Nutrition, Nutrigenomics, and Cancer

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The University of North Carolina at Chapel Hill
UNC: University of National Champions
UNC: University of Nutrition and Cancer
Today’s Presentation

• What is cancer? Collection of related diseases: deadly; expensive; biologically complex; often preventable

• Nutrition and cancer prevention: lessons learned about bioactive food components; obesity

• Mechanistic considerations: importance of nutrigenomics and personalized nutrition
Cancer: A Complex Foe

Hallmarks of all cancer cells

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

Adapted from: Hanahan & Weinberg, Cell (2011)
What is Cancer? Preventable!
(Colditz, et al. Sci Transl Med, 2011)

Diet/Obesity
Smoking
Infection
Sun
Alcohol
Occupation
Family Hx
Pollution
Food additives
Industry pollution

Percent of Cancers Due to Each Factor

10% 20% 30%
Increase Exposure to Anticancer Bioactive Food Components
Reduce Exposure to Dietary Procancer Agents

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

Processed Meat

Smoking
Radiation
Workplace Chemicals
Infections

Carcinogenesis

By ANAHAD O’CONNOR  OCT. 26, 2015

-Strong link for many cancers with processed meats, such as hot dogs, bacon, ham, and cold cuts

-Weak but consistent link with red meat (especially colon cancer)
Carcinogens in Meat

Polycyclic aromatic hydrocarbons (Charbroiled fat)

Heterocyclic amines (meat cooked at high temp, tobacco smoke)

These must be activated by phase I enzymes (P450) (genes encoding P450’s are highly polymorphic)
Obesity and Cancer

Prevalence of obesity has tripled in past 60 years; associated with metabolic syndrome* and other disease states:

- 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

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
Epidemiologic Evidence

- Identified 13 cancer types in which there is sufficient evidence that avoidance of excess body fatness prevents those cancers.

- 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.

Evidence from Animal Models

- 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, suppresses mTOR signaling, reduces inflammation) for many cancers.

- Limited preclinical evidence that intentional weight loss (if severe enough) can reverse the procancer effects of obesity.
Mechanisms Underlying the Obesity-Cancer Link: 2013?

- Microenvironment (EMT, CSCs)

Obesity and Cancer: Underlying Mechanisms

- Adipose Remodeling
- Epigenetic Reprogramming
- Microbiota?
- NF-κB
- COX-2
- uPA/tPA
- VEGF
- Vascular Perturbations
- Growth Factor Signaling
- PI3K/Akt/mTOR

Obesity Metabolic Syndrome

Cancer Risk and Progression

Modified from Allott and Hursting Endocr-Related Cancer 2015
Dietary Energy Balance Modulation of Akt/mTOR Signaling (normal and tumor tissue)

Liver
Prostate
Colon
Pancreas
Mammary

deAngel, et al., *Mol Carcinogenesis*, 2013
Clear Message from the AICR/WCRF and IARC Initiatives:

The cancer research community needs to pivot from the question of whether obesity is an important risk factor for many cancers - it is - to the question of how we can reduce the impact of chronic obesity on cancer.
The Obesity-Cancer Link

Increased InsR/IGF-1R Signaling

Increased Hormone/Growth Factor Signaling

Energy Balance and Cancer Prevention: Transdisciplinary Research Approaches

Epidemiology

Clinical Oncology

Animal Models

Behavioral Science

Basic/Clinical Nutrition

• Pathology
• Molecular Biology
• Immunology
• Endocrinology/Metabolism
• Bioinformatics/Statistics
Co-clinical trials for the development of precision medicine and personalized care

Translational Collaboration: Dietary Weight Loss Trial in Obese Postmenopausal Women

200 High Risk Women: BMI >30 kg/m² No HRT

12-month Weight Loss

RPFNA

Repeat RPFNA

Response Biomarkers

FNA Tissue Markers

Proliferation (Ki-67)

Mammographic Breast Density

Serum
insulin, cytokines, adipokines, E&T, IGF1, IGFBP-3

RPPA;qRT-PCR; insulin, cytokines, adipokines, E&T, IGF1, IGFBP-3; DNA methylation; SNP analysis

Komen Promise Grant; BCRF; R35
Favorable modulation of benign breast tissue and serum risk biomarkers is associated with >10 % weight loss in postmenopausal women

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Does intentional weight loss following chronic obesity in mice reverse the procancer effects of obesity?

Molecular Carcinogenesis 2013

The Enhancing Effects of Obesity on Mammary Tumor Growth and Akt/mTOR Pathway Activation Persist After Weight Loss and Are Reversed by RAD001

Rebecca E. De Angel,¹ Claudio J. Conti,² Karrie E. Wheatley,¹,² Andrew J. Brenner,³ Glen Otto,⁴ Linda A. deGraffenried,¹,⁵ and Stephen D. Hursting¹,²*

Research Article

Obesity-Associated Alterations in Inflammation, Epigenetics, and Mammary Tumor Growth Persist in Formerly Obese Mice

Emily L. Rossi¹, Rebecca E. de Angel², Laura W. Bowers¹, Subreen A. Khatib¹, Laura A. Smith¹, Eric Van Buren³, Priya Bhardwaj⁴, Dilip Giri⁵, Marcos R. Estecio⁶, Melissa A. Troester⁷, Brionna Y. Hair⁷, Erin L. Kirk⁷, Ting Gong⁶, Jianjun Shen⁶, Andrew J. Dannenberg⁴, and Stephen D. Hursting¹,²
Obesity Reversal Normalizes Insulin, Leptin and Adiponectin, But Not Inflammatory Cytokines


**A**

- Week 17
- Week 24

**B**

- Diet switch
- Tumor injection

**C**

- Leptin (ng/mL)

**D**

- Adiponectin (ng/mL)

**E**

- Insulin (ng/mL)

**F**

- Adiponectin (ng/mL)

**G**

- IGFBP1 (ng/mL)

**H**

- IL-6 (ng/mL)
The Adverse Effects of Obesity on MMTV-Wnt-1 Mammary Tumor Growth Are Not Reversed by Moderate Weight Loss

Reduced Representation Bisulfite Sequencing (RRBS)

1. Purification of genomic DNA
2. Restriction enzyme digest
3. Adapter Ligation
4. A-Tailing
5. Bisulfite Conversion
6. PCR Amplification
7. Sequencing

unmethylated cytosines → uracil
Global Mammary Gland Methylation Profiles Are Similar in Obese and Formerly Obese, Relative to Controls

- DIO v Control: 39 genes significantly hypermethylated
- most were regulators of inflammation
- high concordance with DNA methylation profiles in women from CBCS (M. Troester)
- only 2 genes significantly reversed in FOb
Ingenuity Pathway Analysis Suggests Many of the Epigenetically Regulated Genes in Obese and Fob Mice Participate in An Inflammatory Network That Persists After Weight Normalization

Rossi et al., Cancer Prev Res 2016
Weight Loss Surgery Reduces Cancer Incidence in Women

Bariatric surgery (relative to non-surgical controls) reduces cancer risk in morbidly obese patients.

Obesity Reversal Study, Phase 2

Interventions (n=20/group):
17 weeks of DIO diet →

1. Switch to control diet (FOb) + Sham surgery

1. Switch to control diet (FOb) + Bariatric surgery (sleeve gastrectomy)

2. DIO diet throughout + Sham surgery

1. Control diet throughout + Sham surgery

Emily Rossi
CCEP Predoctoral Fellow
Bariatric Surgery and a Low Fat Diet Normalize Body Weight and % Body Fat in Chronically Obese Mice

Body Fat Graph:
- NW Control
- FOB-Surg
- FOB-Diet
- Obese

Body fat (%)

0 20 40 60

NW Control FOB-Surg FOB-Diet Obese

Body fat (%)
Bariatric Surgery (but not weight normalization via LFD) in Chronically Obese Mice Decreases Tumor Burden to Control Levels.
Surgery versus diet/exercise combos this summer:
Can we design a lifestyle regimen that mimics the anticancer effects of surgery?
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.
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