Gut Microbial Metabolism of Plant-Food Bioactives: Impact on Dietary Exposure and Cancer Risk

Johanna W. Lampe, PhD, RD
Cancer Prevention Program, Division of Public Health Sciences
Fred Hutchinson Cancer Research Center
and Dept of Epidemiology, University of Washington, Seattle, USA
Microbes and Cancer

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

- Microbes as modifiers of exposures
  - Metabolizing carcinogens, chemopreventive agents
  - Affecting energetics
  - Indirect metabolic effects
How are biomarkers of cancer susceptibility in humans modulated by constituents of diet?

What differences among individuals influence response to diet?

GENOTYPE-DIET INTERACTIONS

HOST MICROBIOME-DIET INTERACTIONS
Substantial Component of Microbial Genome Dedicated to Xenobiotic Metabolism

Xenobiotics
- phytochemicals
- pyrolysis products
- drugs

Dietary Bioactive Phytochemicals

Phenolics
- Phenolic acids
- Stilbenes
- Curcuminoids
- Chalcones
- Lignans
- Flavonoids
- Isoflavones

Terpenoids
- Phenolic terpenes
- Carotenoids
- Saponins
- Phytosterols

Organosulfurs
- Thiosulfinates

N-containing compounds
- Glucosinolates
- Indoles

Adapted from Scalbert et al, J. Agric. Food Chem. 2011, 59, 4331–48
Cruciferous Vegetables and Cancer

- Cruciferous vegetable intake shows most consistent association with lower risk of certain cancers:
  - lung, colorectal, breast, prostate, pancreatic cancer

- Isothiocyanates and indoles:
  - Are chemopreventive in animal models
  - Decrease inflammation and oxidative stress
  - Induce cell differentiation and apoptosis
  - Improve carcinogen metabolizing capacity

SL Navarro et al, Food Funct, 2:579-87, 2011
Isothiocyanates from Glucosinolates in Cruciferous Vegetables

R-C
N-O-SO₃⁻
S-D-Glucose
Glucosinolate

Glucose

\[ \overset{\text{Thioglucosidase (Myrosinase)}}{\text{SH}} \]

R-C
N-O-SO₃⁻

HSO₄⁻

R-N=C=S
Isothiocyanate

Yuesheng Zhang, Roswell Park Cancer Institute, Buffalo, NY
Availability of Isothiocyanates from Broccoli Sprouts

% of dose

Urinary ITC Excretion Highly Variable Across Cruciferous Vegetable Doses

\[ R = 0.66 \]

7 g crucifer/kg BW  
14 g crucifer/kg BW  
7 g crucifer + 4 g apiaceous /kg BW

**Fecal Bacterial Degradation of Glucosinolates In Vitro Differs by ITC-Excreter Status**

- Low- and high-ITC excreters identified with broccoli dose
- Fecal bacteria incubated with glucoraphanin for 48 h

Urine ITC recovery ranged from 1-28%

Glucoraphanin degradation higher in high-ITC excreters

% ITC in urine after 200 g broccoli

Prospective case-control studies
- Support for reduced risk of colon and breast cancer
- Less clear for prostate cancer

Experimental human studies
- Changes in estrogen metabolite profiles in women
- Decrease in inflammation biomarkers

Experimental animal studies
- Flax lignans reduce colon, lung and mammary tumorigenesis

Mechanisms of action
- Anti-inflammatory
- Anti-proliferative
- Pro-apoptotic

Reviewed by Yoder, Lampe et al, in *Diet-Microbe Interactions in the Gut*, 2015
Gut Bacterial Metabolism of Plant Lignans to Enterolignans, Enterodiol and Enterolactone

- Hydrolysis of glucosides
- Demethylation
- Dehydroxylation
Large interindividual differences in enterodiol and enterlactone pharmacokinetics with dose of secoisolariciresinol diglycoside

Kuijsten et al, J Nutr, 2005
Is There a Unique Gut Microbial Community Structure Associated with Lignan Metabolism?
Gut Microbial Community and Lignan Excretion in Premenopausal Women

- 107 women, 40-45 y
- Participants clustered by dominant bacterial genera (enterotypes).
- No relationship between enterotypes and lignan metabolite phenotypes.
- Gut microbial diversity higher with higher ENL excretion.

Gut Microbiome Associated with Urinary Enterolactone (ENL) Excretion

- GMC composition is significantly different between high and low ENL excreters (MRPP, p<0.0005).
- Association remains significant with adjustment for fiber intake and adiposity.
- Low ENL clusters together

Phylogenetic Distribution of Microbiome in High-ENL Excreters

- Unique genera high ENL excreters
- Distributed across Phyla
Lignans, Gut Microbiome and Colonocyte Cell-Signaling Pathways In Vivo

- Randomized, controlled, crossover trial in healthy subjects:
  - Lignan capsules (50 mg secoisolariciresinol diglucoside)
  - Placebo capsules
- Measuring effects of lignan supplementation on:
  - colonic mucosal mRNA expression (stroma and epithelium)
  - gut microbiome structure
Summary

- Gut microbes modify a variety of dietary constituents to bioactive compounds not found in diet.
- Phytochemicals as consumed are not necessarily as experienced by the host.
- Usual approaches of characterizing diet in epidemiologic studies are unlikely to capture exposure accurately.
- Application of metabolite biomarkers and gut microbial characterization may better explain dietary exposures in relation to risk of cancer and other chronic diseases.