# Energy Balance and Cancer:
# Carcinogenesis and Cancer Survival

## Presentation to
## NCI Board of Scientific Advisors
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- Glycemic load, energy balance, and carcinogenesis in animals and humans
- Obesity-related biomarkers and breast cancer survival
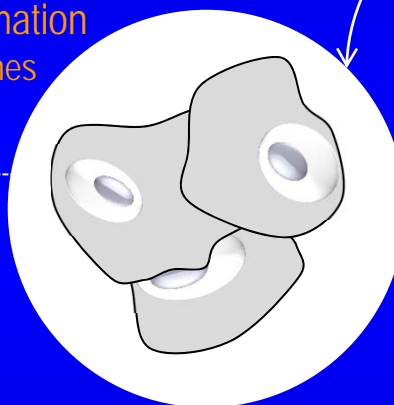
# Glycemic Load, Energy Balance and Cancer:
# A Transdisciplinary Experimental Approach in Animals and Humans

## A Collaboration Between Seattle-TREC Projects 2 and 3

**Colorado State**: Henry Thompson
**Fred Hutchinson:  Marian Neuhouser, Johanna Lampe**

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# Blood Glucose Concentrations After Ingesting High and Low Glycemic Index Foods

New potatoes

Kidney beans

Blood Glucose (mg/dL)

Time (min)
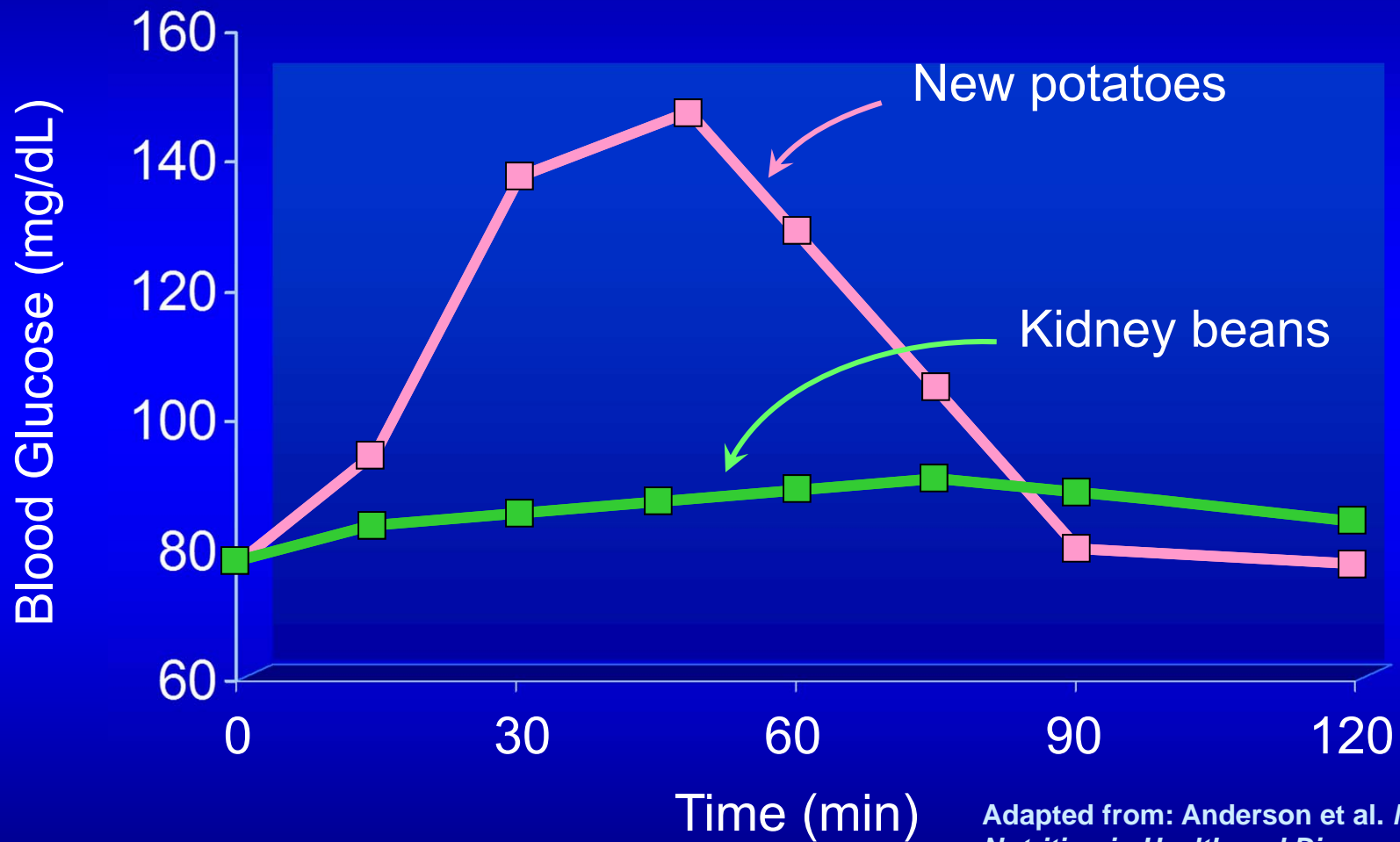
Adapted from: Anderson et al. *Modern Nutrition in Health and Disease*; 2001.

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# Transdisciplinary Animal and Human Experimental Studies

## Rodent Study:

Investigates effect of low vs. high glycemic load experimental diets on carcinogenesis and biomarkers in a preclinical model
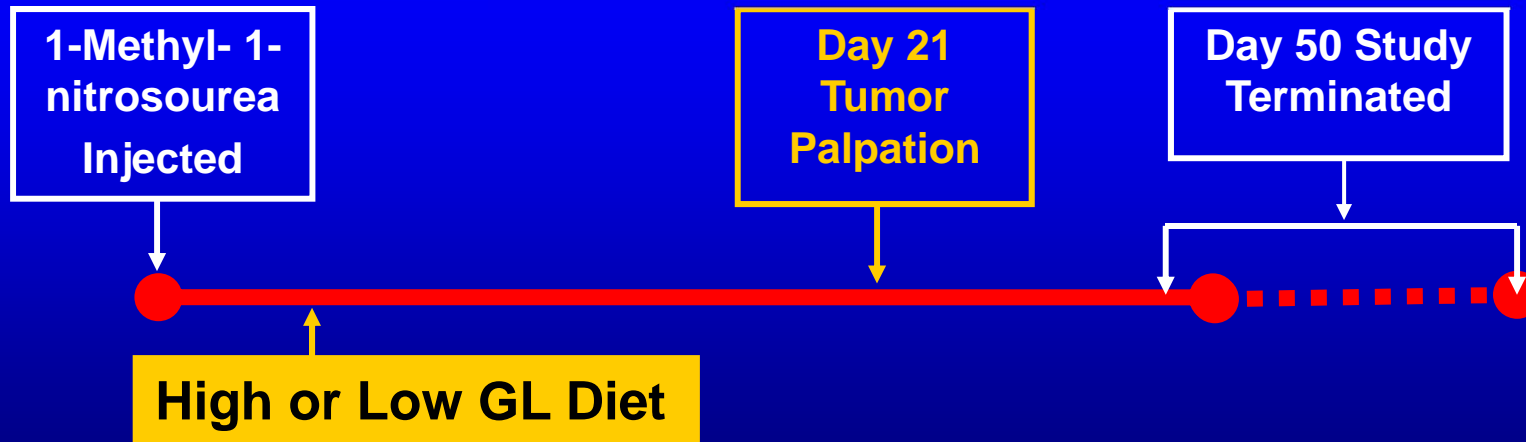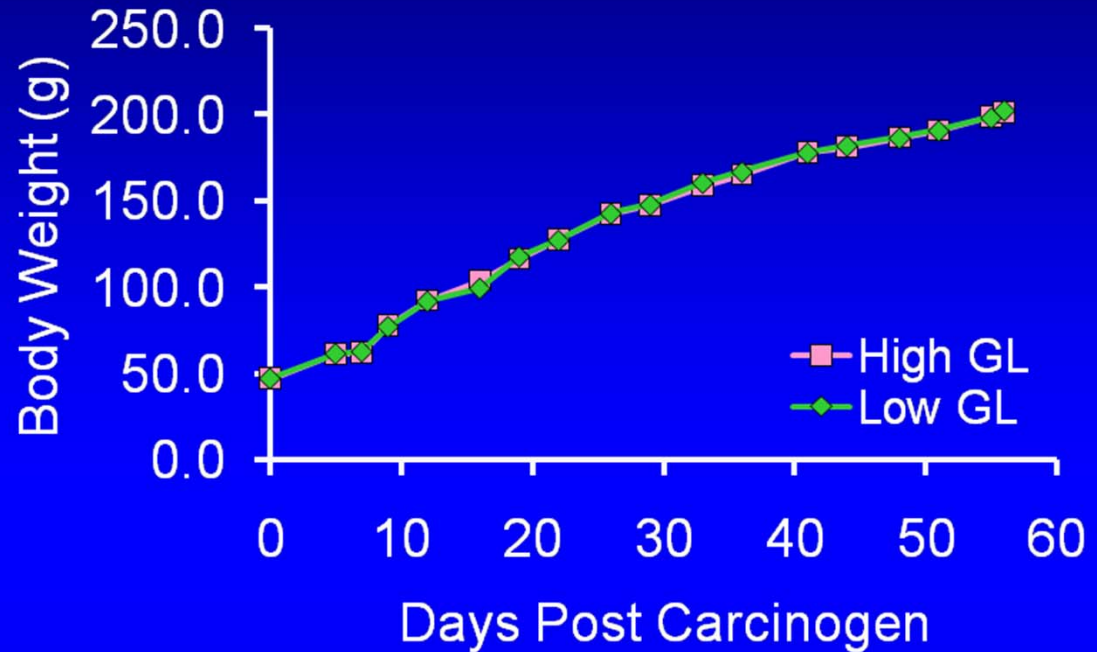
## Human Study:

Investigates effect of low vs. high glycemic load experimental diets on cancer-susceptibility biomarkers

Common set of biomarkers: IGF1, IGFBP3, leptin, adiponectin, IL-6, C-reactive protein, insulin, glucose

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# Pre-Clinical Model for Breast Carcinogenesis

*n* = 60 female
Sprague Dawley rats

**Body Weight (g)** vs **Days Post Carcinogen**

High GL
Low GL

**1-Methyl- 1-nitrosourea Injected**

**Day 21 Tumor Palpation**

**Day 50 Study Terminated**

**High or Low GL Diet**

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# Human Feeding Study Diets
## Average Daily Nutrient Content

| Nutrient | Low-GL | High-GL |
|---|---|---|
| Energy | Isocaloric, weight maintaining | |
| Protein | 20% kcal | 20% kcal |
| Carbohydrate | 50% kcal | 50% kcal |
| Fat | 30% kcal | 30% kcal |
| Glycemic Load | **117** | **244** |

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Glycemic Load (GL) Effects of Diet on Cancer Incidence
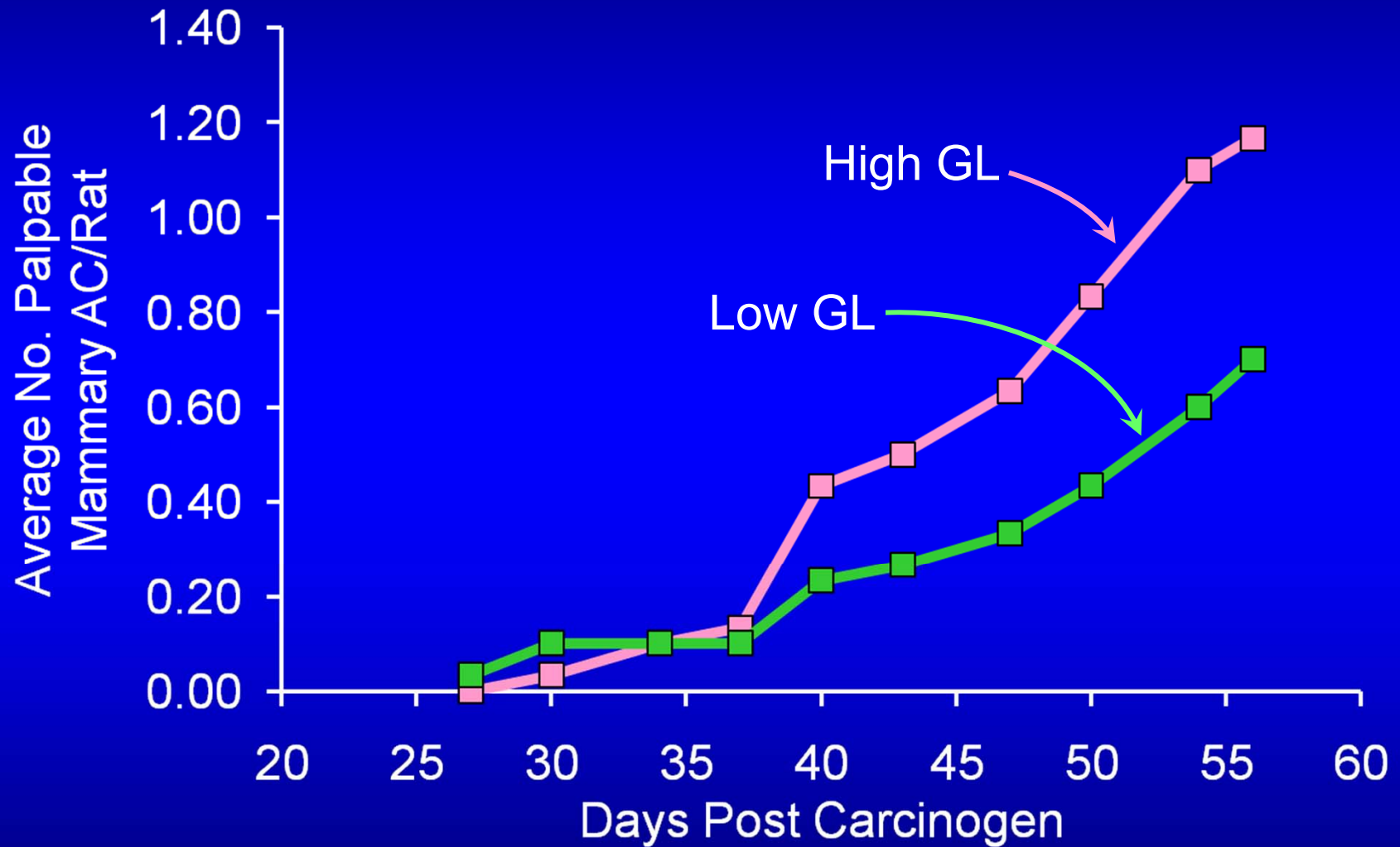
# Glycemic Load (GL) Effects of Diet on Apoptotic Markers in Tumors
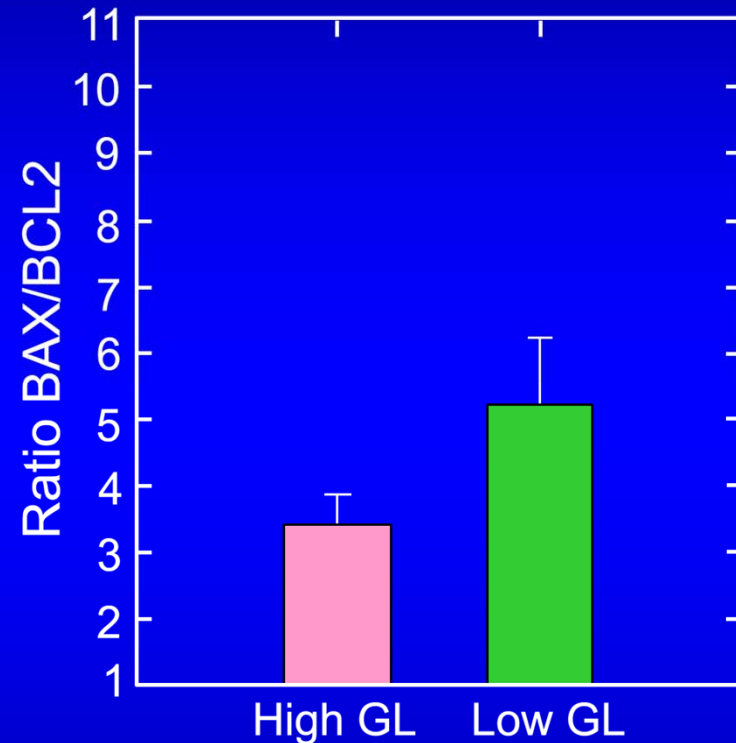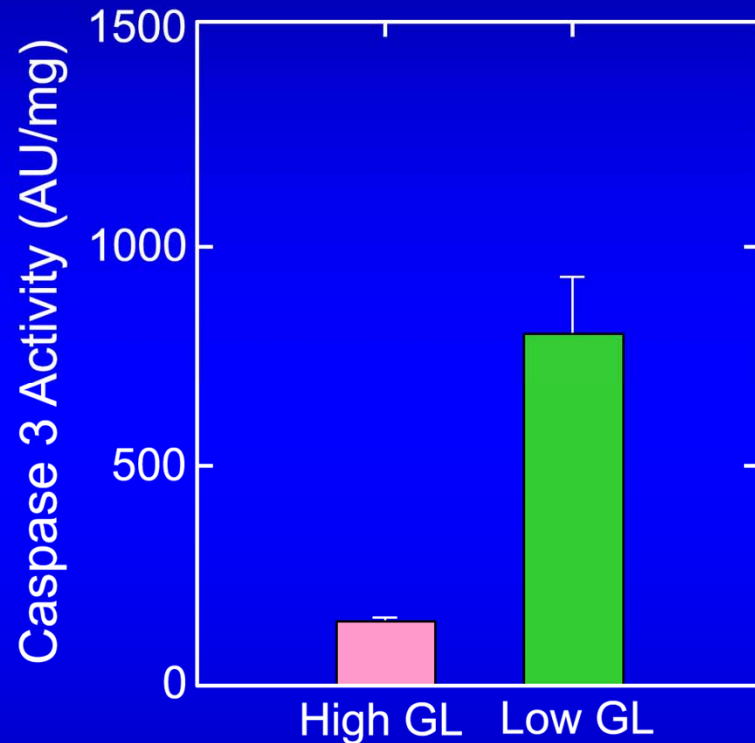


- High glycemic load decreased apoptosis

# Effects of High- vs. Low-Glycemic Load Diet on Cancer-Related Biomarkers in Rats

- Increased plasma:
  - Glucose
  - Insulin
  - Insulin-like growth factor 1
  - Interleukin-6
  - Leptin
- Decreased plasma
  - Adiponectin

# Seattle Project 3: Glycemic Load & Obesity Effects on Cancer Biomarkers

- Investigating effects of low- and high-glycemic load diets on cancer-related biomarkers in humans

- Examining extent to which overweight/obesity modifies response to diets

- Design = human feeding study in 88 individuals aged 18-45 years

# Summary

- Low-glycemic load diets reduced carcinogenic response in the mammary gland
- Low-glycemic load diets favored reduced cell proliferation and a pro-apoptotic environment in carcinogenesis
- Circulating markers: hypothesized directions
- Cellular mechanisms being pursued
- Human trial (Project 3) in progress

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# Overweight, Obesity and Breast Cancer Prognosis

- Overweight and obese breast cancer patients have poorer survival and increased recurrence compared with lighter patients

- Of 34 published studies, statistically significant association in 26, non-significant effect in 4, no effect in 4

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# Study Aim

- Assess associations of obesity biomarkers with breast cancer survival:
    - Adiponectin
    - Insulin
    - Glucose
    - Fructosamine
    - HOMA (marker of insulin resistance)

# Health, Eating, Activity, and Lifestyle (HEAL) Cohort of Breast Cancer Survivors

- Population based (SEER registries)
- Multi-center (WA, LA, New Mexico)
- Multiethnic
- Stage 1–IIIA diagnosed 1995 - 1998
- n= 550 with blood ~ 3 years post-diagnosis
- Excluded: Type 2 DM, recurrence/new primary before blood draw
- Followed mean 6 years

# Participant Characteristics (n=550)

- Mean age: 57, range 31- 89 years
- Mean BMI: 27.3, range 16.2 - 53.3 kg/m$^2$
- SEER Stage
  - Local: n=392
  - Regional: n=158
- Race/ethnicity
  - African-American: n=137
  - White: n=336
  - Hispanic: n=64
  - Other: n=13
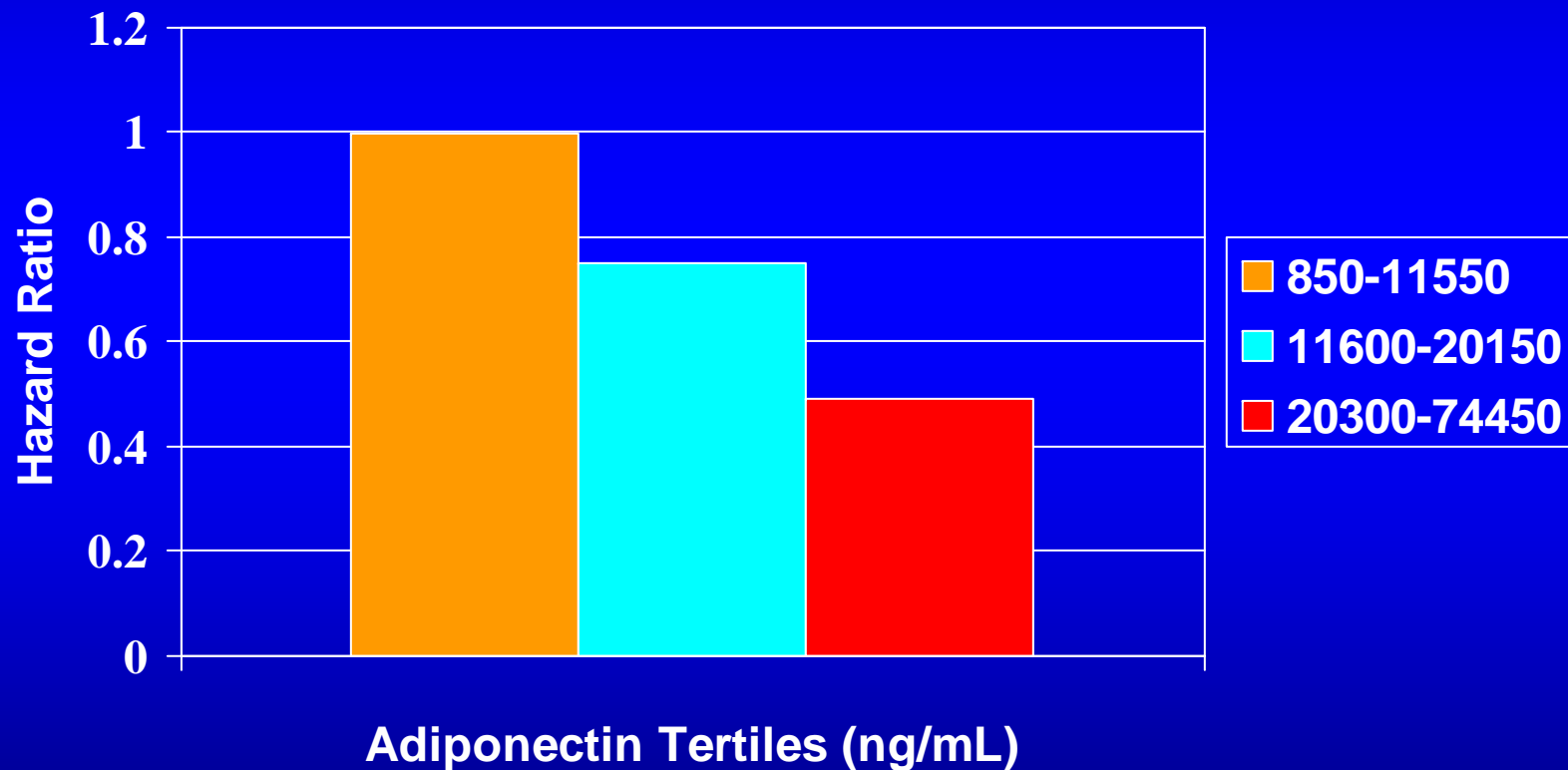
# Insulin Resistance and Breast Cancer Deaths

|  | HR | 95% CI | P (trend) |
|---|---|---|---|
| Insulin | 1.02 | 0.99-1.04 | 0.08 |
| HOMA | 1.07 | 1.01-1.17 | 0.03 |
| Fructosamine | 0.99 | 0.99-1.01 | 0.79 |
| Glucose | 1.00 | 0.99-1.02 | 0.25 |

# Summary

- Increased breast cancer deaths with:
  - Lower levels of adiponectin
  - Increased HOMA ($\uparrow$ insulin resistance)
- Analyses in progress for disease-free survival
- Results suggest biomarkers for association of obesity with reduced breast cancer prognosis

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