Body Weight Status, Inflammation, and Prognostic Markers in Early-Stage Prostate Cancer

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Outline

- Relative risk of cancer mortality in obese men
- Pathophysiologic basis for excess risk
- The case for inflammation/immunity in prostate cancer
- Preliminary results from the “Adiposity and Prostate Cancer” Study
Relative risk of cancer mortality in obese men

Calle EE et al., NEJM, 2003
Obesity and cancer: possible connections

- Inflammation: cytokines
- Adipokines: leptin and adiponectin
- Growth factors: IGF-1
- Energy balance pathways
Adipose tissue inflammation in obesity

Healthy diet and physical activity

Positive energy balance and physical inactivity

Leptin & Inflammatory cells in fat tissue and throughout the body

Leptin and Immunity

La Cava et al., Nature Rev Immunol, 2004
Tumor necrosis factors $\alpha$ (TNF$\alpha$)

- Increased soluble TNF receptors
- Chemokine release (CCL5, CCL2, IL-8)
- Adhesion molecule expression
- MHC class I and II
- Tissue damage (cartilage destruction and bone resorption), metalloproteinase and PGE$_2$ production
- Cytokine release (IL-1, IL-6, GM-CSF)
- Decreased surface TNF receptors
- Angiogenesis
Inflammation as the seventh hallmark of cancer

Colotta F et al. Carcinogenesis 2009;30:1073-1081
The Case for Inflammation / Immunity in Prostate Cancer
Distribution of inflammation, Proliferative Inflammatory Atrophy (PIA), HGPIN, and Prostate Ca in the Human Prostate

Radical prostatectomy specimen

PIA lesion
- Inflammatory infiltrate in and around foci of atrophy
- Increased proliferative index
- Can transition directly to HGPIN or prostate cancer

De Nunzio, Eur Urol 2011
NIH/AARP Diet and Health Study:
Cubic spline regression for prostate cancer incidence and mortality according to BMI

Wright et al. Cancer, 2007
Obesity / Excessive Adiposity and Prostate Cancer

- A threat to prostate cancer prevention and control
- Excess body fat and the pathophysiologic consequences thereof are potential targets for chemoprevention
Adiposity and Outcomes of Clinically Localized Prostate Cancer
NIH/NCI 1R01CA129140

Objectives

- Measure the association of adiposity with risk factors for prostate cancer-specific morbidity and mortality based on more thorough assessment of body size and composition
- Clarify the mediating physiologic mechanisms
Specific Aims

- Conduct a prospective cohort study to measure the association of body fatness with prognostic tumor parameters and biochemical (PSA) failure

- Measure a) fatty acids, b) IGF axis activity, c) modulators of Inflammation, d) and sex steroid hormones in prostate tissue and peri-prostatic fat to analyze which factors mediate the associations

- Explore the effect of post-treatment changes in body weight status on 2-year risk of PSA failure
Mechanistic Model

**AIM 1**

- **Adiposity:**
  - Body Size
    - Weight
    - BMI
    - Waist circumference
  - Body Composition
    - % Total body fat
    - Visceral fat area

**AIM 2**

- **IGF Axis**
  - Free IGF-1, IGFBP-1-3, IGF-1R Signaling
- **Inflammation**
  - WAT-Derived Peptide Hormones, Eicosanoids
- **Steroid Sex Hormones**

Mediators in the Prostate Gland

**AIM 3**

- **Post-Treatment Changes in Adiposity**

Mediators in the Circulation

**Prostate Cancer**

- Presentation & Course:
  - Pathologically advanced tumor
  - PSA Failure ≤ 2 y
Study Design – Recruitment and Data Collection

350 men awaiting RP
- UIC
- Loyola
- Hines VAH
- Stroger/Cook County

Visit 1 (pre-op)
- Consent to f/u for 10 years
- Anthropometrics
- DXA
- Blood
- Lifestyle and Health Surveys (FFQ, physical activity, social, and health)

Visit 2 (1 year post-op)
- Repeat anthros, DXA blood, and surveys

Outcome Ascertainment
- Central Path Review at UIC
- Serial PSAs per usual care
- Medical record review

Surgery
- Fresh non-malignant prostate
- Regional prostatic adipose tissue
## Exposures & Outcomes for Aim 1

<table>
<thead>
<tr>
<th>Exposures</th>
<th>Outcomes – Aim 1</th>
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<tbody>
<tr>
<td>Generalized adiposity</td>
<td>• BMI</td>
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<tr>
<td></td>
<td>• Total body fat</td>
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<tr>
<td></td>
<td>Primary</td>
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<td></td>
<td>• Tumor-positive surgical margins</td>
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<td></td>
<td>• Biochemical failure ≤ 2 years (PSA ≥ 0.1 ng/ml within 2 yrs)</td>
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<tr>
<td>Central Adiposity</td>
<td>• Waist Circumference</td>
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<td>• Waist/Hip ratio</td>
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<td>• Trunk fat mass</td>
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<td>• Visceral adipose tissue mass</td>
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<tr>
<td></td>
<td>Secondary</td>
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<tr>
<td></td>
<td>• Receipt of additional (RT, ADT, other)</td>
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<td></td>
<td>• Clinical Progression</td>
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<td></td>
<td>• Prostate cancer-specific mortality</td>
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<tr>
<td>Other</td>
<td>• Body weight Δ since age 25 &amp; 40 years</td>
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<tr>
<td></td>
<td>Other</td>
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<tr>
<td></td>
<td>• D’Amico 5-yr PSA recurrence risk score</td>
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<td>• Kattan 2, 5, 7, and 10-yr PSA recurrence risk probabilities</td>
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</tbody>
</table>
Dual Energy Absorptiometry (DXA)
Progress Report

- 223 men enrolled as of 10/30/12
- % of eligible subjects consented = 59.2%
- Tissue-based analyses completed in 72-90 subjects (32-40%) depending on analyte
### Studies in Prostate and Adipose Tissue (Aim 2)

<table>
<thead>
<tr>
<th>System/Pathway</th>
<th>Investigator</th>
<th>Analyte</th>
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<tbody>
<tr>
<td>Fatty Acids</td>
<td>Meydani (Tufts)</td>
<td>Oleic/Stearic acid, %Essential FAs</td>
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<tr>
<td>IGF-Axis Activity</td>
<td>Swanson (UIC)</td>
<td>IGF-1 (Total, Free)</td>
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<tr>
<td></td>
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<td>IGFBP 1-3</td>
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<td>IGF-1R mRNA</td>
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<td>Phosphorylated IGF-1R mRNA</td>
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<tr>
<td>Inflammation / Immunity</td>
<td>Fantuzzi (UIC)</td>
<td>Leptin &amp; Adiponectin</td>
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<tr>
<td>White Adipose Tissue (WAT)</td>
<td></td>
<td>IL6</td>
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<tr>
<td>(WAT)-Derived Peptide Hormones</td>
<td></td>
<td>TNF-α</td>
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<tr>
<td></td>
<td>Meydani (Tufts)</td>
<td>MCP-1</td>
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<tr>
<td>Eicosanoids</td>
<td>Meydani (Tufts)</td>
<td>PGE2</td>
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<td>LTB4</td>
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<td>Sex Steroids</td>
<td>Van Breemen (UIC)</td>
<td>Testosterone (Total and Free)</td>
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<td>Prins (UIC)</td>
<td>Dihydrotestosterone</td>
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<td>3-α (17-β) Androstanediol</td>
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<td>3-β Androstanediol</td>
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Preliminary Results - Outline

- Cross-sectional analysis of body weight status prostatic levels of adipocytokines
  - Leptin
  - Adiponectin
  - IL-6
  - TNF-a
- Body weight status and prostate cancer outcomes
- Prostatic adipocytokines and prognostic markers
Lifestyle/Behavioral Interventions

What are we trying to accomplish?

- Prevent spread of the tumor outside of the gland?
- Prevent (or slow) progression of non-organ confined disease?

“Excess body fat and the molecular biologic consequences thereof are potential targets for chemoprevention.”
Summary

- Obesity/excessive adiposity increases the risk of cancer-related morbidity and mortality.

- Our preliminary results convincingly establish that obesity/excessively adiposity increases the concentration of pro-inflammatory factors in the prostate gland of men with early prostate cancer.

- Of the pro-inflammatory factors studied thus, prostatic levels TNFα appears to associate with some risk factors for prostate cancer recurrence after surgery ("treatment failure").
Summary

- Additional analyses in the rest of the cohort are pending. However, if these early results are replicated, we will have established a mechanistic link between obesity and risk of prostate cancer recurrence after “curative” therapy.

- Prostate cancer recurrence in our cohort means that the cancer probably had already spread outside of the gland by the time of surgery. Therefore, our ability to intervene early enough to prevent this may be limited.

- However, an understanding of the molecular biology of the obesity-prostate cancer mortality association would identify drug targets that could complement lifestyle and behavioral interventions to prevent further cancer progression.
Acknowledgements

UROLOGY

University of Illinois at Chicago (UIC)
Leslie Deane, MD
Stewart B. Lipson, MD
Gail Prins, PhD

Loyola University Medical Center
Robert C. Flanigan, MD (Site PI)
Marcus Quek, MD

Hines VAH
Jeffrey Branch, MD (Site PI)
Nicholas Friedman, MD

Stroger Hospital
Courtney Hollowell, MD (Site PI)
Patricia Vidal, MD
Marin Sekosan

NUTRITION/HEALTH PROMOTION

UIC
Giamila Fantuzzi, PhD*
Maria Pini, MS / Karla Castellanos, MS
Carol Braunschweig, PhD, MPH
Marian Fitzgibbon, PhD
Sandra Gomez, MS

Tufts University
Mohsen Meydani, PhD, DVM

*A special “thank you” to Dr. Giamila Fantuzzi for providing several of the figures adapted for this presentation*
Acknowledgements

PATHOLOGY

UIC
Andre Balla, MD, PhD
Vicky Macias, MD

Loyola University Medical Center
Guliz Barkan, MD

SCHOOL OF PHARMACY
University of Illinois at Chicago (UIC)
Steven Swanson, PhD
Richard van Breemen, PhD

PROJECT MANAGER
Daisy Cintron, MA

Site Coordinators
Linda Millbrandt (Loyola)
Anne Garabedian (Hines VA)
Jasmine Cleofe (Stroger)

Statistical Support
Young Ku-Choi, PhD (deceased)
Li Liu, PhD
Firas Dabbous, Graduate Research Assistant

CTSA at UIC
Phlebotomy support

UIC Grants Manager
Paul Racinski, MA
Thank you.