



The Role of Body Size and Fat in Breast Cancer

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Obesity and Breast Cancer Risk

- **Relationship between obesity and breast cancer risk may depend upon time period of exposure**
 - **Premenopausal women:**
 - Obesity found to be either not associated or protective in relationship to premenopausal breast cancer risk (Ursin et al 1995).
 - Obesity results in anovulatory menstrual cycles or secondary amenorrhea
 - extremely obese women
 - moderately obese women

Obesity and Breast Cancer Risk

- **Postmenopausal women:**

- Obesity and weight gain in adulthood increases breast cancer risk after menopause (Huang et al 1997; Van den Brandt et al 2000)
 - Greater estrogen exposure in obese postmenopausal women due to increased endogenous production of estrogen through the conversion of androstenedione in peripheral body fat.
 - Decreased SHBG (sex hormone binding globulin) leading to increased bio-available fractions of estrogens and androgens.
 - Obese postmenopausal women also have increased circulating insulin levels, known to stimulate breast cancer cell lines.
 - Obese women are thought to have higher insulin growth factor (IGF-1) levels

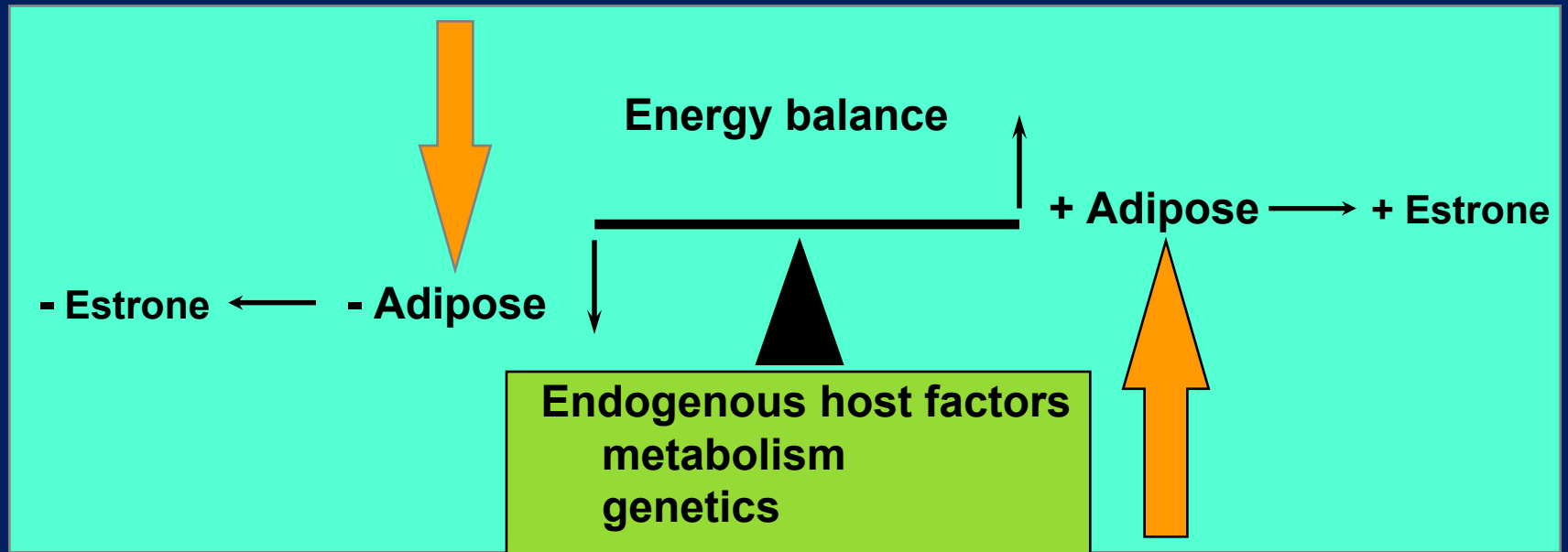
Energy Balance and Development of Breast Cancer

Intensity

Type

Duration

Exercise



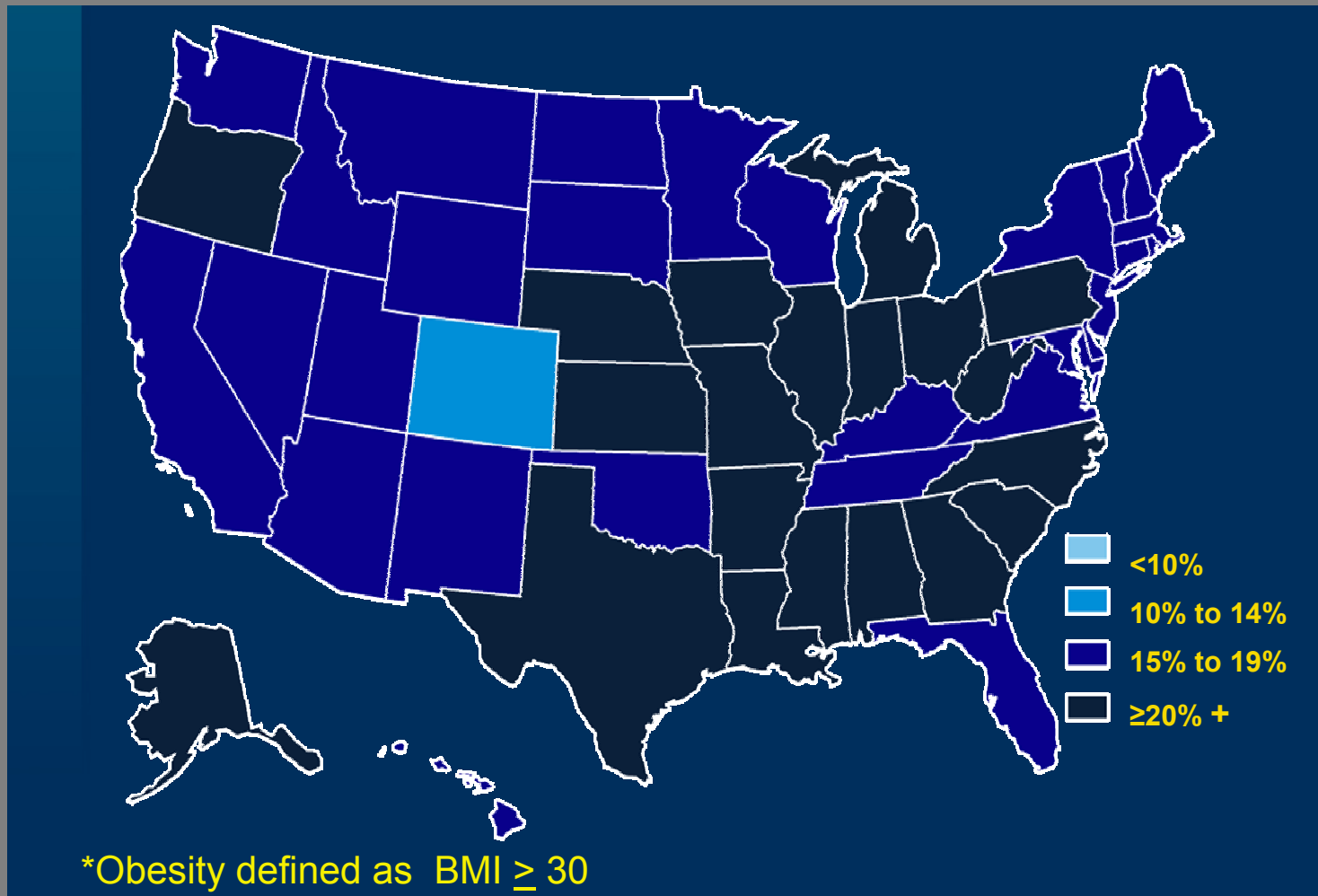
Food Intake

Amount

Type

Frequency

Prevalence of *Obesity Among U.S. Adults BRFSS, 2000



Reasons for Rise in Prevalence of Obesity

- **Reliance on technology**

- Increasing amounts of time spent in sedentary activity
 - computers and entertainment equipment

- **Dietary changes**

- Fast food consumption
 - Americans are eating out more often
- Larger portion sizes



Genetic and Environmental Contributions to Obesity

- **Genetic Factors**

- 40 to 70% of the variation in obesity-related phenotypes is thought to be heritable (Comuzzie and Allison, 1998)

- **Behavioral factors**

- appetite control
- motivation to exercise

- **Composition of diet**

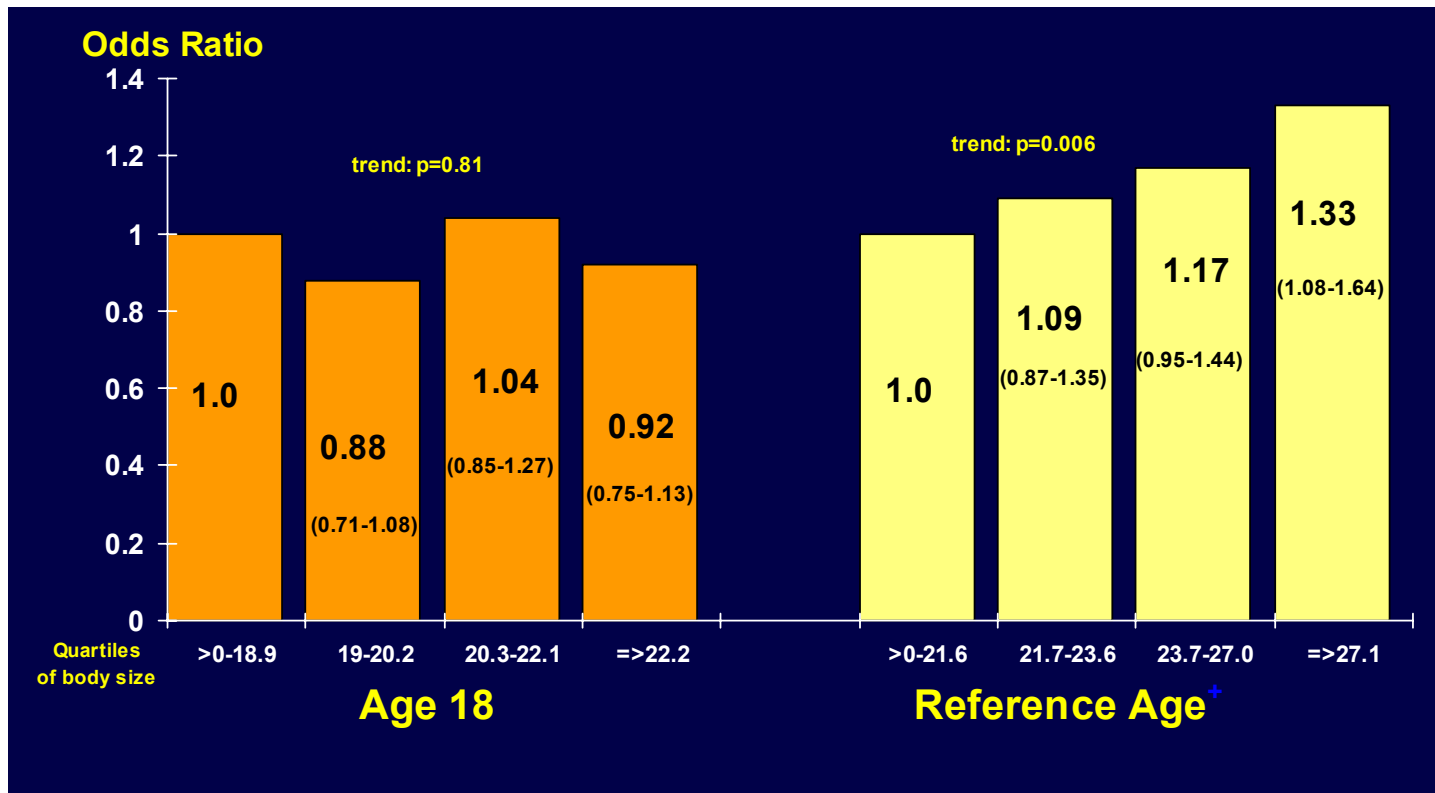
- food availability and portion size
- food content of diet (Hill and Peters 1998)

- **Urbanization**

- promotion of a sedentary lifestyle

- **Culture**

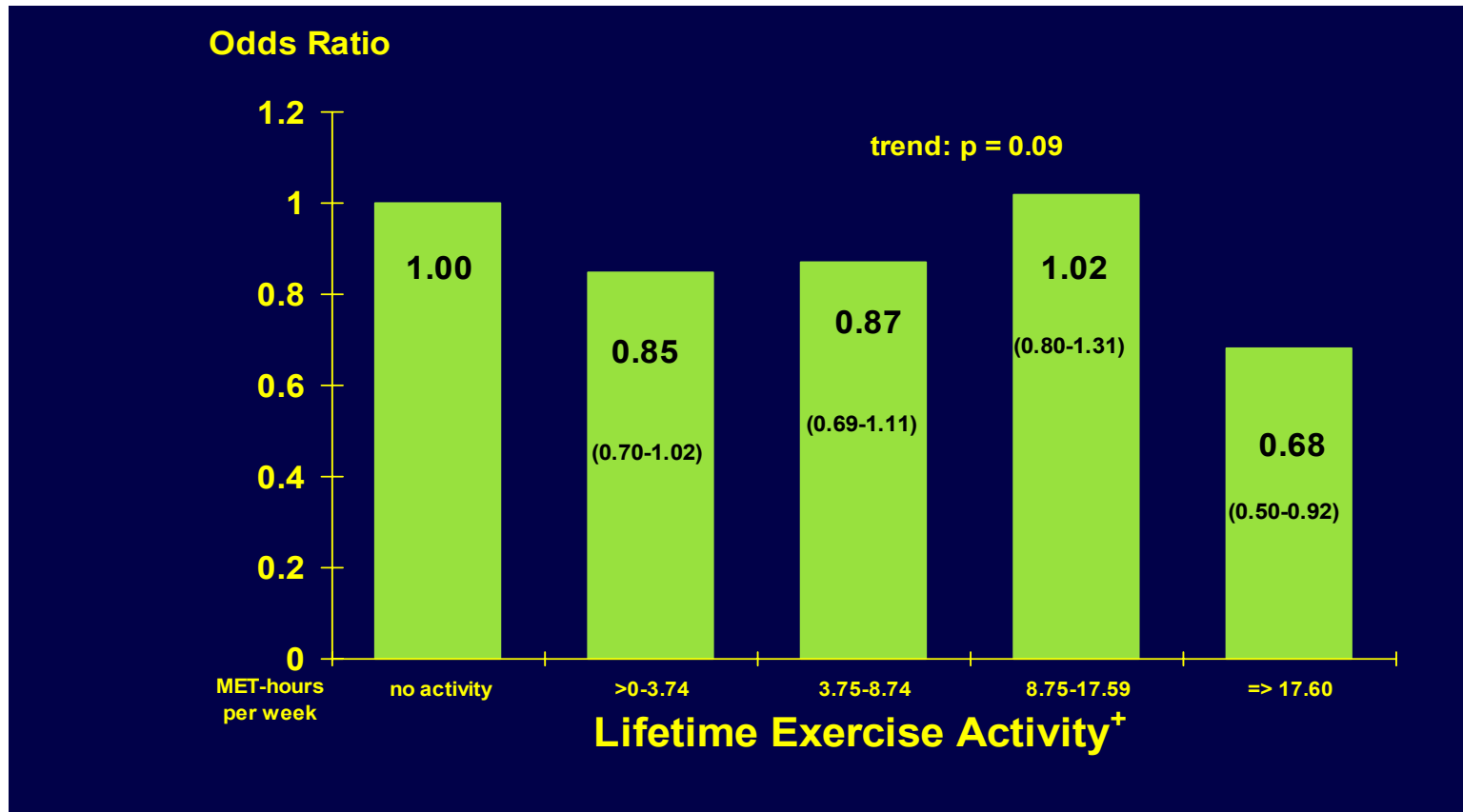
Body Size* at Age 18 and Reference+ Age in Relationship to Breast Cancer Risk Among Postmenopausal Women



*weight (kg)/height²(m)

⁺ 1 year prior to breast cancer diagnosis for cases corresponding date for controls

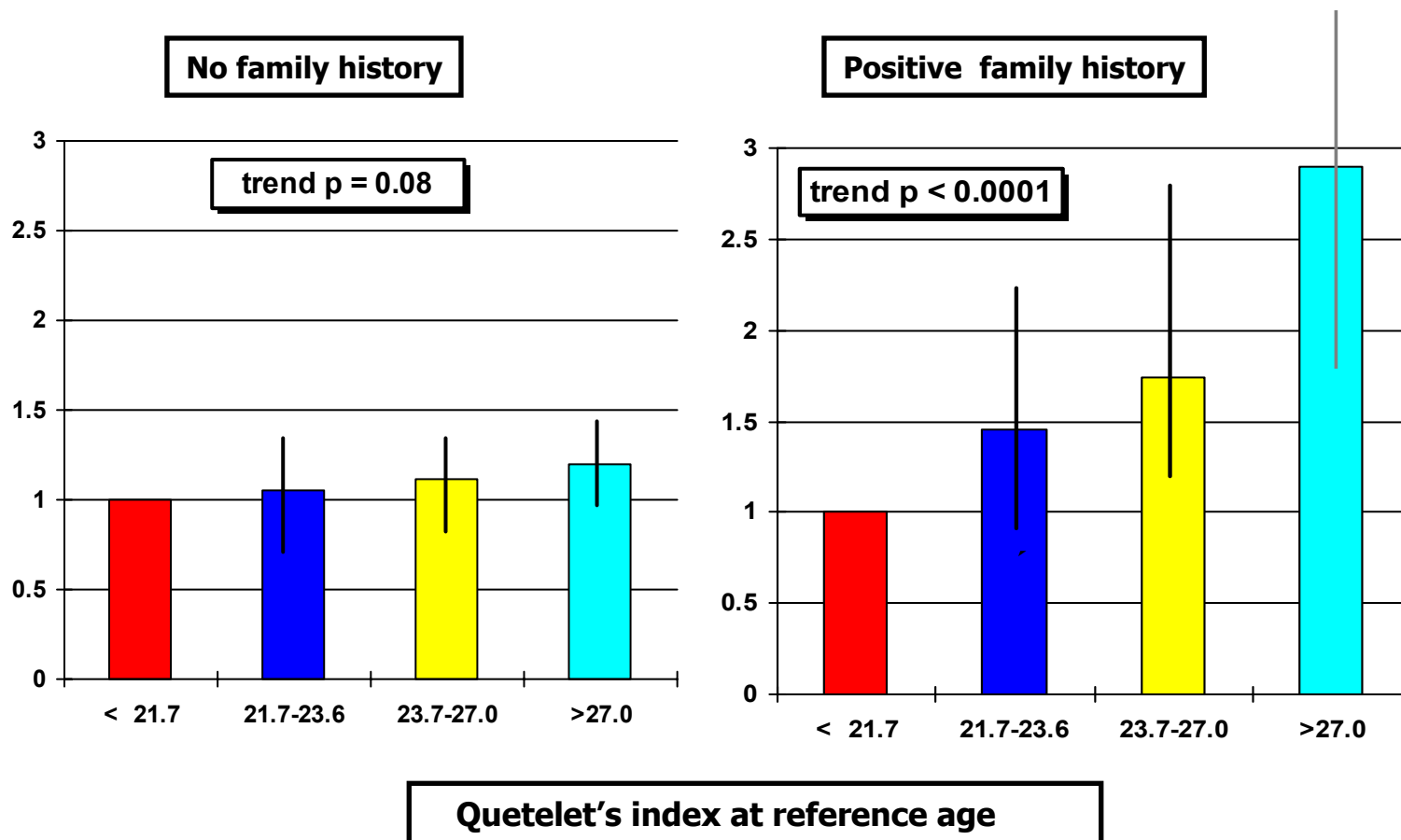
Lifetime Exercise Activity⁺ and Postmenopausal Breast Cancer Risk¹ Among Women Aged 55 to 72



+ Average MET-hours of exercise activity per week from menarche until the reference age.

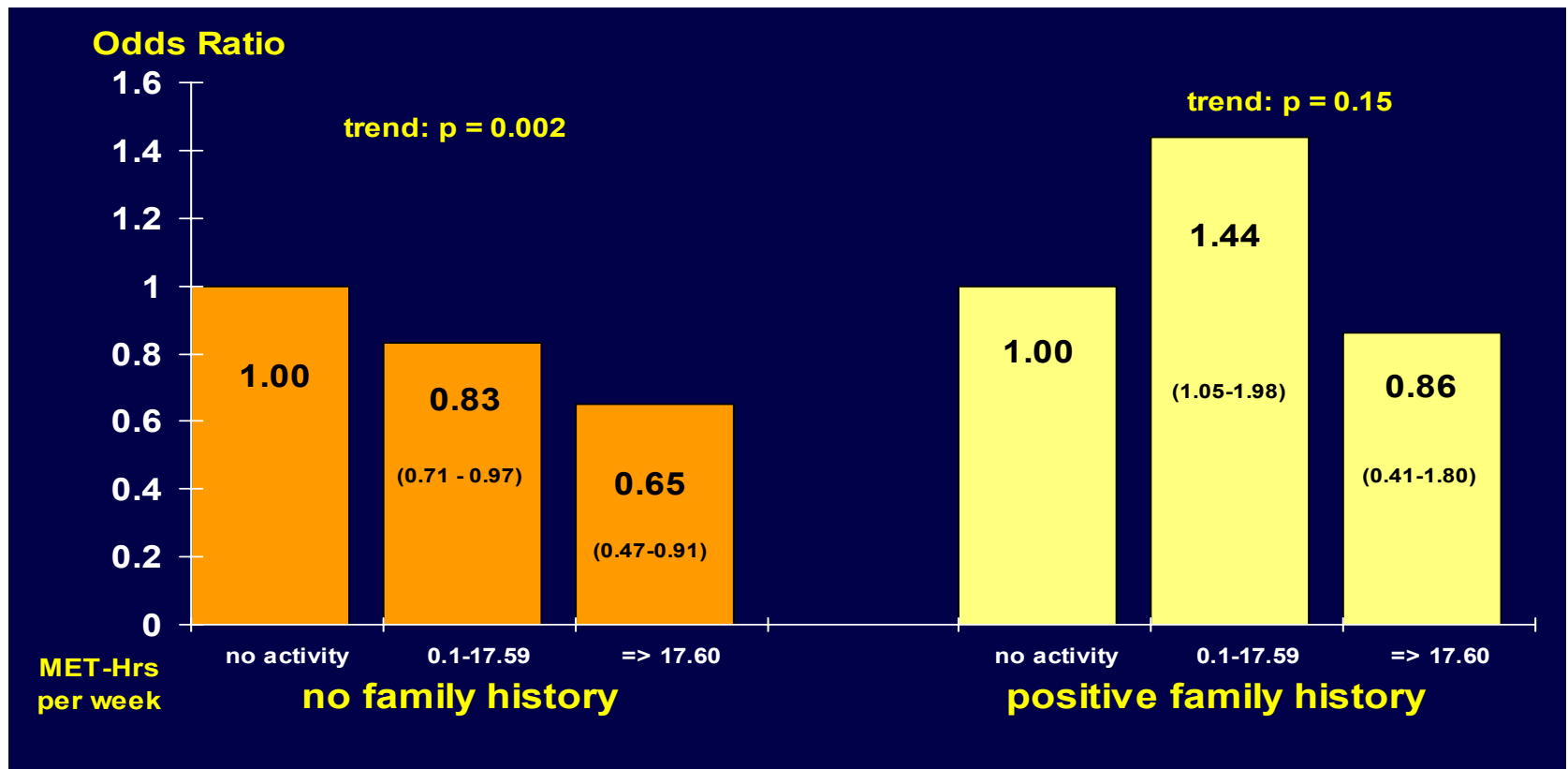
¹ Adjusted for categorical body-mass index at reference age, ages at first term pregnancy, menarche, menopause, family history and interviewer

Breast Cancer Risk of Postmenopausal Women Aged 55-72: Effects of Quetelet's Index at Reference Age and Family History



Adjusted for ages at menarche, menopause, and first term pregnancy, interviewer, and lifetime exercise activity: Data from 1894 cases and 1637 controls

Lifetime Exercise Activity⁺ and Breast Cancer Risk¹ among Postmenopausal Women by Family History of Breast Cancer



+ Average MET-hours of exercise activity per week from menarche until the reference age.

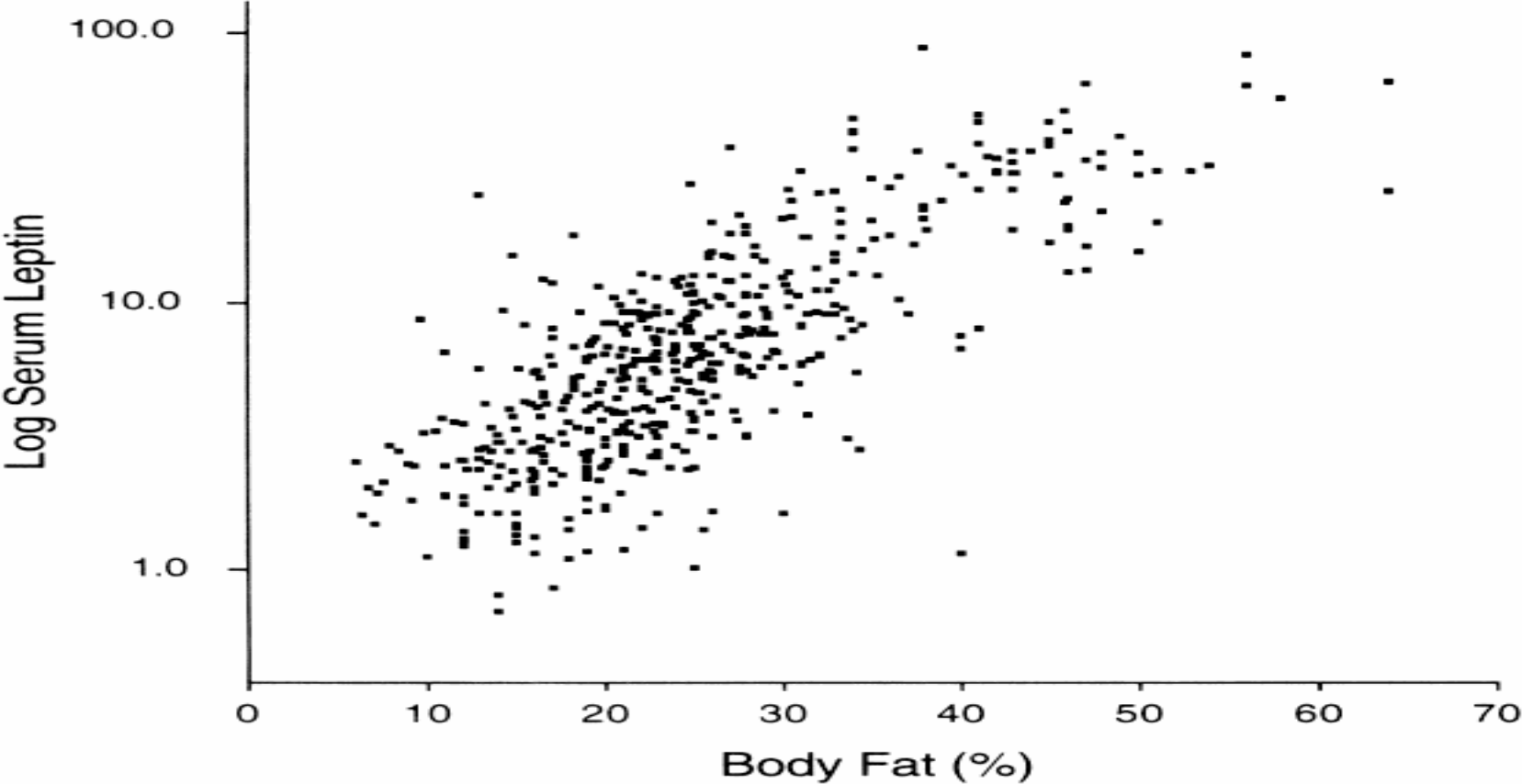
¹ Adjusted for categorical terms for body-mass index at reference age, ages at first term pregnancy menarche, menopause, and interviewer

Breast Cancer Risk Among Postmenopausal Women Aged 55 to 72

Summary of Results

- **Body Size and Family History**
 - Obese women with a family history at much greater risk than obese women without a family history of breast cancer
- **Exercise and Family History**
 - Stronger protective effect of lifetime strenuous exercise independent of body size among women without a family history

Relationship* between Leptin and Body Fat

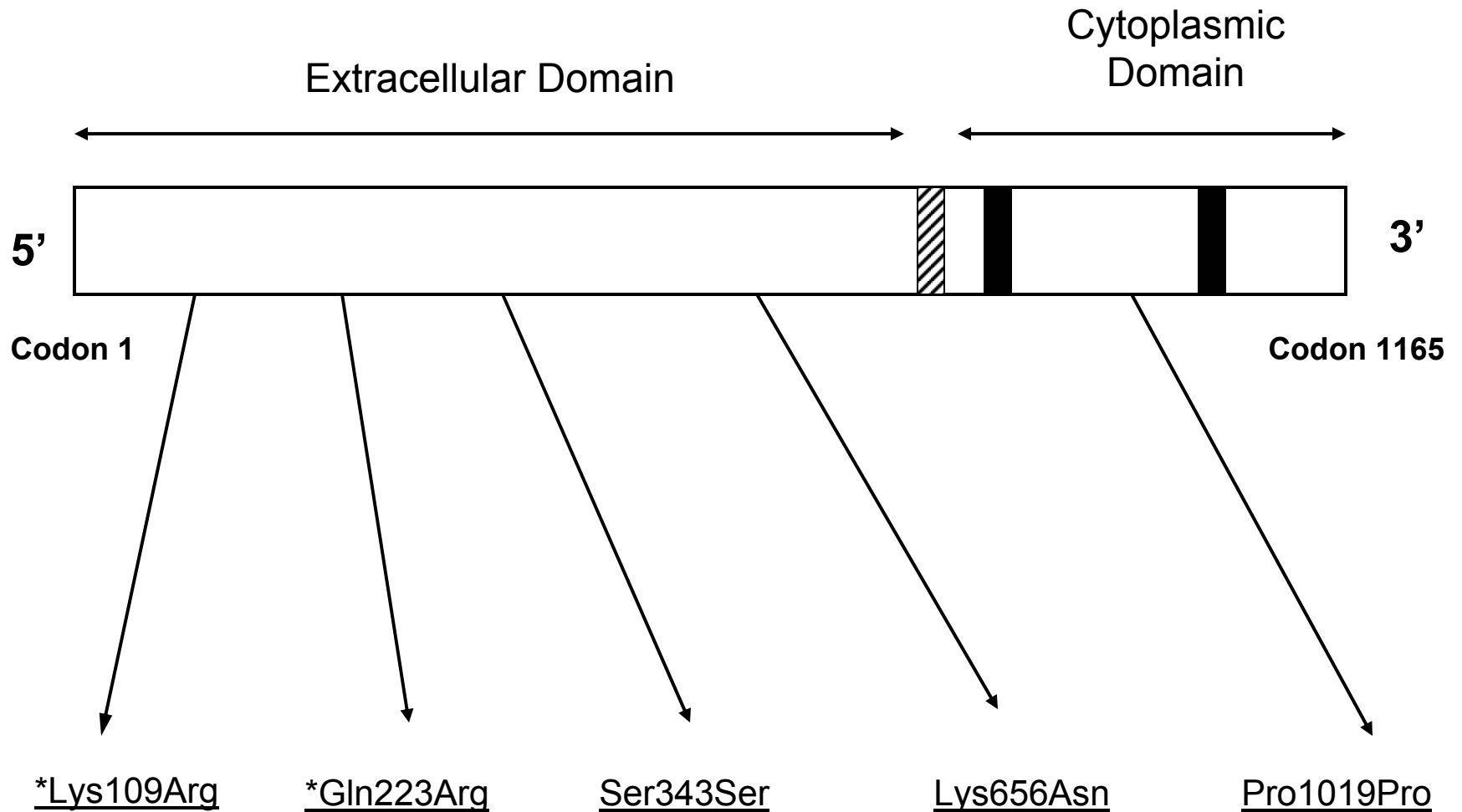


*From Considine et al 1996 and Caro et al 1996

Leptin Receptor Gene (OB-R or LEP-R)

- **Identified in 1995 by Tartaglia**
- **Function**
 - binds to free-circulating leptin released from adipose tissue
- **Polymorphisms**
 - over 12 polymorphic variants have been identified in the intronic and exonic regions of OB-R
 - variants potentially affecting receptor structure and/or function
 - 3 SNPS resulting in amino acid substitutions
 - 1 insertion/deletion polymorphism
- **Location**
 - located on chromosome 1 (1p32)

Human Leptin Receptor cDNA Coding Region



Results from Postmenopausal Women (n=38)

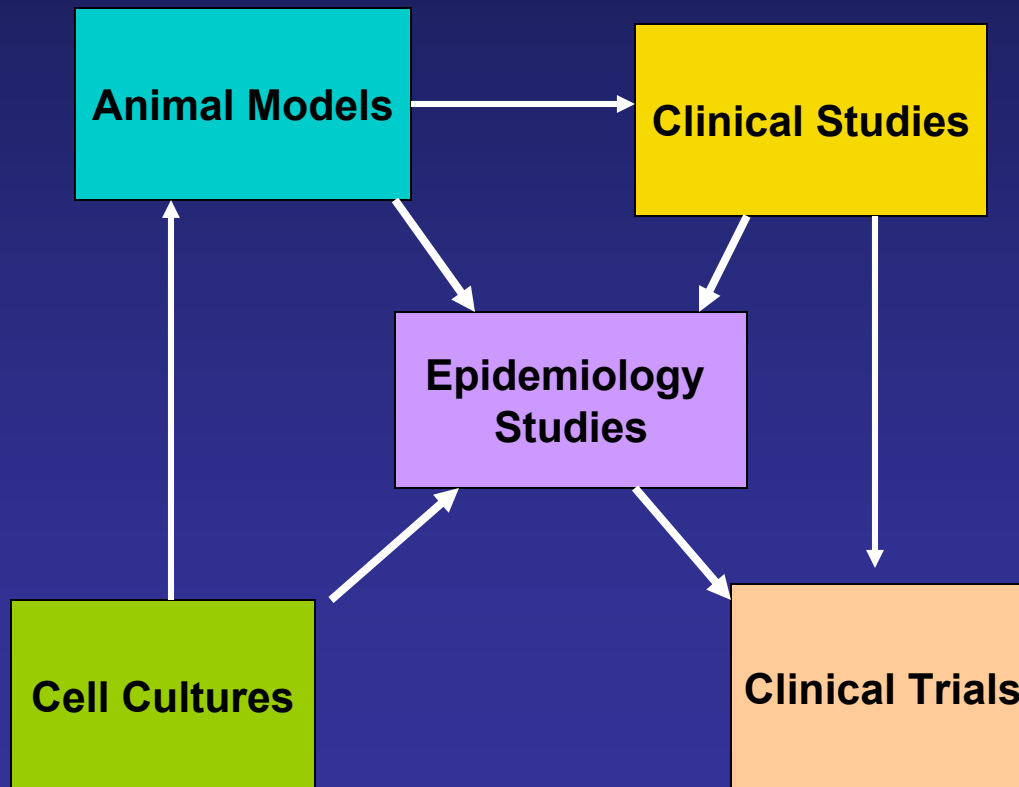
	<u>N</u>	<u>%</u>
<u>Study Population:</u>		
Age	mean = 59.51	
African Americans	9	27.3
Caucasians	25	65.7
Current Use of HRT	18	47.4
Current Use of Anti-depressants	16	44.7
Body-mass index	mean = 36.74	
Percent body fat	mean = 47.30	

Mean BMI and Percent Body Fat by OB-R Variants

	<u>Gln/Gln</u>	<u>Gln/Arg</u>	<u>Arg/Arg</u>
<u>Gln223Arg</u>	(n = 8)	(16)	(14)
Percent Body Fat	42.02	43.86	46.41
Body Mass Index	36.16	46.40	48.98
<u>Lys109Arg</u>	(n = 3)	(14)	(19)
Percent Body Fat	38.27	45.33	50.45**
Body Mass Index	32.12	36.64	37.49

** p < 0.06

Integrated Study Designs of Breast Cancer: Evaluation of Exercise, Diet and Obesity



Present and Future Epidemiology Studies

**‘Genetics, obesity and breast cancer risk’ (funded by CBCRP, 2003)
(Carpenter¹, Ingles², and John³)**

- 1: UCLA Center of Human Nutrition
- 2: USC/Norris Comprehensive Cancer Center
- 3: Northern California Cancer Center

**‘Association of DNA repair gene variations with breast cancer risk as a function of age’ (in review by NCI)
(Anton-Culver¹, Ziogas¹, Peel¹, Mohrenweiser¹, Carpenter²)**

- 1: UCI Division of Epidemiology
- 2: UCLA Center of Human Nutrition

Present and Future Clinical Studies

‘Fruit, Vegetable and Exercise Intervention among Breast Cancer Survivors’ (start-up funding UCLA-CNRU)

(Heber¹, Li¹, and Carpenter¹)

1: UCLA Center of Human Nutrition

‘Effect of Diet and Exercise on Ductal Cells and Fluid Composition among healthy high-risk women’ (future proposed research)

(Heber¹, Love^{1,2}, and Carpenter¹)

1: UCLA Center of Human Nutrition/UCLA Department of Surgery

2: Susan Love MD Breast Cancer Foundation

