Colorectal cancer prevention versus survival: Does the evidence agree?

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Harvard T.H. Chan School of Public Health
WCRF/AICR Risk Factors for CRC Risk

**Increases Risk**
- Body Fatness
- Red / Processed Meat
- Alcohol

**Decreases Risk**
- Physical Activity
- Fiber/Wholegrains
- Calcium
For colorectal cancer, the observational data for incidence are based on 600+ reports.

The observational data for survival are based on a handful of studies.
Risk Factors for CRC Prognosis
very tentative!

**Increases Risk**
- Body Fatness (?)
- Underweight
- High Glycemic Load
- High Fructose Diet
- Western Diet

**Decreases Risk**
- Physical Activity
- Coffee
- Omega-3 fatty acids
Compared to studies on CRC incidence, studies of survival are limited by:

- Much fewer data
- Conceptual issues
- Methodologic issues
Conceptual issues:

Primary tumor removed - post diagnostic effect must be on metastasis, not on primary tumor.

Pre-diagnostic diet can affect tumor subtype.

Methodologic issues:

Pre-diagnostic exposure is correlated with post-diagnostic exposure

Tumor present → reverse causation
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Tumor present $\rightarrow$ reverse causation
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<tr>
<th>Comparison</th>
<th>RR (95% CI)</th>
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<tr>
<td>Underweight vs Normal</td>
<td>1.33 (1.20-1.47)</td>
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<td>Overweight vs Normal</td>
<td>0.84 (0.67-0.97)</td>
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<tr>
<td>Obesity vs Normal</td>
<td>0.95 (0.80-1.30)</td>
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**Post Diagnostic Body Weight and CRC – Specific Mortality in CRC Patients (meta-analysis)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Time Window After Diagnosis</th>
<th>Disease Free Survival</th>
<th>Overall Survival</th>
</tr>
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<tbody>
<tr>
<td>Meyerhardt 2006</td>
<td>III</td>
<td>7.1 months Post chemo</td>
<td>.55 (0.33-0.91)</td>
<td>.37 (0.16-0.82)</td>
</tr>
<tr>
<td>Meyerhardt 2006</td>
<td>I-III (f)</td>
<td>22 months</td>
<td>.39 (.18-.82)</td>
<td>.43 (.25-.74)</td>
</tr>
<tr>
<td>Meyerhardt 2009</td>
<td>I-III (m)</td>
<td>15 months</td>
<td>.47 (.24-.92)</td>
<td>.59 (.41-.86)</td>
</tr>
<tr>
<td>Baade 2011</td>
<td>I-III</td>
<td>5 months</td>
<td>.88 (.68-1.15)</td>
<td>.75 (.60-.94)</td>
</tr>
<tr>
<td>Kuiper 2012</td>
<td>I-III (f)</td>
<td>1.5 years</td>
<td>.29 (.11-.77)</td>
<td>.41 (.21-.81)</td>
</tr>
<tr>
<td>Boyle 2013</td>
<td>I-IV</td>
<td>0</td>
<td>.91 (.58-1.42)</td>
<td>.66 (.44-.98)</td>
</tr>
<tr>
<td>Campbell 2013</td>
<td>I-III</td>
<td>1.4 years</td>
<td>.87 (.61-1.24)</td>
<td>.58 (.47-.71)</td>
</tr>
<tr>
<td>Arem 2014</td>
<td>I-III</td>
<td>4.2 years</td>
<td>.84 (.66-1.07)</td>
<td>.80 (.68-.95)</td>
</tr>
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</table>
“Reverse causation” -

Does low body weight worsen prognosis or does progressing tumor lower body weight (e.g. cachexia)?

Does physical activity improve prognosis or does a progressing tumor make it more difficult to be physically active?
Conceptual issues:

Primary tumor removed - post diagnostic effect must be on metastasis, not on primary tumor.

Pre-diagnostic diet can affect tumor subtype.

Methodologic issues:

Pre-diagnostic exposure is correlated with post-diagnostic exposure

Tumor present → reverse causation
<table>
<thead>
<tr>
<th>Pre-diagnostic</th>
<th>Post-diagnostic</th>
</tr>
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<tbody>
<tr>
<td>Diet, Exercise</td>
<td>Diet, Exercise</td>
</tr>
</tbody>
</table>

Observational; $r \sim 0.5 - 0.6$

RCT, $r \sim 0$

Diagnosis

Metastatic Seeding

Risk

Survivorship
## Pre-diagnostic Body Weight and CRC – Specific Mortality in CRC Patients (meta-analysis)

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<tr>
<th>Comparison</th>
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<tr>
<td>Underweight vs Normal</td>
<td>1.54 (0.99-2.40)</td>
</tr>
<tr>
<td>Overweight vs Normal</td>
<td>1.05 (0.96-1.14)</td>
</tr>
<tr>
<td>Obesity vs Normal</td>
<td>1.22 (1.003-1.35)</td>
</tr>
</tbody>
</table>
# Pre-diagnostic Physical Activity and CRC Survival

<table>
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<tr>
<th>Study</th>
<th>Stage</th>
<th>Time Window Before Diagnosis</th>
<th>Disease Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayden 2006</td>
<td>I-IV</td>
<td>5.3 years</td>
<td><strong>0.73</strong> (0.54-1.00)</td>
<td>0.77 (0.58-1.03)</td>
</tr>
<tr>
<td>Meyerhardt 2006</td>
<td>I-III (f)</td>
<td>6 months</td>
<td><strong>0.83</strong> (0.44-1.67)</td>
<td>0.95 (0.57-1.55)</td>
</tr>
<tr>
<td>Kuiper 2012</td>
<td>I-III (f)</td>
<td>5.6 years</td>
<td><strong>0.68</strong> (0.41-1.13)</td>
<td>0.63 (0.42-0.96)</td>
</tr>
<tr>
<td>Campbell 2013</td>
<td>I-III</td>
<td>6.8 years</td>
<td><strong>0.78</strong> (0.57-1.08)</td>
<td>0.72 (0.58-0.89)</td>
</tr>
<tr>
<td>Arem 2014</td>
<td>I-III</td>
<td>7.8 years</td>
<td><strong>0.53</strong> (0.27-1.03)</td>
<td>0.69 (0.49-0.98)</td>
</tr>
</tbody>
</table>
Correlation between pre- and post-diagnostic exposure

If we see an association between post-diagnostic exposure and survival, could this occur simply because post-diagnostic exposure is highly correlated with pre-diagnostic exposure?
Conceptual issues:

Primary tumor removed - post diagnostic effect must be on metastasis, not on primary tumor.

Pre-diagnostic diet can affect tumor subtype.

Methodologic issues:

Pre-diagnostic exposure is correlated with post-diagnostic exposure

Tumor present  →  reverse causation
Very Few Diet And Survival Cohorts

- American Cancer Society Cohort (CPS II)
- Nurses’ Health Study (NHS)
- Health Professionals Follow-Up Study (HPFS)
- CALBG 89803 (RCT stage 3 Colon cancer-administered FFQ 6 mos after treatment)
Dietary Patterns

• **Western** and **prudent** pattern diets predictive of heart disease, diabetes, colorectal cancer

• **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

HR for CRC Recurrence or Death

Quintiles of Dietary Pattern

Western diet

Prudent diet

P, trend < 0.001

Dietary Patterns

- Western and prudent pattern diets predictive of heart disease, diabetes, colorectal cancer

- Prudent pattern: high intakes of vegetables, fruit, legumes, whole grains, fish, and poultry

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Pre-diagnosis Red and Processed Meat by Servings / Week

- 2315 local and regional CRC participating in CPS II

<table>
<thead>
<tr>
<th>Mean Intake (servings/week)</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5 (SD 1.0)</td>
<td>3.8 (SD 1.1)</td>
<td>6.0 (SD 1.3)</td>
<td>10.4 (SD 3.4)</td>
<td></td>
</tr>
<tr>
<td>All cause mortality</td>
<td>1.00</td>
<td>1.18 (0.98-1.43)</td>
<td>1.13 (0.92-1.37)</td>
<td>1.29 (1.05-1.59)</td>
<td>0.03</td>
</tr>
<tr>
<td>CRC mortality</td>
<td>1.00</td>
<td>1.35 (0.87-2.11)</td>
<td>1.28 (0.96-1.71)</td>
<td>1.09 (0.79-1.51)</td>
<td>0.54</td>
</tr>
<tr>
<td>CV Disease Mortality</td>
<td>1.00</td>
<td>1.14 (0.94-1.55)</td>
<td>0.99 (0.60-1.63)</td>
<td>1.63 (1.00-2.67)</td>
<td>0.08</td>
</tr>
</tbody>
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J Clin Oncol 31:2773-2782.
Post-diagnosis Red and Processed Meat by Servings / Week

- 1186 local and regional CRC participating in CPS II with post diagnosis assessment of diet

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
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<td>All cause mortality</td>
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<td>(0.89-1.55)</td>
<td>(0.84-1.52)</td>
<td>(0.68-1.30)</td>
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<td>(0.76-2.15)</td>
<td>(0.53-1.64)</td>
<td>(0.61-1.98)</td>
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<td>1.00</td>
<td>1.09</td>
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<td>0.42</td>
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<td></td>
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<td>(0.60-2.02)</td>
<td>(0.43-1.71)</td>
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J Clin Oncol 31:2773-2782.
Post-diagnostic Dietary Glycemic Load and CRC Survival

DCRC-free Survival Multivariable HR (95% CI)

Dietary Glycemic Load (Quintiles)

P trend <0.001

1 2 3 4 5
Glycemic Load in Colon Cancer Patients

Quintiles of Glycemic Load

Hazard Ratio for Cancer Recurrence or Death

Meyerhardt, J. et al JNCI 2012
Disease Free Survival
Multivariate HR (95% CI)

CRC Stage III (CALBG 89803)

P trend=0.03

Sugar Sweetened Beverage

<2/mo
2/mo-2/wk
3-6/wk
1-2/day
>2/day

M Fuchs PLoS One 2014
Multivariate HRs for CRC recurrence or death according to combinations of BMI, physical activity, and sugar-sweetened beverage intake.

BMI = body mass index in kg/m²; PA = physical activity in MET-hours per week; wk = week, d = day. Intermediate = BMI ≥ 25 kg/m² and PA ≥ 18 MET-hours per week or BMI < 25 kg/m² and PA < 18 MET-hours per week.

Fuchs MA PLoS One 2014
NHS/HPFS studies (AICR abstracts)

• Chen Yuan – Influence of a dietary insulin index on survival in CRC patients (#006)

• Emily Zoltick – Sugar sweetened beverage and sugar intakes and CRC survival (#008)

• NaNa Keum – A high insulinogenic diet and CRC survival by tumor molecular markers (#054)
CRC Stage III (CALBG 89803)

Disease Free Survival
Multivariable HP (95% CI)

P trend=0.002

Total Coffee (Cups/Day)

0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6
<1 1 2-3 ≥4

B Guercco J Clin Oncol 2015
Conceptual issues:

Primary tumor removed - post diagnostic effect must be on metastasis, not on primary tumor.

Pre-diagnostic diet can affect tumor subtype.

Methodologic issues:

Pre-diagnostic exposure is correlated with post-diagnostic exposure

Tumor present $\rightarrow$ reverse causation
Figure: Kaplan-Meier Curve Displaying Overall Survival of Colorectal Cancer by Stage Among Men 60–75 Years of Age Diagnosed in 1998–2000.
Diagnosis (Colectomy)

Risk (large intestine)

Metastatic Seeding

Survivorship (liver, other sites)
Normal Liver
Non-Alcoholic Fatty Liver Disease
Inflamed Fatty Liver Disease
Hepatic fibrosis increases incidence of liver metastasis from CRC.
Kondo Br J Cancer. 2016

Fatty liver decreases incidence of liver metastases from CRC.
Murono Int J Colorectal Dis. 2013
## Risk Factors for CRC Prognosis

**very tentative!**

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<tr>
<td>Underweight</td>
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Risk Factors for Fatty Liver Disease

**Increases Risk**
- Body Fatness
- Underweight *(No)*
- High Glycemic Load
- High Fructose Diet
- Western Diet

**Decreases Risk**
- Physical Activity
- Coffee
- Omega-3 fatty acids
Conceptual issues:

Primary tumor removed - post diagnostic effect must be on metastasis, not on primary tumor.

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Methodologic issues:

Pre-diagnostic exposure is correlated with post-diagnostic exposure

Tumor present → reverse causation
A Chan NEJM 2007
NHS, HPFS: Aspirin, COX-2, CRC Survival

Multivariable Adjusted HR

0 1 2 3 4 5

COX-2-positive Primary Cancer

COX-2-negative Primary Cancer

Post-diagnostic Regular Aspirin Use
Pre-diagnostic Aspirin and CRC

Aspirin Use

Cox-2+ tumors prevented
Aspirin use prevents occurrence of COX-2+ CRCs

CRCs that occur in aspirin users are less likely to be COX-2+

Post-diagnostic aspirin use is effective against COX-2+

Therefore, is post-diagnostic aspirin use less effective in CRC patients who had use aspirin prior to diagnosis?
NHS, HPFS: Aspirin and CRC Survival

- Aspirin Non-Users
  - Pre-diagnostic
- Aspirin Users
  - Pre-diagnostic
  - Post-diagnostic Regular Aspirin Use

Multivariable Adjusted HR

0.2

0.4

0.6

0.8

1.0

1.2

1.4

1.6
HR for post-diagnosis change in N-3 fatty acid intake and CRC mortality in HPFS

![Graph showing the relationship between change in N-3 fatty acid intake and CRC mortality. The x-axis represents the change in intake (g/day), and the y-axis represents multivariate-adjusted HR. The trend is significant with a P_trend < 0.001.](Song M et al. Gut-BMJ, 2016)
Conclusions

Excess adiposity is likely to worsen prognosis, but this is obscured by disease-induced weight loss.

Physical activity is likely to be beneficial, but reverse causation is difficult to exclude.

A high glycemic diet and added sugar, especially when combined with a sedentary lifestyle worsens prognosis. These could be acting in the liver.

The effect of an exposure on prognosis can be modified the presence or absence of the same exposure in the pre-diagnostic period.
Risk Factors for CRC Prognosis
very tentative!

Increases Risk
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