Fermented Foods: Intake and Implications for Cancer Risk

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DISCLOSURE

No Relevant Financial Relationship
Objectives

- Describe the various types of fermentation and fermented food products.
- Discuss the observational and experimental data available on intake of fermented foods and cancer risk.
  - Pickled fish
  - Pickled vegetables
  - Fermented milk and flowered-rind cheeses
Fermentation Facts

- Fermentation is oldest and still one of most economical methods of producing and preserving foods acceptable to man.
- Earliest evidence of production of fermented beverages dates from 8000 years ago in the Caucasus region.
- 5000 years ago, Chinese building Great Wall were eating fermented mixed vegetables.
- Asian cultures pioneered ways to produce meat-like flavors and textures from vegetable proteins.
- Much of economically developing world depends on various fermented foods as staples of their diets.
Why ferment?

- Preserve foods between time of harvest and consumption
- Render foods resistant to microbial spoilage and development of food toxins
- Make foods less likely to transfer pathogenic microorganisms
- Enrich diet through development of diverse flavors, aromas, and textures in food substrates
- Enrich biologically with protein, essential amino acids, essential fatty acids, and vitamins
- Reduce antinutrient content
- Decrease cooking time and fuel requirement

Types of Fermentation

Alcoholic \textit{(Saccharomyces)}
- Glucose: $\text{C}_6\text{H}_{12}\text{O}_6 \rightarrow 2 \text{C}_2\text{H}_5\text{OH} + 2 \text{CO}_2$

Acetic acid \textit{(Acetobacter)}
- Ethanol: $\text{C}_2\text{H}_5\text{OH} + \text{O}_2 \rightarrow \text{CH}_3\text{COOH} + \text{H}_2\text{O}$

Lactic Acid \textit{(Leuconostoc, Lactobacillus, Streptococcus)}
- Glucose: $\text{C}_6\text{H}_{12}\text{O}_6 \rightarrow 2 \text{CH}_3\text{CHOHCOOH}$
- Lactose: $\text{C}_{12}\text{H}_{22}\text{O}_{11} + \text{H}_2\text{O} \rightarrow 4 \text{CH}_3\text{CHOHCOOH}$

Heterolactic
- Glucose: $\text{C}_6\text{H}_{12}\text{O}_6 \rightarrow \text{CH}_3\text{CHOHCOOH} + \text{C}_2\text{H}_5\text{OH} + \text{CO}_2$

Alkaline \textit{(Bacillus subtilis)}
- Proteins $\rightarrow$ peptides + amino acids + NH$_3$
What fermented foods do we eat?

- Legumes
- Grains
- Vegetables
- Fruit
- Milk
- Fish
- Meat

North America
- Sauerkraut
- Relishes
- Sourdough breads
- Cultured milk
- Mikyuk (Alaska)

Central & South America
- Curdito
- Chocolate

Africa & Mid-East
- Grain gruels
- Injera (Ethopia)
- Kumis
- Kefir

SE Asia
- Tempeh (Indonesia)
- Idli (India)
- Fish sauces

Western Europe & Russia
- Sauerkraut
- Sourdough breads
- Salami
- Cultured milk

Japan, Korea, China
- Kimchi
- Natto
- Soy sauce
- Fish
- Fish sauces

Pickling (fermenting in water with or without salt)

- Preserving, soaking or storing in vinegar or brine.
- Salt added to:
  - Promote degradation of proteins
  - Retard the growth of undesirable, putrefactive microorganisms
  - Allow desirable, NaCl-tolerant (halotolerant), fermentative species such as lactic acid bacteria to grow
- Fermentation products generated:
  - May cause adverse effects:
    -- N-nitroso compounds (NOCs), mycotoxins
  - May offer health benefits:
    -- anti-microbials; viable bacteria in non-pasturized products
Salted Fish Intake and Nasopharyngeal Cancer: Dose-Response Analysis in Case-Control Studies

- High rates in Hong Kong, Singapore, southern China.
- Hypothesized interaction with EBV infection.
- Association appears stronger for early life exposure to salted fish (0-3 y)

AICR/WCRF: http://dietandcancerreport.org
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.
- High-salt diets may facilitate infection and increase virulence.

Beevers et al, J Hypertens, 22:1475, 2004
Areas at high-risk for GC, pickled foods eaten daily

Meta analysis of 60 studies of pickled foods and GC risk:
50 case-control
10 prospective

RESULTS
Overall:
- OR = 1.52 (95% CI 1.37–1.68)

Case-control:
- OR = 1.56 (95% CI 1.39–1.75)

Cohort:
- OR = 1.32 (95% CI 1.10–1.59)
Fresh and Pickled Vegetable Consumption and Gastric Cancer in Japan and Korea

- High *H. pylori* seroprevalence in Japan and Korea (~60%)

- Meta analysis of studies of vegetables and GC risk:
  - 8 fresh: OR = 0.62, 95% CI = 0.46–0.85
  - 14 pickled: OR = 1.28, 95% CI = 1.06–1.53

Endogenous $N$-Nitrosoo Compounds (ENOC) and Gastric Cancer in EPIC-EURGAST Study

- NDMA intake estimated and ENOC index calculated from heme iron intake and apparent total NOC formation.
- ENOC, but not NDMA, associated with non-cardia gastric cancer risk.
- Suggested interaction between NOC exposure and $H. pylori$ infection.

<table>
<thead>
<tr>
<th>$H. pylori$ Infection</th>
<th>Cases</th>
<th>Controls</th>
<th>ENOC (continuous) OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>111</td>
<td>717</td>
<td>1.82 (1.32-2.51)</td>
</tr>
<tr>
<td>NO</td>
<td>12</td>
<td>369</td>
<td>0.15 (0.01-4.06)</td>
</tr>
</tbody>
</table>

$P$ for interaction 0.09

Jakszyn et al, Carcinogenesis, 27:1497, 2006
Nitroso compound (ENNG) synergistically affects *H pylori*-induced gastric cancer in non-human primates

- Rhesus monkeys treated with ENNG, HP, or ENNG + HP
- *H pylori* infection and ENNG synergistically induce neoplastic transformation of gastric epithelial cells; each factor alone did not.
- Genes showed statistically significant treatment differences in gastric biopsies taken at 5 y.

Fermented Milk Products

- Nearly every civilization and country has fermented milks: cow, sheep, goat, camel, water buffalo, reindeer, mare.
- Fresh milk ferments naturally, which lowers pH and preserves.
- Lactose fermented to lactic acid
- Final products are determined by conditions during fermentation.
- Yogurt, kefir, kumis (mare milk), shubat (camel milk), quark, piimä, filmjölk, crème fraîche, smetana, skyr, some cheeses.
## Milk, Dairy Products, and Risk of Cancer: Evidence from Human Population Studies

### Table: Milk, Dairy Products, and Cancer Risk

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cancer Site</th>
<th>Exposure</th>
<th>Cancer Site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DECREASED RISK</strong></td>
<td></td>
<td><strong>INCREASED RISK</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Convincing</strong></td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td>Milk</td>
<td>Colorectum</td>
<td>Diets high in calcium</td>
</tr>
<tr>
<td><strong>Limited -- suggestive</strong></td>
<td>Milk</td>
<td>Bladder</td>
<td>Milk and dairy products, Cheese</td>
</tr>
</tbody>
</table>

AICR/WCRF: [http://dietandcancerreport.org](http://dietandcancerreport.org)
Dairy Products and Bladder Cancer Risk in a Swedish Cohort

- Prospective cohort study of 82,022 Swedish men and women.
- Completed 96-item food frequency questionnaire in 1997.
- 9.4 y of follow-up: 485 developed bladder cancer.
- No effect of total dairy, milk, and cheese, but 38% reduction in risk between no intake and highest quartile of cultured milk products.

Fermented Milk Products and Bladder Cancer in Dutch Cohort

- Prospective cohort study of 120,852 men and women in the Netherlands Cohort Study on Diet and Cancer.
- Completed 150-item food frequency questionnaire in 1986.
- 16.3 y of follow-up: 1549 developed bladder cancer.
- No effect of total dairy, but men and women in 2nd quintile of cultured milk products had 29% lower risk of bladder cancer.

Models adjusted for age, smoking status, number of cigarettes smoked, smoking duration, and intakes of vegetables, fruits, meat, beverages, energy, and fat.

Cultured Dairy Products as Modifiers of the Gut Microbiome and Gut Physiology

- Source of probiotics, mostly *Lactobacillus* and *Bifidobacterium*
- Probiotic-supplemented yogurt in mice and humans:
  -- did not appreciably alter the composition of the gut microbiota
  -- induced transcriptional and metabolic changes reflecting increases in carbohydrate metabolism

Effect of Camembert on Gut Microbiome in Rodents

- Flowered-rind soft cheeses contain live bacteria.
- Camembert microbes can survive intestinal transit.
- Camembert feeding did not modify gut bacterial populations.

- Had a beneficial influence on intestinal metabolism
  - Decrease in azoreductase activity and NH3 concentration
  - Increase in mucolytic activities
  - Increase proportion of ursodeoxycholic resulting from chenodeoxycholic epimerisation
  - Increase β-galactosidases
  - Decrease azoreductases and nitrate reductases

Fermented Foods and Cancer: SUMMARY

- Fermented foods as a group include a variety of foods.
- They are not consumed in isolation and traditional cuisines high in some types of fermented foods also include other foods that may be considered healthy or less healthy.
- Mechanistic studies have identified components of fermented foods that influence risk of some cancers.
  - $N$-nitrosocompounds in pickled vegetables and fish
  - Interactions between diet and microbial infections may increase risk
- More mechanistic studies are needed to follow up on epidemiologic findings.
  - Identify ways to minimize risk and increase beneficial effects
Thank you for your attention