What Is Cancer?

Stephen D. Hursting, PhD, MPH

Department of Nutrition, Nutrition Research Institute, and the Lineberger Comprehensive Cancer Center
The University of North Carolina at Chapel Hill
General COI Statement

I have no relevant relationships to disclose.
Today’s Presentation

• What is cancer?
  deadly; expensive; biologically complex; often preventable

• Cancer prevention: lessons learned about phytochemicals; obesity

• Mechanistic considerations and future directions
What is Cancer?

- *Webster’s:*

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

- *US National Cancer Institute:*

A collection of related diseases in which some of the body’s cells begin to divide without stopping and spread to surrounding tissues. If the spread is not controlled, it can result in death.
In 2010, cancer became the world’s leading cause of death.
Leading Causes of Death, All Races and Both Genders, U.S.  
(NCHS, CDC, U.S. Department of Health and Human Services, 2016)

**Rank Order and Number of Deaths**

<table>
<thead>
<tr>
<th><strong>ALL CAUSES</strong></th>
<th>2,467,819</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases of the heart</td>
<td>592,321</td>
</tr>
<tr>
<td>Malignant neoplasms (cancer)</td>
<td>585,720</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</td>
<td>50,472</td>
</tr>
<tr>
<td>nephrosis</td>
<td></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**
Estimated Cancer Deaths in the US in 2014

<table>
<thead>
<tr>
<th>Site</th>
<th>Men</th>
<th>Women</th>
<th>Source: American Cancer Society, 2016.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>28%</td>
<td>26%</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>Prostate</td>
<td>10%</td>
<td>15%</td>
<td>Breast</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td>9%</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
<td>7%</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5%</td>
<td>5%</td>
<td>Ovary</td>
</tr>
<tr>
<td>Leukemia</td>
<td>5%</td>
<td>4%</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>3%</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>4%</td>
<td>3%</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td>3%</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td>3%</td>
<td>Liver &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td>23%</td>
<td>Brain &amp; other nervous system</td>
</tr>
</tbody>
</table>

**Men: 310,010**
**Women: 275,710**
What is Cancer? A Huge Economic Burden

In the US in 2010:

Cancer Treatment Costs: $124.6 billion (~5% of health care $)
Projection by 2020: $158-207 billion (depending on rate of ↑)

Worldwide in 2008:

Cancer Treatment Costs: ~$850 billion
Morbidity and Premature Mortality Costs: $1.7 trillion
(heart disease second at $753 billion)

American Cancer Society, 2014
What is Cancer?
The final stage of a complex biological process
Cancer: A Complex Foe

Hallmarks of all cancer cells

- Metabolic Reprogramming
- Dysregulated death signals and immune surveillance
- Sustained angiogenesis
- Inflammation
- Genomic instability
- Tissue invasion and metastasis
- Limitless replicative potential (telomerase, TICs)

Adapted from: Hanahan & Weinberg, Cell (2011)
Cancer Process

- Tumor initiation
- Tumor formation
- Tumor progression
- Matrix remodeling
  - EMT
- Intravasation
- Extravasation
- Metastases

Cancer Hallmarks

- Genomic instability
- Sustained Proliferative Signaling
- Evasion of Anti-growth Signaling
- Resistance to Apoptosis
- Replicative Immortality
- Dysregulated Metabolism
- Tumor Promoting Inflammation
- Immune System Evasion
- Tumor Microenvironment
- Angiogenesis

Block et al., Seminars in Oncol, 2015
What is Cancer? Preventable!

Percent of Cancers Due to Each Factor

- Diet
- Smoking
- Infection
- Sun
- Alcohol
- Occupation
- Family Hx
- Pollution
- Food additives
- Industrial products

10% 20% 30%

# 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>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>Lung</td>
<td>49%</td>
<td>3%</td>
</tr>
<tr>
<td>Liver</td>
<td>28%</td>
<td>5%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>10%</td>
<td>1%</td>
</tr>
</tbody>
</table>

American Cancer Society, 2015
### RECOMMENDATIONS

#### BODY FATNESS
Be as lean as possible within the normal range of body weight

#### PHYSICAL ACTIVITY
Be physically active as part of everyday life

#### FOODS AND DRINKS THAT PROMOTE WEIGHT GAIN
- Limit consumption of energy-dense foods
- Avoid sugary drinks

#### PLANT FOODS
Eat mostly foods of plant origin

#### ANIMAL FOODS
Limit intake of red meat and avoid processed meat

#### ALCOHOLIC DRINKS
Limit alcoholic drinks

#### PRESERVATION, PROCESSING, PREPARATION
- Limit consumption of salt
- Avoid mouldy cereals (grains) or pulses (legumes)

#### DIETARY SUPPLEMENTS
Aim to meet nutritional needs through diet alone

#### BREASTFEEDING
Mothers to breastfeed; children to be breastfed

#### CANCER SURVIVORS
Follow the recommendations for cancer prevention

---

**AICR/WCRF Expert Report Recommendations**

1997  
2007  
2007-

[www.aicr.org](http://www.aicr.org)
Reduce Exposure to Pro-Cancer Agents

Dietary carcinogens
heterocyclic amines, aflatoxin, polycyclic aromatic hydrocarbons, nitrates, etc.

Processed Meat

Smoking
Radiation
Workplace Chemicals
Infections

Carcinogenesis
Carcinogens in Foods

Polycyclic aromatic hydrocarbons (charbroiled fat)

Heterocyclic amines (meat cooked at high temp)
Fruits and Vegetables Contain Many Bioactive Components that Impact Carcinogenesis-Related Processes.
Bioactive Food Components Influence Cancer Processes

- DNA Repair
- Hormonal Regulation
- Energy Metabolism
- Carcinogen Metabolism
- Cell Cycle
- Immune Function
The US Obesity Epidemic

Flegal, et al., JAMA 2016:

• **38% US Adults Obese** (BMI >30.0 kg/m²)
  – 35.2% men, 40.5% women

• **7.7% US Adults Extremely Obese** (BMI >40.0 kg/m²)
  – 5.5% men; 9.7% women
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

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
Body Fatness and Cancer — Viewpoint of the IARC Working Group

Béatrice Lauby-Secretan, Ph.D., Chiara Scoccianti, Ph.D., Dana Loomis, Ph.D., Yann Grosse, Ph.D., Franca Bianchini, Ph.D., and Kurt Straif, M.P.H., M.D., Ph.D., for the International Agency for Research on Cancer Handbook Working Group

NEJM, August 25, 2016
• Identified 13 cancer types in which there is sufficient evidence that avoidance of excess body fatness prevents those cancers. colon and rectum, oesophagus (adenocarcinoma), kidney (renal cell), breast (post-menopausal), endometrium, gastric cardia, liver, gall bladder, pancreas, ovary, thyroid, multiple myeloma, meningioma.

• Intentional weight loss in obese people may reduce risk of some cancers (based primarily on bariatric surgery studies), but the number and quality of weight loss studies was deemed insufficient for formal evaluation.

• Obesity consistently promotes cancer in rodent models of the same cancer types shown to be associated with obesity in humans; number of studies for many sites is limited.

• Sufficient evidence in experimental models for a cancer preventive effect of calorie restriction (which prevents obesity) for many cancer sites.

• Limited preclinical evidence that intentional weight loss (if severe enough) can reverse the procancer effects of obesity.
Underlying Mechanisms

- Obesity is associated with significant metabolic and endocrine abnormalities, including alterations in sex-hormone metabolism, insulin/insulin-like growth factor (IGF) signaling, adipokines, and inflammatory pathways.

- Possible contributors (but limited evidence): gut microbiome, angiogenesis, bioenergetic reprogramming, stemness, antitumor immune responses, and epigenetic reprogramming.
Obesity and Cancer: Underlying Mechanisms

Mechanisms Underlying the Obesity-Cancer Link: 2013?

1. Microenvironment (EMT, CSCs)
2. Epigenetic Reprogramming
3. Obesity and Metabolic Syndrome
4. Physical Activity
5. Energy Intake
6. Chronic Positive Energy Balance
7. Growth Factor Signaling
8. Vascular Perturbations
9. Inflammation
10. PI3K/Akt/mTOR
11. ER
12. Microbiota?

Allott and Hursting
Endocr-Related Cancer 2015
Energy Balance and Cancer Prevention: Transdisciplinary Research Approaches

- Epidemiology
  - Pathology
  - Molecular Biology
  - Immunology
  - Endocrinology/Metabolism
  - Bioinformatics/Statistics

- Behavioral Science

- Clinical Oncology

- Animal Models

- Basic/Clinical Nutrition
Cancer results from a complex interaction between an individual’s genetic make-up and the environmental (including dietary) agents they are exposed to.

**Challenge in Preventing or Treating Cancer:**

- Every tumor is different
- Every person is different
Genotype Influences the Response to Diet

- Food preference
- Food tolerance
- Absorption
- Transport
- Metabolism
- Effects in target tissues

Lampe and Potter, in Gene-Envir Interactions (2006)
Take Home Messages from Today’s Presentation

• **What is cancer?** A group of diseases characterized by uncontrolled growth and spread of abnormal cells; major killer; expensive; complex but increasingly understood biology; many cancers preventable, with diet a key factor.

• **Diet and cancer prevention:** current focus on plant-based dietary patterns and obesity prevention/reversal

• **Future progress:** transdisciplinary research leading to effective mechanism-based approaches; personalized.