Can a High Fat, Low Fiber Diet Increase the Risk of Colon Cancer?

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Cape Town, 2 December 2015
The Power of Epidemiology

<table>
<thead>
<tr>
<th>Increase Risk</th>
<th>Decrease Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Red meat</em></td>
<td><em>Fiber</em></td>
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<tr>
<td>Animal fat</td>
<td>Vegetables</td>
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<tr>
<td><em>Processed</em> meats</td>
<td>Calcium</td>
</tr>
<tr>
<td>Obesity</td>
<td>Fish oils</td>
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<tr>
<td>Inactivity</td>
<td>Antioxidants, selenium</td>
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<tr>
<td>Alcohol</td>
<td>Folic acid</td>
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<tr>
<td>Cigarettes</td>
<td>Postmenopausal hormones</td>
</tr>
</tbody>
</table>

* Evidence “convincing” 2010 Continuous Update Report from the World Cancer Research Fund review and meta-analysis of 43 cohort or randomized controlled trials

Approximately 90% of GI cancers are due to differences in diet

*Doll & Peto J Natl Cancer Inst 1981*
Fiber

- Complex carbohydrate in diet from plant sources that escapes small bowel digestion and thus reaches the colon: food for the colonic microbiota

- First attributed to low colon cancer prevalence in Africans by Burkitt

- EPIC study showed decreased risk of colonic adenomas and colorectal cancer with fiber, estimated 40% risk reduction in populations with low dietary fiber that doubled their fiber intake (Bingham et al. Lancet 2003 361:1496)
After correction of the risk estimates with more detailed dietary data carried out on the sub-sample of EPIC participants, the study showed that an approximate doubling of fibre intake was associated with a 40% reduction in colorectal cancer incidence. Previous studies might have missed these effects because both the average and the range of fibre intake in the populations studied were much lower than those in EPIC participants — particularly of cereal fibre.
Red Meat & Fat

• Red Meat:
  – increase luminal carcinogens through heme, microbial metabolism of protein residues, and ‘braaing’ – heterocyclic amines

• Fat:
  – induces hepatic synthesis of bile acids; colonic microbes convert BA to $2^y$ BA which are carcinogenic
  – Taurine FA induce a blossom of *Bilophilia wadsworthia* which produce $H_2S$ which is genotoxic
  – Saturated fat has inflammatory actions mediated through prostanoid metabolism.
Fruit and Vegetables

• Suppress colon cancer due antioxidant and antineoplastic properties due to their contents of vitamins (vitamin C, folate), micronutrients (selenium, calcium), and bioactive phytochemical compounds, such as phenolics, generally categorized as phenolic acids, flavonoids, stilbenes, coumarins, and tannins
Colon Cancer is a Westernized Disease
- It takes 1 generation to change

Le Marchand. Journal of the National Cancer Institute Monographs No. 26, 1999
Westernization

- Westernization has been associated with dramatic increases in expected lifespan from less than 25 before the Industrial Revolution to over 80 years today.
- This change is too rapid to be attributed to genetic evolution.
- But it can to the remarkable ability of humans to adapt to their environment.
- Ability to avoid life-threatening events such as perinatal complications, acute infections, trauma and war.

Emergence of “westernized diseases”, which include colon cancer: present the most serious threat to public health in the USA today.
Food

- From what we know of the process of evolution, dietary needs of every organism are genetically determined, and some have argued that our health will be better maintained by the diet that first established *Homo Sapiens* in the Paleolithic Era in Africa, a period that lasted from about 2.5 million years ago to 11,000 years ago.

- Coprolite analysis from cave dwellers hundreds of thousands of years ago show evidence of high grain consumption.
The Western Diet

- Grilled or fried meat
- Fat
- Carbohydrate
- Alcohol
- Preservatives
- Fruit and vegies??
- Fiber???????????
Hypothesis

*It is not the Diet*

*It is the Microbiome-Metabolome*
MUCOSAL INFLAMMATION, CANCER RISK↑

FOOD

DIGESTION

AMINO ACIDS
GLUCOSE
FATTY ACIDS
VITAMINS

RESIDUES

HI MEAT/FAT
H₂S, NH₄, bile acids

FERMENTATION

H₂ → CH₄

HI FIBER
BUTYRATE
FOLATE
BIOTIN
polyphenols

MUCOSAL HEALTH
Integration of the enzymes of bacterial groups identified by the Human Intestinal Tract Chip (HITChip), host metabolic enzymes, and fecal and urinary metabolites by $^1$H NMR (O’Keefe et al 2015)
Microbial Products: the “Good” and the “Bad”

- Short chain fatty acids: acetate, propionate, butyrate
- Hydrogen, methane, hydrogen sulfide
- Secondary bile acids
- Vitamins
- Polyphenols
- Toxins, inflammatory agents
- Anti-inflammatory substances

So final risk is determined by BALANCE
Saccharolytic Fermentation

$$59 \text{C}_6\text{H}_{12}\text{O}_6 + 38 \text{H}_2\text{O} \rightarrow 60 \text{acetate} + 22 \text{propionate} + 18 \text{butyrate} + 96 \text{CO}_2 + 256 \text{H}^+$$
The Remarkable Actions of Enhanced Butyrogenesis

**Genomic instability and epigenetic regulation**
- HDAC inhibition
- p53-dependent and p53-independent mechanisms
- Regulation of transcription factor activity (e.g., Sp1, Sp3)
- p21 expression
- Regulation of cyclins and cyclin-dependent kinases
- miRNA regulation

**Apoptosis and cell cycle regulation**

**Inflammation and immune response**
- Activation of GPR43 and GPR109A
- Pro-inflammatory cytokines
- Reduced COX2 expression
- Reduced NF-κB expression

**Cellular metabolism**
- HIF-1α downregulation
- Decreased angiogenesis
- Decreased glycolysis
- Decreased c-myc transcription

**Regulated expression of nutrient transporters and metabolic enzymes**

**MUCOSAL DEFENCE**
- Barrier function
- Mucin synthesis
- Trefoil factors
- HSP
- Antimicrobial peptides
- Transglutamase activity

**ANTI-CARCINOGEN**

**CANCER RISK**

*Fig. 2. Summary of the anti-tumorigenic effects of butyrate. HDAC, histone deacetlyase; miRNA, micro-RNA; GPR43, G-protein coupled receptor 43; GPR109A, G-protein coupled receptor 109A; ROS, reactive oxygen species; COX2, cyclooxygenase-2; HIF-1α, hypoxia inducible factor.*
“Gene-Regulating Chemoprevention”

Current studies and clinical trials strongly suggest that HDAC inhibitors such as trichostatin A and sub-eroylanilide hydroxamic acid, which like butyrate, induce p21Waf1/Cip1 expression, are effective in arresting cancer cell proliferation and lead to differentiation (as in acute promelocytic anemia) or apoptosis.
Utilized gnotobiotic mouse models colonized with wild-type or mutant strains of a butyrate-producing bacterium to demonstrate that fiber does have a potent tumor-suppressive effect but in a microbiota- and butyrate-dependent manner.
• This study examined whether a HRM diet altered miRNA expression in rectal mucosa tissue of healthy volunteers, and if supplementation with butyrylated resistant starch (HRM+HAMSB) modified this response.
• In a randomized cross-over design, 23 volunteers undertook four 4-week dietary interventions; an HRM diet (300 g/day lean red meat) and an HRM+HAMSB diet (HRM with 40 g/day butyrylated high amylose maize starch), preceded by an entry diet and separated by a washout.
miR17–92, miR16, and miR21 levels in rectal biopsies from participants in the HRM and resistant starch trial. Rectal biopsies collected at the end of each 4-week diet (, P < 0.05; , P < 0.01). Expression measured by real-time RT-. A, miR17–92 miRNA levels shown for each diet. B, summary of miR17–92 levels for the intervention diets, presented as percent change from entry diet. C, miR16 and miR21 levels shown for each diet. The mean SEM of the 23 participants is shown for each diet. Entry, entry diet; HRM, red meat diet; HRM?HAMSB, red meat and resistant starch diet.
Fruit and Vegetables

DIETARY POLYPHENOLS

Polyphenol metabolites produced by gut microbiota

Modulation of enzymes (up-regulation or down-regulation)

Anti-inflammatory effects (inhibition of Cox-2, NFkB, AP-1, TNFa, IL-6, VEGF)

↓ Cell proliferation  ↑ Apoptosis

↓ Carcinogenesis

The Synthesis of Vitamins by the Colonic Microbiota

O’Keefe et al J Nutr 2009

- Folate
- Biotin
- Thiamin
- B12

Dietary and Colonic Evacuates

Units: Folate, Biotin, and thiamin: mg/d (mg), B12: ug/d (ug)
Addition of 0.2% deoxycholic acid for 8–10 months to the diet of 18 wild-type mice induced colonic tumors in 17, and cancer in 10. Addition of the antioxidant chlorogenic acid at 0.007% to the DOC-supplemented diet significantly reduced tumor formation.
Figure 2. Dissimilatory metabolism of $N$-containing substrates in the large gut, and the physiologic significance of the end products of amino acid fermentation.
African-African American Studies

- Africans rarely get colon polyps or cancer $\leq 5:100,000$

- African Americans have the highest prevalence of colon cancer in the USA: $>65:100,000$

Protocol

• A series of studies on groups of 12-20 normal healthy subjects from each population, aged 50-65

• Compared differences in:
  – Diet
  – Colonoscopy
  – Fecal and colonic microbiota
  – Fecal and colonic microbial metabolites
  – Mucosal inflammation (CD3+, CD68+) and proliferation (Ki67) as biomarkers of cancer risk
Colonoscopy Findings

African Americans characterized by polyps (9/20) and diverticulae (14/20)

African colons were characterized by lymphocytic colitis (7/20) and parasites
Epithelial Proliferation as a Biomarker of Colon Cancer Risk

O’Keefe et al. Am J Gastroenterology 1999
Diet, microbiota, and microbial metabolites in colon cancer risk in rural Africans and African Americans\textsuperscript{1–4}

Junhui Ou, Franck Carbonero, Erwin G Zoetendal, James P DeLany, Mei Wang, Keith Newton, H Rex Gaskins, and Stephen JD O’Keefe

African Americans: Enterotype I
\textit{Bacteroides} dominant
\textit{Alistipes, Syntrophococcus, Streptococcus, Collinsella}

Zulu Africans: Enterotype II \textit{Prevotella} dominant
\textit{Dialister, Oscilispira, Succinivibrio, Xylanibacter}
Diet, microbiota, and microbial metabolites in colon cancer risk in rural Africans and African Americans$^{1-4}$


Am J Clin Nutr 2013:
Targeted Analysis

• Africans had higher levels of fecal and colonic microbial butyrate producers (qPCR) and butyrate levels (GC)

• African Americans had higher levels of secondary bile acid synthesizing bacteria (qPCR) and secondary bile acids (LC-MS)
But there are other environmental differences than might provide the explanation

e.g.
• Food storage, preservation, and preparation
• Sanitation
• Housing
• Electricity
• Transport
• Physical activity
Is it the Diet?

African-American Diet Exchange
ARTICLE
Received 23 May 2014 | Accepted 20 Jan 2015 | Published 28 Apr 2015

Fat, fibre and cancer risk in African Americans and rural Africans

Stephen J.D. O’Keefe¹, Jia V. Li², Leo Lahti³,⁴, Junhai Ou¹, Franck Carbonero⁵,⁶, Khaled Mohammed¹,
Joram M. Posma², James Kinross², Elaine Wahl¹, Elizabeth Ruder⁶, Kishore Vipperla¹, Vasudevan Naidoo⁷,
Lungile Mtshali⁷, Sebastian Tims³, Philippe G.B. Puylaert³, James DeLany⁸, Alyssa Krasinskas⁹,
Ann C. Benefiel⁵, Hatem O. Kaseb¹, Keith Newton⁷, Jeremy K. Nicholson², Willem M. de Vos³,⁴,¹⁰,
H. Rex Gaskins⁵ & Erwin G. Zoetendal³
The Dietary Switch

<table>
<thead>
<tr>
<th></th>
<th>Fat</th>
<th>Fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native Africans g/d</td>
<td>134</td>
<td>7</td>
</tr>
<tr>
<td>African Americans g/d</td>
<td>51</td>
<td>55</td>
</tr>
</tbody>
</table>
You can change your biomarkers of colon cancer risk within 2 weeks of change to an African or western diet.
Targeted Analysis: Butyrate

Functional Gene for Butyrate Production  Short Chain Fatty Acids

Graphs showing gene copies and metabolite concentrations before and after treatment.
Targeted Analysis: Bile Acids

Functional Gene for Secondary Bile Acid Synthesis

Secondary Bile Acids

![Graph showing changes in 7α-dehydroxybacteria copies/g feces and microgram/mole/g feces before and after treatment for African American and native African populations.](image-url)
Impressively, Africanization of the diet increased the quantities of butyrate in total colonic evacuates 2.5 times whilst westernization reduced quantities by half. On the other hand, Africanization reduced colonic secondary bile acids by 70%, and westernization increased them by 400%.
Butyrate-producers (BcoA) vs. Bilophila wadsworthia (tpA)

Methanogenic Archaea (mcrA) vs. Fusobacterium nucleatum

Sulfate-reducing bacteria (dsrA) vs. Acetogens (acs)
High fiber feeding in Americans was associated with a shift from correlations between Bacteroides and potential butyrate-producing groups (*Roseburia intestinalis* et rel. and *Clostridium symbiosum* et rel.) towards stronger co-occurrence patterns including Firmicutes that are typically associated with complex carbohydrate fermentation.

Africans had stronger co-occurrence patterns between the genus-level taxa when consuming their usual high fiber diet, which included butyrate producers *Eubacterium rectale* et rel. and *Clostridium symbiosum* et rel., and bacteria associated with complex carbohydrate utilization, for example *Oscillospira guillermondii* et rel. Reduction in fiber consumption led to opposite associations.
Global Analysis: Metabolome

OPLS-DA scores plots of $^1$H NMR fecal spectra obtained from African Americans (AA) and native Africans (NA) during the home environment period (HE) and post dietary intervention (DI). These demonstrate clear class separation between HE and DI time point in each population. Peaks pointing upwards represent higher concentrations of metabolites in DI compared with HE and vice versa. The color of the peaks represents the correlation ($r^2$) of the peaks with the classification (e.g. HE or DI).
Switch: Urine

<table>
<thead>
<tr>
<th>Urinary Metabolites</th>
<th>Chemical shift</th>
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<tbody>
<tr>
<td>N-acetyl S-methyl-L-cysteine sulfoxide</td>
<td>2.78</td>
</tr>
<tr>
<td>3-methylthiopyruvic acid sulfoxide</td>
<td>2.81</td>
</tr>
<tr>
<td>3-methylthioacetic acid sulfoxide</td>
<td>2.76</td>
</tr>
<tr>
<td>S-methyl-L-cysteine sulfoxide</td>
<td>2.84</td>
</tr>
<tr>
<td>p-cresyl sulfate</td>
<td>2.35</td>
</tr>
<tr>
<td>phenylacetylglutamine</td>
<td>2.27</td>
</tr>
<tr>
<td>3-hydroxyisovalerate</td>
<td>1.27</td>
</tr>
<tr>
<td>2-methylpropan-2-ol*</td>
<td>1.14</td>
</tr>
<tr>
<td>alanine</td>
<td>1.49</td>
</tr>
<tr>
<td>valine</td>
<td>0.99</td>
</tr>
<tr>
<td>isoleucine</td>
<td>0.93</td>
</tr>
<tr>
<td>carnitine*</td>
<td>3.23</td>
</tr>
<tr>
<td>O-acetylaminobutyric acid*</td>
<td>2.15</td>
</tr>
<tr>
<td>N6-acetyllysine*</td>
<td>1.99</td>
</tr>
<tr>
<td>citrate</td>
<td>2.53</td>
</tr>
<tr>
<td>creatine</td>
<td>3.94</td>
</tr>
<tr>
<td>creatinine</td>
<td>4.065</td>
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<tr>
<td>trigonelline</td>
<td>4.44</td>
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<tr>
<td>4-hydroxyhippurate</td>
<td>6.97</td>
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<tr>
<td>3-hydroxyxynandate</td>
<td>6.92</td>
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<tr>
<td>2-methylglutarate or methylsuccinate*</td>
<td>1.07</td>
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<tr>
<td>methylamine*</td>
<td>2.64</td>
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<tr>
<td>dimethylamine</td>
<td>2.73</td>
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<tr>
<td>trimethylamine-N-oxide</td>
<td>3.27</td>
</tr>
<tr>
<td>choline*</td>
<td>3.2</td>
</tr>
<tr>
<td>formate</td>
<td>8.46</td>
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**African American (AA) HE2 (N=8) vs. DI2 (N=7)**

<table>
<thead>
<tr>
<th></th>
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<th>p</th>
<th>q</th>
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</thead>
<tbody>
<tr>
<td>N-acetyl S-methyl-L-cysteine sulfoxide</td>
<td>0.87</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>3-methylthiopyruvic acid sulfoxide</td>
<td>0.9</td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>3-methylthioacetic acid sulfoxide</td>
<td>0.69</td>
<td>0.002</td>
<td>0.12</td>
</tr>
<tr>
<td>S-methyl-L-cysteine sulfoxide</td>
<td>0.71</td>
<td>0.003</td>
<td>0.13</td>
</tr>
<tr>
<td>p-cresyl sulfate</td>
<td>0.79</td>
<td>&lt;0.001</td>
<td>0.07</td>
</tr>
<tr>
<td>phenylacetylglutamine</td>
<td>0.57</td>
<td>0.03</td>
<td>0.33</td>
</tr>
<tr>
<td>3-hydroxyisovalerate</td>
<td>0.81</td>
<td>&lt;0.001</td>
<td>0.01</td>
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<tr>
<td>2-methylpropan-2-ol*</td>
<td>0.51</td>
<td>0.04</td>
<td>0.39</td>
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<tr>
<td>alanine</td>
<td>0.75</td>
<td>0.002</td>
<td>0.12</td>
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<tr>
<td>valine</td>
<td>0.63</td>
<td>0.01</td>
<td>0.25</td>
</tr>
<tr>
<td>isoleucine</td>
<td>0.61</td>
<td>0.001</td>
<td>0.01</td>
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<tr>
<td>carnitine</td>
<td>0.58</td>
<td>0.02</td>
<td>0.07</td>
</tr>
<tr>
<td>O-acetylaminobutyric acid*</td>
<td>0.71</td>
<td>&lt;0.001</td>
<td>0.004</td>
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</table>

**Native African (NA) HE2 (N=12) vs. DI2 (N=12)**

<table>
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<tr>
<th></th>
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<tbody>
<tr>
<td>N-acetyl S-methyl-L-cysteine sulfoxide</td>
<td>0.73</td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>3-methylthiopyruvic acid sulfoxide</td>
<td>0.77</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>3-methylthioacetic acid sulfoxide</td>
<td>0.83</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>S-methyl-L-cysteine sulfoxide</td>
<td>0.73</td>
<td>&lt;0.001</td>
<td>0.003</td>
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<tr>
<td>p-cresyl sulfate</td>
<td>0.77</td>
<td>&lt;0.001</td>
<td>0.001</td>
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<tr>
<td>phenylacetylglutamine</td>
<td>0.83</td>
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<tr>
<td>3-hydroxyisovalerate</td>
<td>0.51</td>
<td>0.006</td>
<td>0.04</td>
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<tr>
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<td>0.54</td>
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<td>alanine</td>
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<td>valine</td>
<td>0.63</td>
<td>0.002</td>
<td>0.01</td>
</tr>
<tr>
<td>isoleucine</td>
<td>0.62</td>
<td>0.002</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease

Zeneng Wang\textsuperscript{1,2}, Elizabeth Klipfell\textsuperscript{1,2}, Brian J. Bennett\textsuperscript{3}, Robert Koeth\textsuperscript{1}, Bruce S. Levison\textsuperscript{1,2}, Brandon DuGar\textsuperscript{1}, Ariel E. Feldstein\textsuperscript{1,2}, Earl B. Britt\textsuperscript{1,2}, Xiaoming Fu\textsuperscript{1,2}, Yoon-Mi Chung\textsuperscript{1,2}, Yuping Wu\textsuperscript{4}, Phil Schauer\textsuperscript{5}, Jonathan D. Smith\textsuperscript{1,6}, Hooman Allayee\textsuperscript{7}, W. H. Wilson Tang\textsuperscript{1,2,6}, Joseph A. DiDonato\textsuperscript{1,2}, Aldons J. Lusis\textsuperscript{3}, and Stanley L. Hazen\textsuperscript{1,2,6,8}
Integration of the enzymes of bacterial groups identified by the Human Intestinal Tract Chip (HITChip), host metabolic enzymes, and fecal and urinary metabolites by $^1$H NMR (Posma J, “MetaboIoNetworks’, Bioinformatics 2014)
butyrate was exclusively associated with microbial groups that are known to contain butyrate producers, well exemplified by *Roseburia intestinalis* et rel, *Eubacterium rectale* et rel, and *Clostridium symbiosum* et rel.
Summary

• The microbiota behaves as a community wherein intermicrobial interaction strives to produce a metabolic phenotype that supports colonic health and function.

• It has a genetically determined need for food residues derived from a *healthy balanced diet*.

• Provision of an *imbalance diet* leads to disturbance in structure and function, with unopposed production of metabolites that can induce inflammation and proliferation which increase risk of neoplasia.
Conclusions

- From epidemiological studies, we know that westernization of the diet leads to an increase in colon cancer within one generation.
- Our results show that a change in diet composition produces immediate effects on the metabolic phenotype of the colonic contents associated with reciprocal mucosal biomarkers of cancer risk.
- Our results suggest that current guidelines for the consumption of fiber rich foods are too low and increasing the fiber to >50g/d and reducing fat by half in African Americans, and indeed in all populations consuming a western diet, is likely to have an immediate effect on colon cancer risk.
- They warn against westernization of the African diet, where reduction in fiber intake will lead to suppression of butyrogenesis and a rapid progression of chronic colonic inflammation to cancer.
Age-Specific Cancer Incidence Rates, 1994-2008
Alaska Native and US White Populations

Colon and Rectum, Men and Women Combined

Rate per 100,000 population

Age
0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80+

AK Native
US White
Yup’ik Alaskans: high meat and fat, low fiber, extreme cancer risk
**Fecal Bile Acid Concentrations**

Split By: group
Error Bars: ± 1 Standard Error(s)

**Major Fecal Short Chain Fatty Acids**

Split By: groups
Error Bars: ± 1 Standard Error(s)

Acknowledgements

O’Keefe Lab:
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• Jim DeLany (Endocrine), Alyssa Krasinskas (Pathology), Priya Iyer (UPCI), Elaine Wahl (CTRC)

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• Jeremy Nicholson, James Kinross, Jia Li

deVoss Lab: Microbiology, Wageningen University, The Netherlands
• Erwin Zoetendal, Leo Lahti

Gaskins Lab: University of Illinois at Urbana: Genomic Biology
• Rex Gaskins, Gerardo Nava, Franck Carbonera

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deVoss: The Spinoza Award of the Netherlands Organization for Scientific Research, the ERC Advanced Grant 250172 (Microbes Inside) of the European Research Council and the Academy of Finland (Grant 141140).
We feel really guilty. The fat in beef & dairy is killing you people by the millions.

We think it would be best if we went our separate ways.