The Microbiome and Cancer

Johanna W. Lampe, PhD, RD
Meredith A.J. Hullar, PhD
Division of Public Health Sciences
Fred Hutchinson Cancer Research Center, Seattle WA
Class of 100+ diseases in which a group of cells display:
- uncontrolled growth
- invasion that intrudes upon and destroys adjacent tissues
- sometimes metastasis, or spreading to other locations in the body via lymph or blood

Starts from a single cell that has lost control of its normal growth and replication processes due to changes in genetic information in the cell.

Effect of genetic alterations or damage accumulated within cells over time.
Exposures and Cellular Processes Linked to Cancer

Involvement of Microbial Processes

Exposures and microbial processes

- DNA repair
- Carcinogen metabolism
- Hormonal regulation
- Inflammation
- Immune function
- Proliferation
- Apoptosis
- Differentiation

Adapted from WCRF/AICR 2007 Expert Report
Microbes and Cancer

Microbes as infectious agents
- Account for ~20% of cancers worldwide
- Cervical, liver and gastric cancers
- Direct effects

Microbes as modifiers of physiology

Microbes as modifiers of exposures
- Metabolizing carcinogens, chemopreventive agents
- Affecting energetics
*Helicobacter pylori* Infection and Cancer

- Causal factor in gastric adenocarcinoma.
- Chronic colonization causes inflammation and ulceration.
- Only a fraction of colonized individuals develop gastric cancer.
**Prevalence of *Helicobacter pylori* Associated with Lower Risk of Esophageal Adenocarcinoma**


<table>
<thead>
<tr>
<th>Study name</th>
<th>Group by histology</th>
<th>P value</th>
<th>Odds Ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chow 1998</td>
<td>Adenocarcinoma</td>
<td>0.086</td>
<td>0.333</td>
</tr>
<tr>
<td>Vicary 1998</td>
<td>Adenocarcinoma</td>
<td>0.084</td>
<td>0.333</td>
</tr>
<tr>
<td>Lord 2000</td>
<td>Adenocarcinoma</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Vieth 2000</td>
<td>Adenocarcinoma</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Weston 2000</td>
<td>Adenocarcinoma</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Siman 2001</td>
<td>Adenocarcinoma</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>El-Omar 2003</td>
<td>Squamous cell carcinoma</td>
<td>0.088</td>
<td>0.333</td>
</tr>
<tr>
<td>Wu AH 2003</td>
<td>Squamous cell carcinoma</td>
<td>0.207</td>
<td>0.333</td>
</tr>
<tr>
<td>Ye 2004</td>
<td>Squamous cell carcinoma</td>
<td>0.572</td>
<td>0.333</td>
</tr>
<tr>
<td>de Meehen 2005</td>
<td>Barrett esophagus</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Pooled data</td>
<td>Barrett esophagus</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Newton 1997</td>
<td>Barrett esophagus</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Vicary 1998</td>
<td>Barrett esophagus</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Lord 2000</td>
<td>Barrett esophagus</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Vieth 2000</td>
<td>Barrett esophagus</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Weston 2000</td>
<td>Barrett esophagus</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Rugge 2000</td>
<td>Barrett esophagus</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Fernandez 2005</td>
<td>Barrett esophagus</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Pooled data</td>
<td>Adenocarcinoma</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Random effects model

Less disease

More disease
Streptococcus bovis and Colon Cancer

- Minor gut colonizer in 5-16% of adults
- Cause of septicemia and endocarditis
- Strong association between S. bovis bacteremia and colorectal cancer, but debate over temporality
- Experimentally, S. bovis has been shown to:
  - Promote inflammation
  - Upregulate COX-2 production \textit{in vitro}
  - Be carcinogenic in a rat model of colon tumorigenesis

Mechanisms by Which the Microbiome May Directly Influence Cancer Risk

- Reduce competition by less-desirable bacteria
- Interact with mucosal-associated immune system
- Regulate tight junctions and mucosal barrier function in epithelium
- Influence signal transduction pathways relevant to cell proliferation and apoptosis

- The gut microbiota:
  - The largest collection of microbes in the human body: ~10-100 trillion organisms
  - 100s of species in 6 main phyla
Bacterial Diversity in the Human Gut

>90% are Firmicutes & Bacteroidetes

Only 6 major phyla

The Gut Microbiome and Cancer Risk in Humans

Differences in community structure may be a biomarker of adverse health outcomes

- Diabetes
  - Larsen et al., 2010, *PlosOne*, 2:e9085
- IBD
  - Marchesi et al., 2007, *J Proteome Res*, 6:546
- Obesity

Studies show differences in the human gut community associated with colorectal cancer and adenomas

- Sobhani et al., 2011, *PlosOne*, 6:e16393

No prospective studies in humans that directly link changes in the gut microbiome to onset of cancer
WE ARE WHAT WE EAT: Mammals and Their Gut Microbes Cluster by Diet

Ley, RE et al., Science, 2008, 320:1647
Relationship of Diet and the Gut Microbiome to Cancer Risk

Dietary constituents - Fuel availability

Energy imbalance

Gut bacteria

Normal Cells
- Proliferation
- Inflammation
- DNA damage
- Failed apoptosis

Tumor
Gut Microbial Metabolism -- Designed to make the most of the situation

- Fermentation
- Nitrate reduction
- Sulfate reduction
- Hydrolysis
  - glycosides
  - glucuronide conjugates
Gut Bacterial Metabolism Modify Diet † Disease Relationships

Carbohydrates  Phytochemicals  Fat  Protein

Diet

Gut Microbiota

Colonic Epithelium

Isothiocyanates are derived from glucosinolates in cruciferous vegetables.
Inverse association between urinary ITC excretion and aflatoxin-DNA adducts – Interindividual variation in ITC bioavailability

- N=200, Qidong, China
- Randomized, parallel arm, 2-week trial
- 400 umol glucosinolate/d vs. placebo
- Urinary ITC recovery 1-45% of 400 µmol glucosinolate dose

Gut Microbial Metabolism
Modifying Effects of Diet on Cancer Risk

Microbial Nitrate Reductase

Nitrate $\rightarrow$ Nitrite
$\text{NO}_3^-$ $\rightarrow$ $\text{NO}_2^-$

$N$-nitroso compounds
nitrosamines
nitrosamides
nitrosoguanidine

$\rightarrow$ DNA adducts
$\rightarrow$ DNA damage
Microbial Community Affects Exposure to Dietary Metabolites

17 obese men, randomized cross-over design

4 weeks of weight-reduction diets:
  - high-protein; med carb
  - high-protein; low-carb

HPLC diet resulted in decrease in fecal cancer-protective metabolites and increased concentrations of hazardous metabolites.

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>HPMC</th>
<th>HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, %</td>
<td>13</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Fat, %</td>
<td>37</td>
<td>37</td>
<td>66</td>
</tr>
<tr>
<td>Carb, %</td>
<td>50</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>NSP, g</td>
<td>22</td>
<td>9</td>
<td>13</td>
</tr>
</tbody>
</table>

a,b,c significantly different p<0.001
Diet Shifts Microbial Community and Affects Exposure to Dietary Metabolites

-shift in gut microbial community and metabolites with diet
-HPLC diet also:
- decreased proportion of butyrate in fecal SCFAs
- reduced Roseburia/Eubacterium rectale group of bacteria.
- reduced concentrations of fiber-derived, phenolic acids.

Distribution of Metabolic Pathways in the Gut Microbiome

Comparison of Taxonomic and Functional Variations in the Human Gut Microbiome

18 fecal microbiomes from MZ twins and their mothers
Suggests a core microbiome at the level of metabolic function with high redundancy

The Microbiome and Cancer: Which came first, the chicken or the egg?

Challenges and Gaps

STUDY DESIGN ISSUES
- Lack of prospective studies
- Small sample sizes
- Lack of well-characterized human populations (e.g., diet and other exposures)
- Need for standardized collection, storage, testing procedures

THE MEASUREMENT FOCUS: An Integration of Omics
Beyond the microbiome......
- Metagenome
- Metaproteome
- Metabolome

- Requires strong collaborative efforts among microbial ecologists, computational biologists, epidemiologists, nutritionists, toxicologists, etc.
Cancer risk is combinatorial, modified by bacterial factors, host responses, and host-microbe interactions.

The microbiome needs to be considered in the context of host exposures in order to understand its impact on cancer risk and to design prevention strategies.

Diet influences gut microbial community.

Gut microbial metabolism modifies dietary components, producing both beneficial and harmful compounds.

Differences in gut microbial communities are manifest in metabolic phenotype differences.