Colorectal Cancer

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• There is relatively little racial / ethnic variation in colorectal cancer (CRC) mortality in U.S.

• However, worldwide incidence rates vary approximately 20-fold, with the lowest rates in India and the highest in U.S. and Japan

• International differences and migrant data show that CRC is highly sensitive to changes in lifestyle
Age-standardized Incidence Rates of CRC (Men)

- China
- Japan
- Poland
- Spain
- Sweden
- The Netherlands
- United Kingdom
- USA

Age-standardized Incidence Rates of CRC (Women)

- China
- Japan
- Poland
- Spain
- Sweden
- The Netherlands
- United Kingdom
- USA

Consumptions of Fat & Meat in Japan

Incidence and Mortality Rates In Japan

Kono, S. Eur J Can Prev 2004
Western Diet & Lifestyle → Energy Imbalance

High energy intake
Western Diet Pattern
Obesity

Physical Activity
Western Dietary Pattern*

- Red meat
- Processed meats
- High fat dairy
- Sweets
- Refined grain products
- Less whole grain fiber

* Factor analysis (principal components)
Meta-Analysis of Risk of CRC for an Increase of 1 Portion of All Meat

Summary
OR=1.14

Sandhu et al., CEBP 2001
Meta-Analysis of Risk of CRC for an Increase for 1 Portion of Red Meat

Summary OR = 1.17

Sandhu et al., CEBP 2001
Meta-Analysis of Risk of CRC for an Increase of 1 Portion of Processed Meat

Summary OR = 1.4
Western Dietary Pattern and Risk of Adenomas and Colon Cancer In Men (HPFS)

Wu et al. Cancer Causes & Control 2004

Colon cancer

Large distal adenomas

P trend = 0.05

P trend = 0.04
Western Dietary Pattern and Colon Cancer Risk in Women, The Nurses’ Health Study (NHS)

Fung et al., *Arch Intern Med* (in press)
Leisure-Time Physical Activity and Colon Cancer Risk in Women (NHS)

Martinez et al. JNCI 1997

P trend = 0.02

Multivariate RR vs. MET-hours per week

Martinez et al. JNCI 1997
Waist to Hip Ratio and Colon Cancer Risk in Men

Giovannucci et al., JNCI 1995
Giovannucci et al., CCC 1995; J Nutr 2002

- High Insulin (C-peptide)
  - GH Receptors
  - Pituitary Growth Hormone (GH) Secretion
  - Bioactive IGF-1 Secretion
  - IGFBP-1
  - IGFBP-2
  - IGFBP-3
  - Colorectal Cancer

- ↓ Physical Activity
- ↑ BMI
- ↑ Waist Circumference
- ↓ High Starch
- ↓ Processed Meats
- ↓ Western Diet
- ↓ Sucrose

- ↑ IGF-1 Secretion
- ↓ IGFBP-1
- ↓ IGFBP-2
- ↓ IGFBP-3
- ↑ IGF-1

- High Starch
- Processed Meats
- Western Diet
- Sucrose
Relative Risk of Colorectal Cancer in Men (PHS)


IGFBP-3

IGF-I

RR

Q1 Q2 Q3 Q4 Q5

2.5 (1.2-5.5)

0.3 (0.1-0.7)
RR of Colorectal Cancer and High Risk Adenoma in Women (NHS)

Giovannucci E, et al. *CEBP* 2000
C-peptide Levels (a marker of insulin production) and Risk of Colorectal Cancer in Men (PHS)

Total Calcium Intake and Colorectal Cancer
Pooled Analysis from 10 Cohorts

Cho et al., JNCI 2004
Plasma 25(OH) Vitamin D and Colorectal Cancer
Nurses’ Health Study

Feskanich D. et al., CEBP 2004
Vitamin D Status Modify the Effect of Calcium on Adenoma Recurrence (The Calcium Polyp Prevention Study)

RR of colorectal cancer in Men (PHS)

- RR of colorectal cancer in Men (PHS) with different levels of skim milk intake (glass):
  - Never/rarely: 3.1 (1.3-7.2)
  - >1/mo-4/wk: 2.2 (1.0-5.2)
  - >5/wk-2+/d: 1.1 (0.4-2.7)

Folate & Related Genetic Factor
Relative Risk and 95% CI of Colon Cancer in Women (NHS)

Giovannucci et al., *Ann Intern Med* 1998
<table>
<thead>
<tr>
<th>Nutrient</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>0.96</td>
<td>0.69-1.33</td>
<td></td>
</tr>
<tr>
<td>Folate</td>
<td>0.68</td>
<td>0.50-0.93†</td>
<td>P ≤ .05</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>1.05</td>
<td>0.78-1.40</td>
<td></td>
</tr>
<tr>
<td>Folate</td>
<td>0.64</td>
<td>0.47-0.87‡</td>
<td>P ≤ .01</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>1.24</td>
<td>0.90-1.71</td>
<td></td>
</tr>
<tr>
<td>Folate</td>
<td>0.53</td>
<td>0.38-0.76§</td>
<td>P ≤ .001</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>1.05</td>
<td>0.78-1.41</td>
<td></td>
</tr>
<tr>
<td>Folate</td>
<td>0.62</td>
<td>0.45-0.86‡</td>
<td>P ≤ .01</td>
</tr>
<tr>
<td>β-carotene</td>
<td>0.79</td>
<td>0.58-1.06</td>
<td></td>
</tr>
<tr>
<td>Folate</td>
<td>0.68</td>
<td>0.51-0.89‡</td>
<td>P ≤ .01</td>
</tr>
</tbody>
</table>

* Model included folate and specified nutrient, age, sex, total energy intake, BMI, alcohol consumption, family history, saturated fat and dietary fiber intake, indications of endoscopy, and prior history of endoscopy.

Giovannucci, *JNCI*, 1993
Folate Intake and Adenoma Studies

- Giovannucci, 1993 (M)
- Giovannucci, 1993 (F)
- Benito, 1993
- Bird, 1995 (M & F, diet)
  (M, RBC)
- Bouton-Rualt, 1996 (F)
- Tseng, 1996 (F)
  (M)

OR for high vs. low category for folate

- 0.27
- 0.35
- 0.50
- 0.53
- 0.63
- 0.66
- 0.76
- 0.84

• significant
• non-significant
Cohort Studies of Folate & Colon Cancer

Giovannucci, 1995 (M)
Glynn, 1996 (M)**
Giovannucci, 1998 (F)
Kato, 1999 (F)
Su, 2001 (M) (F)

RR for high vs. low category for folate

**plasma-based; other studies dietary based
High Alcohol / Low Folate vs. Low Alcohol / High Folate

**Relative Risk**

- Su, 2001 (M)
- Giovannucci, 2000 (F)
- Freudenheim, 1991 (M)
- Giovannucci, 1993 (adenoma)
- Giovannucci, 1995 (M)
- Glynn, 1996 (M)
- Baron, 1998 (adenoma)
- Kato, 1999 (F)
- Giovannucci, 2000 (F)
- Su, 2001 (M)

**Significance**
- Significant
- Non-significant
MTHFR
Methylene TH4 reductase
OR of Colorectal Cancer by MTHFR Genotype and Plasma Folate Status PHS

Ma et al., Cancer Res 1997

<table>
<thead>
<tr>
<th>MTHFR genotype</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ala/ala &amp; ala/val</td>
<td>1.5</td>
</tr>
<tr>
<td>val/val</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Ma et al., Cancer Res 1997
Age-adjusted OR of colorectal cancer by MTHFR genotype and alcohol intake

Ma et al., Cancer Res 1997
Multivariate OR of Colorectal Adenoma by MTHFR Genotype and Alcohol Intake

HPFS

P, interaction=0.09

Giovannucci, unpublished

MTHFR genotype

Odds Ratio

0.5
1
1.5
2
2.5
3
3.5
4
4.5
5

<5
5-30
>30

Alcohol Intake (g / day)
Summary: Epidemiologic Evidence Supporting a Role of Folate and Alcohol

- Adenoma studies; case-control and cohort studies of cancer
- Low folate status with high alcohol intake (an anti-folate) -> highest risk
- $677C \rightarrow T$ polymorphism of a key metabolic enzyme in MTHFR provide evidence on a role of folate in DNA synthesis and DNA methylation and tumor development
- Recent evidence suggests that vitamin B6 is also protective
Increased Cell Growth → Adenoma I → Adenoma II → Adenoma III → Cancer

- Smoking
- aspirin* (-)
- folate (-)
- alcohol
- vitamin D (-)
- calcium* (-)
- fiber*
- physical activity (-)
- body size
- Western diet
- insulin, IGF
- estrogens* (-)

*Results supported by randomized trial