Nutrition and Cancer Prevention: What Do We Know? What Can You Do?

Stephen D. Hursting, PhD, MPH

Professor, Nutrition Research Institute, Department of Nutrition and the Lineberger Comprehensive Cancer Center
University of North Carolina
Today’s Presentation

• What is cancer?

• Cancer prevention: Diet recommendations (focus on phytochemicals, obesity prevention)

• Examples of nutrition and cancer prevention research at the NRI
What is Cancer?

• *Webster’s:*

A malignant tumor of potentially unlimited growth that expands locally by invasion and systemically by metastasis.

• *American Cancer Society:*

A group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death.
What is Cancer?

The final stage of a multi-step process

- Carcinogen
- Initiation: Initiators begin the process of changing the DNA in some of the cells.
- Promotion: Promoters enhance the development of abnormal cells.
- Tumor formation

Noncancerous (benign) tumor

Cancerous (malignant) tumor releases cells into the bloodstream (metastasis)
Magnitude of the Cancer Problem in the World (Men and women Combined: 2014 estimates)

• #1 cause of death worldwide--Over 8.3 million cancer deaths/year

• Over 14 million new cancer cases—forecast to rise to ~25 million new cases by 2030 unless new preventive strategies are developed

Global Cancer Report, IARC, 2014
Leading Causes of Death, All Races and Both Genders, U.S.  
(NCHS, CDC, U.S. Department of Health and Human Services, 2014)

Rank Order and Number of Deaths

<table>
<thead>
<tr>
<th>ALL CAUSES</th>
<th>2,465,932</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases of the heart</td>
<td>596,577 (24% of deaths)</td>
</tr>
<tr>
<td><strong>Malignant neoplasms (cancer)</strong></td>
<td>585,720 (23% of deaths)</td>
</tr>
<tr>
<td>Chronic lower respiratory disease</td>
<td>137,789</td>
</tr>
<tr>
<td>Cerebrovascular disease (stroke)</td>
<td>129,180</td>
</tr>
<tr>
<td>Unintentional injuries (accidents)</td>
<td>118,043</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>83,308</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>68,905</td>
</tr>
<tr>
<td>Nephritis, nephrotic syndrome, and nephrosis</td>
<td>50,472</td>
</tr>
<tr>
<td>Pneumonia and influenza</td>
<td>50,003</td>
</tr>
<tr>
<td>Suicide</td>
<td>37,793</td>
</tr>
</tbody>
</table>

• *Lifetime risk of dying from cancer: 1 in 4*
1940’s Advertisement from the United Kingdom
Estimated Cancer Deaths in the US in 2014

<table>
<thead>
<tr>
<th>Cause</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>310,010</td>
<td>275,710</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
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<tr>
<td>Colon &amp; rectum</td>
<td></td>
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<tr>
<td>Pancreas</td>
<td></td>
<td></td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td></td>
<td></td>
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<tr>
<td>Leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td></td>
<td></td>
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<tr>
<td>All other sites</td>
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</tr>
</tbody>
</table>

Men 26%  Women 26%
Lung & bronchus  15%
Breast  9%
Colon & rectum  7%
Pancreas  5%
Ovary  4%
Leukemia  3%
Uterine corpus  3%
Non-Hodgkin lymphoma  3%
Liver & intrahepatic bile duct  3%
Brain & other nervous system  2%
All other sites  23%

Source: American Cancer Society, 2014.
Death Rates for All Cancers By Sex, 1975-2008

Source: American Cancer Society, 2014.
### 5-Year Survival Rates for Major Cancers in US

<table>
<thead>
<tr>
<th>Organ</th>
<th>If Localized</th>
<th>If Metastasized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>49%</td>
<td>3%</td>
</tr>
<tr>
<td>Colon</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Breast</td>
<td>98%</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>100%</td>
<td>32%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>10%</td>
<td>1%</td>
</tr>
</tbody>
</table>
The Economic Costs of Cancer

In the US in 2008:

Cancer Treatment Costs: $104 billion (~5% of health care $)
Cancer Morbidity:  >$180 billion

Worldwide in 2008:

Cancer Treatment Costs:  ~$850 billion
Morbidity and Premature Mortality Costs:  $895 billion
(heart disease second at $753 billion)

American Cancer Society, 2010
Cancer: A Complex Foe

The essential aberrations of cancer

- Altered Growth and Energetics
- Inflammation
- Genomic instability
- Tissue invasion and metastasis
- Evading death signals and immune surveillance
- Sustained angiogenesis
- Immortal; Limitless growth potential

Adapted from: Hanahan & Weinberg, Cell (2011)
<table>
<thead>
<tr>
<th>RECOMMENDATIONS</th>
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</thead>
<tbody>
<tr>
<td><strong>BODY FATNESS</strong></td>
</tr>
<tr>
<td>Be as lean as possible within the normal range of body weight</td>
</tr>
<tr>
<td><strong>PHYSICAL ACTIVITY</strong></td>
</tr>
<tr>
<td>Be physically active as part of everyday life</td>
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<tr>
<td><strong>FOODS AND DRINKS THAT PROMOTE WEIGHT GAIN</strong></td>
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<tr>
<td>Limit consumption of energy-dense foods</td>
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<tr>
<td>Avoid sugary drinks</td>
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<tr>
<td><strong>PLANT FOODS</strong></td>
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<tr>
<td>Eat mostly foods of plant origin</td>
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<tr>
<td><strong>ANIMAL FOODS</strong></td>
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<tr>
<td>Limit intake of red meat and avoid processed meat</td>
</tr>
<tr>
<td><strong>ALCOHOLIC DRINKS</strong></td>
</tr>
<tr>
<td>Limit alcoholic drinks</td>
</tr>
<tr>
<td><strong>PRESERVATION, PROCESSING, PREPARATION</strong></td>
</tr>
<tr>
<td>Limit consumption of salt</td>
</tr>
<tr>
<td>Avoid mouldy cereals (grains) or pulses (legumes)</td>
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<tr>
<td><strong>DIETARY SUPPLEMENTS</strong></td>
</tr>
<tr>
<td>Aim to meet nutritional needs through diet alone</td>
</tr>
<tr>
<td><strong>BREASTFEEDING</strong></td>
</tr>
<tr>
<td>Mothers to breastfeed; children to be breastfed</td>
</tr>
<tr>
<td><strong>CANCER SURVIVORS</strong></td>
</tr>
<tr>
<td>Follow the recommendations for cancer prevention</td>
</tr>
</tbody>
</table>

AICR/WCRF Expert Report

Recommendations

1997

2007

Continuous Update Program

www.aicr.org
Diets should contain a variety of plant-based foods
Bioactive Food Components Influence Cancer Processes

DNA Repair

Carcinogen Metabolism

Hormonal Regulation

Cell Cycle

Energy Metabolism

Immune Function

Bioactive Food Components
The Shape of Things to Come. The Economist 12/11/03

(http://www.economist.com/displaystory.cfm?story_id=2282754)
The US Obesity Epidemic

Ogden, et al., JAMA 2014:

- **69% of US Adults Overweight or Obese** (BMI >25.0 kg/m²)
- **36% US Adults Obese** (BMI >30.0 kg/m²)
- **6.5% US Adults Extremely Obese** (BMI >40.0 kg/m²)
Metabolic Syndrome

Describes a state of metabolic dysregulation characterized by:

- Insulin resistance, hyperglycemia*
- Dyslipidemia (↑triglycerides*, ↓HDL-C*)
- ↑Waist circumference*
- Hypertension*
- Proinflammatory state (↑cytokines, ↑chemokines)
- Vascular perturbations (↑PAI-1, ↑VEGF)
- Altered adipokines (↑leptin, ↓adiponectin)
- Elevated insulin-like growth factor (IGF)-1

Associated with many types of cancer
25% (144K) cancer deaths/year in US caused by overweight/obesity

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial</td>
<td>49%</td>
</tr>
<tr>
<td>Esophageal</td>
<td>35%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>28%</td>
</tr>
<tr>
<td>Kidney</td>
<td>24%</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>21%</td>
</tr>
<tr>
<td>Breast</td>
<td>19%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>9%</td>
</tr>
</tbody>
</table>

| Total Cancers     | ~25%       |

Source: American Institute for Cancer Research, 2014
American Society of Clinical Oncology Position Statement on Obesity and Cancer


Obesity:
- a central challenge in cancer prevention and care
- leading preventable cause of cancer in US
- can increase risk of cancer recurrence, lower survival
- by 2030, ~500,000 Americans/yr diagnosed with obesity-related cancer unless corrective action
Will Warfarin Still be in Use a Year from Now?

LOOMING QUESTION:
How to Decrease Cancer Risk in the ~720 Million Adults Worldwide Currently Obese?

Need a mechanistic approach to identify targets and strategies to break obesity-cancer links
Modeling Energy Balance and Human Cancer in Mice by Altering Key Genes and Pathways

Hursting, et al., Mutation Res., 2005
Molecular Profiling of Wnt-1 Tumors Relative to Well-Characterized Human and Murine Mammary Tumors

Dr. Sarah Dunlap
Energy Balance and Cancer Prevention

Energy in
• Amount
• Type
• Pattern

Energy Balance:
kcal in = kcal out

Energy out
• Physical Activity
• Routine Metabolism
• Thermoregulation
• Growth
• Storage
Calorie Restriction (~20% Reduction in Energy) Extends Lifespan in Multiple Species

- Yeast (S. cerevisiae)
- Worm (C. elegans)
- Fly (D. melanogaster)
- Bowl and Doily Spider
- Labrador Retriever
- Hereford Cow

% Increase in Longevity (versus ad libitum-fed controls)

Control

8.5 yrs.

Calorie Restricted

9.0 yrs.

27.8 yrs.

27.9 yrs.

81125
Weindruch: CR Study in Rhesus Monkeys (Colman, et al., Science 2009)

81010
Growth Factor Levels and Wnt-1 Mammary Tumor Growth in Lean, Overweight and Obese Mice

<table>
<thead>
<tr>
<th></th>
<th>IGF-1 (ng/ml)</th>
<th>Insulin (pg/ml)</th>
<th>Leptin (ng/ml)</th>
<th>Adiponectin (ng/ml)</th>
<th>L/A</th>
<th>Tumor Vol (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR (30%)</strong></td>
<td>390</td>
<td>380</td>
<td>1.9</td>
<td>9.5</td>
<td>0.2</td>
<td>120</td>
</tr>
<tr>
<td>29% body fat</td>
<td></td>
<td></td>
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<tr>
<td><strong>Overweight</strong></td>
<td>526</td>
<td>398</td>
<td>5.3</td>
<td>9.2</td>
<td>0.6</td>
<td>510</td>
</tr>
<tr>
<td>35% body fat</td>
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<tr>
<td><strong>DIO</strong></td>
<td>718</td>
<td>596</td>
<td>16</td>
<td>9.1</td>
<td>1.8</td>
<td>1485</td>
</tr>
<tr>
<td>47% body fat</td>
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</tbody>
</table>

n=12 mice/group

Dr. Nomeli Nunez

Genetic Reduction of Systemic IGF-1

~75% of IGF-1 in serum is produced by liver

Ecuadorians with Laron Syndrome have very low IGF-1 and inflammatory cytokines, increased longevity, and virtually no cancer or diabetes. 

NY Times 2/16/11.
Wnt-1 Mammary Tumor Growth in Wild-Type Control and Liver IGF-1 Deficient (LID) Mice

Dr. Nikki Ford

Ford, et al. Endocrine-Related Cancer, 2013
Dietary Energy Balance Modulation of Akt/mTOR Signaling (normal and tumor tissue)

Skin
Liver
Prostate
Colon
Pancreas
Mammary

Hursting, et al., Cancer Res, 2007
Moore, et al., Cancer Prev Res, 2008;
Olivo-Marston, et al., Mol Carcinogenesis 2009
deAngel, et al., Mol Carcinogenesis, 2013

(Insulin, IGF-1)

Calorie Restriction
Obesity

RTK

PI3K

Akt

mTOR

GSK-3

4E-BP1

p70S6K

Cyclin D

Proliferation

Translation

S6 ribosomal

Translation Proliferation

PI3K

Akt

mTOR

GSK-3

4E-BP1

p70S6K

Cyclin D

Proliferation

Translation

S6 ribosomal

Translation Proliferation
The mTOR Inhibitor RAD001 (Afinitor®) Inhibits Wnt-1 Mammary Tumor Growth in Lean, Control and Obese Mice

Energy Balance and Breast Cancer Prevention: Transdisciplinary Research Approaches
Integrated Phase II Trial and Animal Studies of Lovaza® (omega-3-acid ethyl esters)

C. Fabian, MD

High-Risk Women

Lovaza (4g/d)

Placebo

1 yr

Serum/Benign Breast Tissue Biomarkers

1. Response: Ki-67, cytomorphology
2. Mechanism: qRTPCR: ER-genes; miR’s
   Proteomics: mTOR, MAPK signaling; Cytokines

Change in Biomarkers

Mouse Models

Lovaza (208 mg/kg diet)

Placebo

3 mos

Cancer Endpoint

Breast Cancer Research Foundation Grant; Susan Komen Foundation Grant
Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States

Lola Rahib¹, Benjamin D. Smith², Rhonda Aizenberg¹, Allison B. Rosenzweig¹, Julie M. Fleshman¹, and Lynn M. Matrisian¹
Obesity Causes Inflammation in Pancreas and Adipose Tissue

Crown-like Structures (CLS) (Macrophage/Adipocyte/Epithelial Tumor Cell Interactions)

Lean with normal metabolic function
- Inflammation
- Metabolic control
- Vascular function

Obese with mild metabolic dysfunction
- ↑ Inflammation
- ↓ Metabolic control
- ↔ Vascular function

Obese with full metabolic dysfunction
- ↑↑ Inflammation
- ↔ Metabolic control
- ↓ Vascular function

M2 macrophage
CD4⁺ T cell
Adipocyte
Blood vessel

Anti-inflammatory adipokines
- Adiponectin
- SFRP5

Necrotic adipocyte
Crown-like structure

Pro-inflammatory adipokines
- Leptin
- ANGPTL2
- Resistin
- TNF
- RBP4
- IL-6
- Lipocalin 2
- NAMPT

Macrophage/Adipocyte/Epithelial Tumor Cell Interactions
Dietary Energy Balance Affects Pancreatic Tumor-Free Survival in Kras Ink4a<sup>+</sup>/- Mice

Lashinger, et al., Cancer Prev Res 2013
Take-Home Messages

• Many cancers (~2 out of 3) are preventable

• Recommendations:
  1. consume diet rich in vegetables, fruits, whole grains, and lean protein
  2. avoid weight gain (and limit sugary food/drink)
  3. be physically active
  4. avoid tobacco; alcohol in moderation
  5. follow your doctor’s recommendations on screening (eg, colonoscopy; mammography; prostate exams; pap smears; skin checks)

• Ongoing transdisciplinary research at NRI is focused on molecular and metabolic targets and intervention strategies to prevent cancer
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Andrew Dannenberg

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