Interventions in Cancer Survivors; Issues and Challenges in this Population

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Conflicts

- Consulting:
  - Novartis
  - Proctor & Gamble
  - Zymogenetics
  - Metagenetics
- Stocks
  - Merck

Issues in Cancer Survivors

- Pre-diagnosis obesity, sedentariness, diet patterns

- Diagnosis – physical and emotional effects

- Treatment effects:
  - Surgical effects: direct & lymphedema
  - Adjuvant/neoadjuvant chemotherapy, radiation:
    - Cardiotoxicity
    - Neurotoxicity
    - Fatigue
    - Immune depression
    - Appetite & taste
  - Hormonal agents: musculoskeletal, cardiac effects
  - Steroids
  - Targeted therapies

What is Known: Physical Activity Interventions

- Data for breast, prostate,colorectal, children, ovary, other cancer survivors:
  - Can be recruited:
    - Breast > other
    - Post- primary treatment > during primary treatment
  - Most studies performed in higher-incidence, easier to recruit cancers
  - Quality of life, fatigue, fitness, etc: monitored/gym > home
  - Weight loss is minimal without calorie reduction (as for non-cancer populations)

What is Known: Behavioral Weight Loss Interventions

- Breast
  - Accrual, retention, adherence good
  - Weight loss effect: group + individual > individual only > home
  - Diet or exercise without caloric reduction and weight loss goals produce minimal weight loss
  - Weight loss effect of behavioral interventions lower than in women without cancer?
- No definitive data for other cancers

Breast Cancer Survivors: Weight Loss

- Several feasibility randomized trials

- N=48 – 495+

- Most tested reduced calorie, reduced fat, increased vegetables/fruits

- C. Thomson (Nutr Ca 2010), N=40, 6-mos., BMI 31.8
  - Low carb: - 6.9%
  - Low fat: -7.6%

- H. Thompson RCT in progress (BMC Ca 2011)
  - N=370, 6 months
  - RCT: low carb vs. low fat vs. control
  - Group + individual counseling

Weight Loss Interventions in Breast Cancer Survivors

Study	Type of Intervention	Mean Baseline BMI	N	% Weight Loss: 6 months	% Weight Loss: 12 months
Djuric	Indiv. + group	35	48		9.8
Rock (HWMS)	Group + phone	31	85	7 (4 mos.)	8
Rock (SHAPE)	Group	?	259	5.5	4.5 (18 mos.)
Rock (ENERGY, ongoing)	Group + phone/email	?	first 103	4.3	
Goodwin (LISA)	Indiv. phone, DPP-based	31.3	338	5.6	6.1

Modified Diabetes Prevention Program/Look Ahead in Cancer Survivors

- LISA (Goodwin, PI): breast cancer RCT
  - Individual phone counseling
  - 6% weight loss at 12 months
- Seattle pilots (McTiernan, PI):
  - Breast cancer uncontrolled (after therapy)
    - Group with 2-4 individual meetings, N=17
    - 6% weight loss at 6 months
  - Prostate cancer RCT (diagnosis to surgery)
    - Individual, N=19
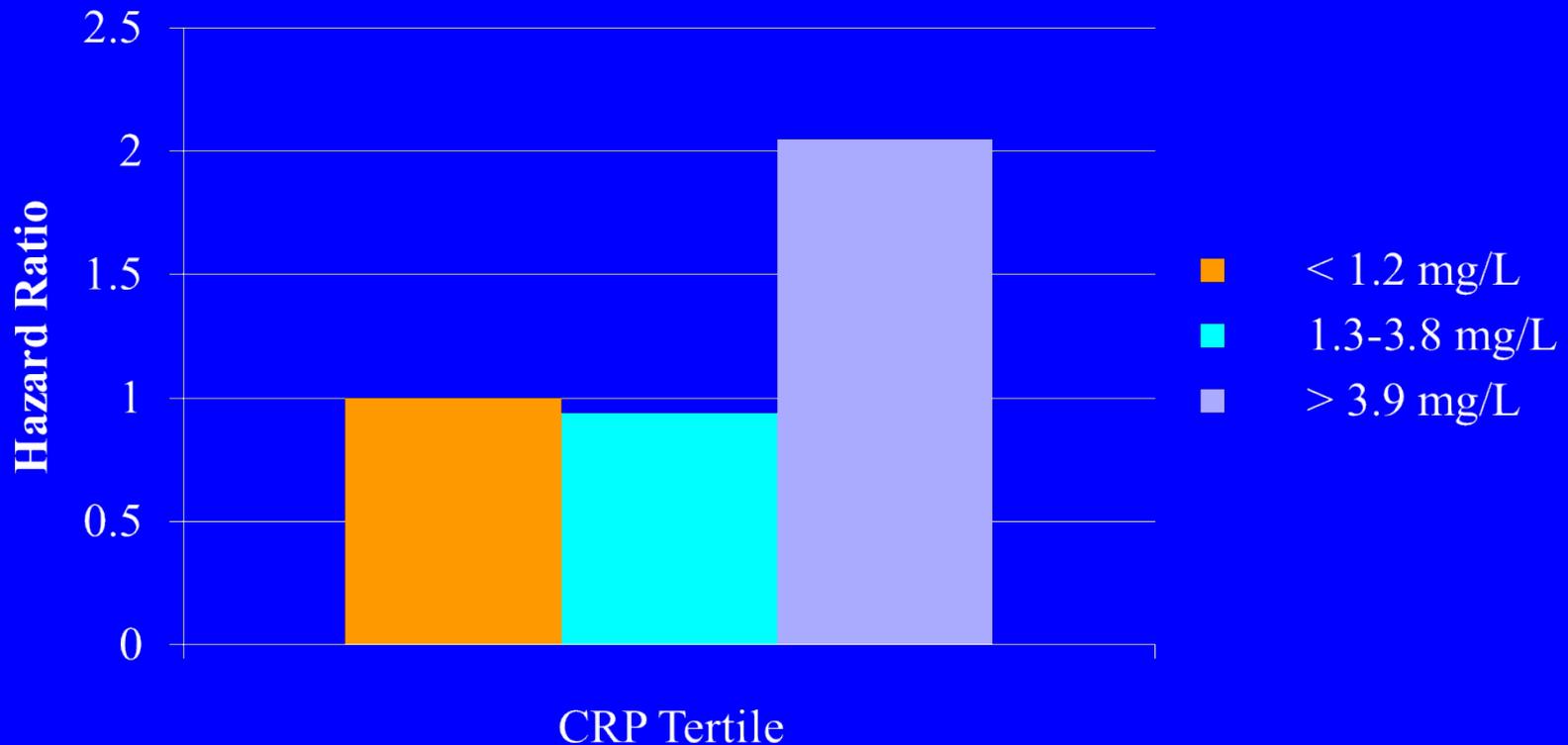   - 3% weight loss at 6 <u>weeks</u>
- Yale breast cancer pilot ongoing (Irwin, PI)

Considerations for Weight Loss Interventions for Cancer Survivors

- Intervention proven in other populations (Diabetes Prevention Program/Look Ahead)
- Target process (insulin, inflammation, sex hormones, other): may affect intervention choice
- Target outcomes (e.g. survival, quality of life)
- Individual survivor needs:
  - Ongoing therapies
  - Exercise limitations, taste/appetite, fatigue
  - Dealing with recurrences & disease progression
  - Adverse effects of weight loss
- Co-morbidities, non-cancer mortality risk

Inflammation and Prognosis

Risk of Death by C-Reactive Protein
(HEAL , 734 stage I-IIIa breast cancer survivors, followed mean 3.8 years)

P trend =0.01

Legend:
- ■ < 1.2 mg/L
- ■ 1.3-3.8 mg/L
- ■ > 3.9 mg/L

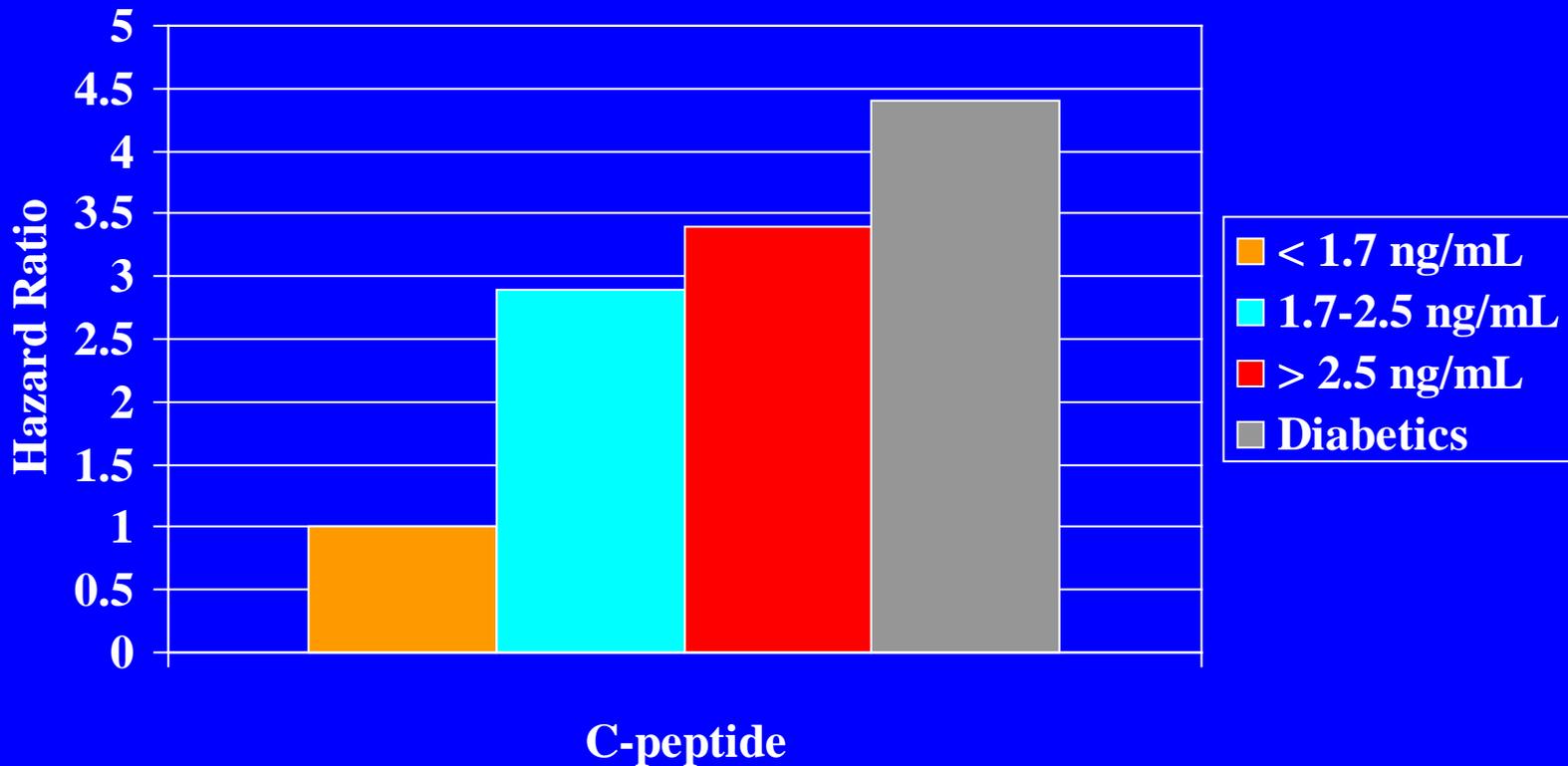Y-axis: Hazard Ratio (0, 0.5, 1, 1.5, 2, 2.5)
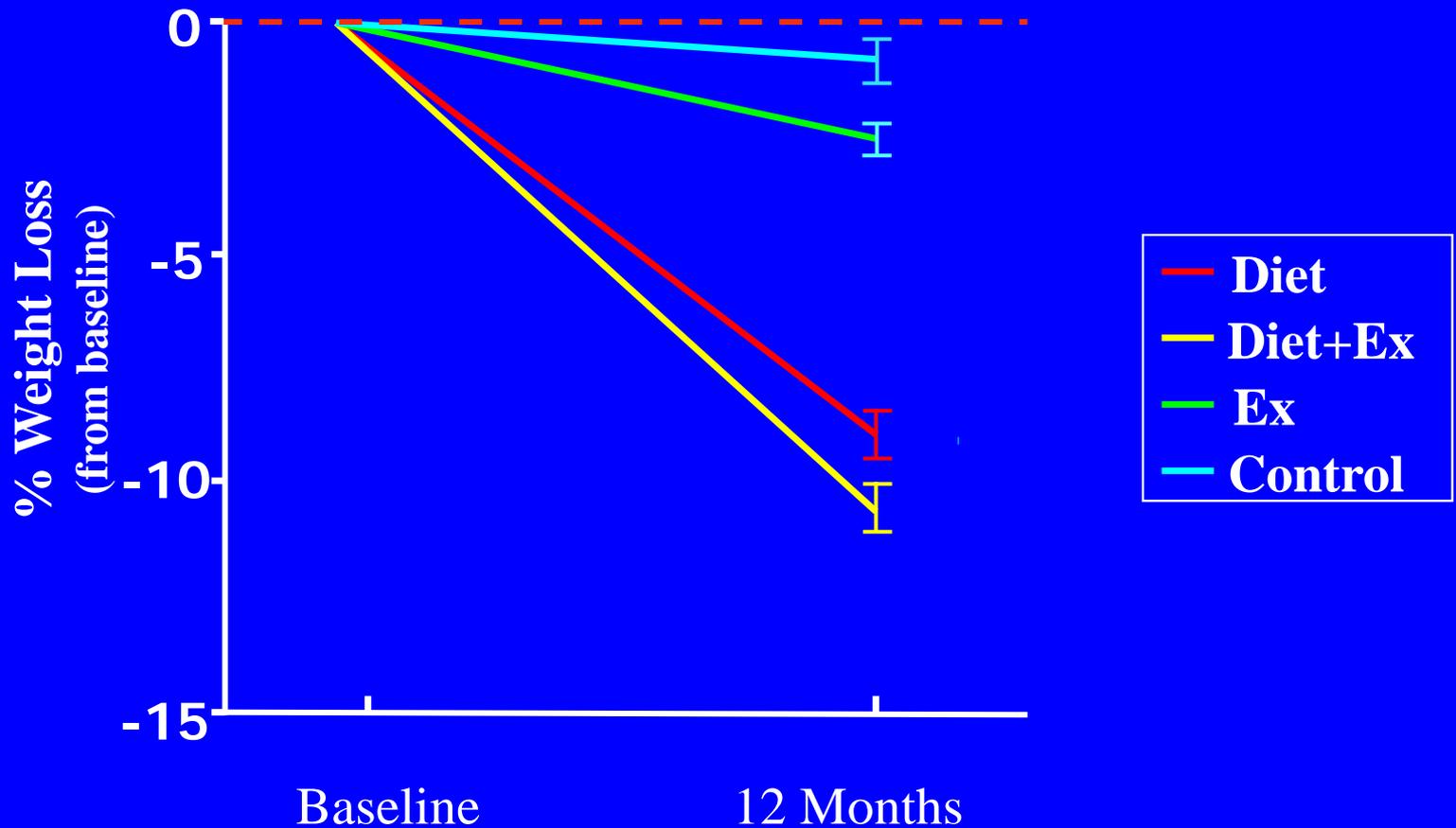X-axis: CRP Tertile

Pierce et al. J Clin Oncol 2009; 27(21):3437-44.

Insulin & Prognosis

Risk of Breast Cancer Death by C-peptide (HEAL, 571 stage I-IIIa patients, followed up mean 4.1 years)
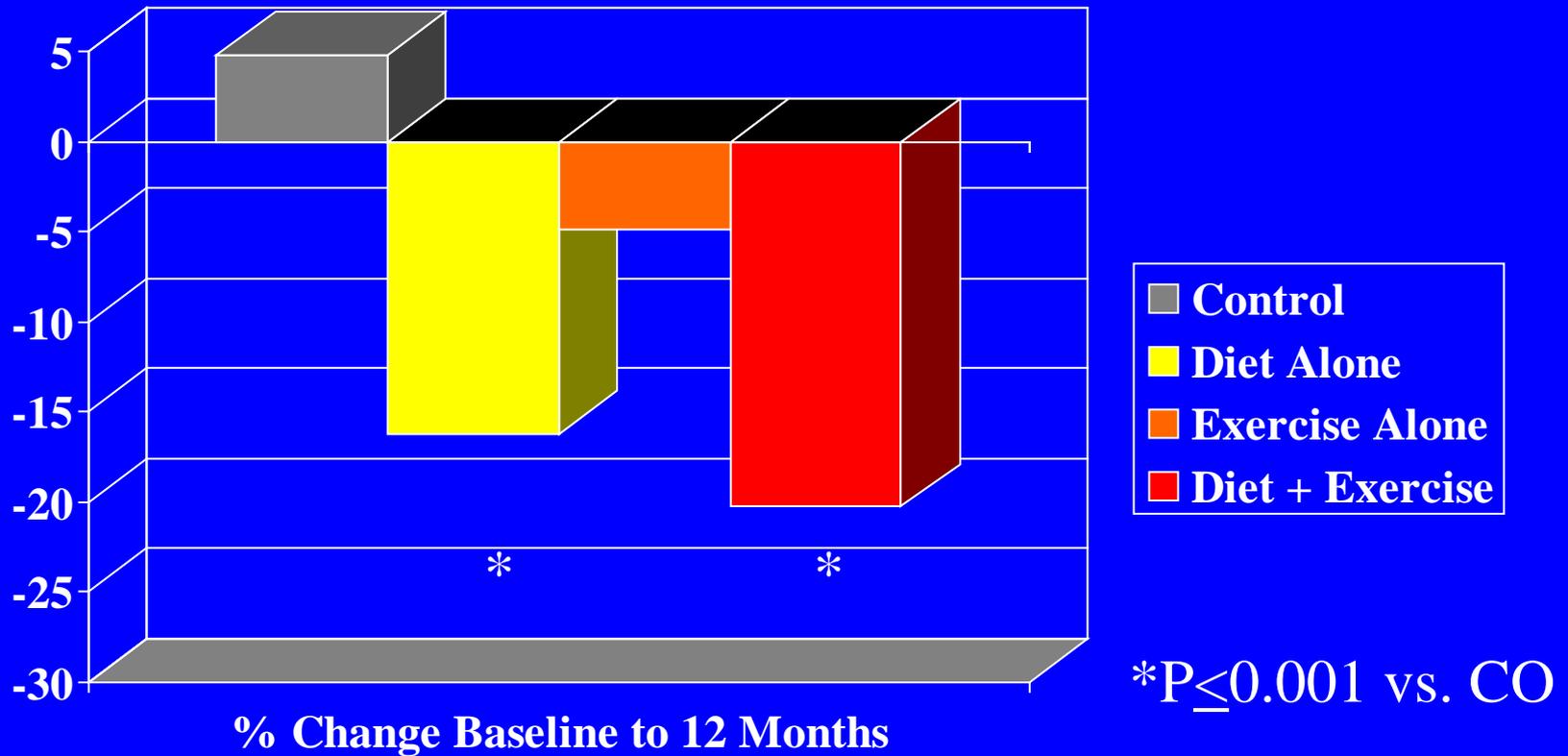
P trend = 0.03

Hazard Ratio

C-peptide

< 1.7 ng/mL
1.7-2.5 ng/mL
> 2.5 ng/mL
Diabetics

Irwin et al. JCO Jan 1;29(1):47-53
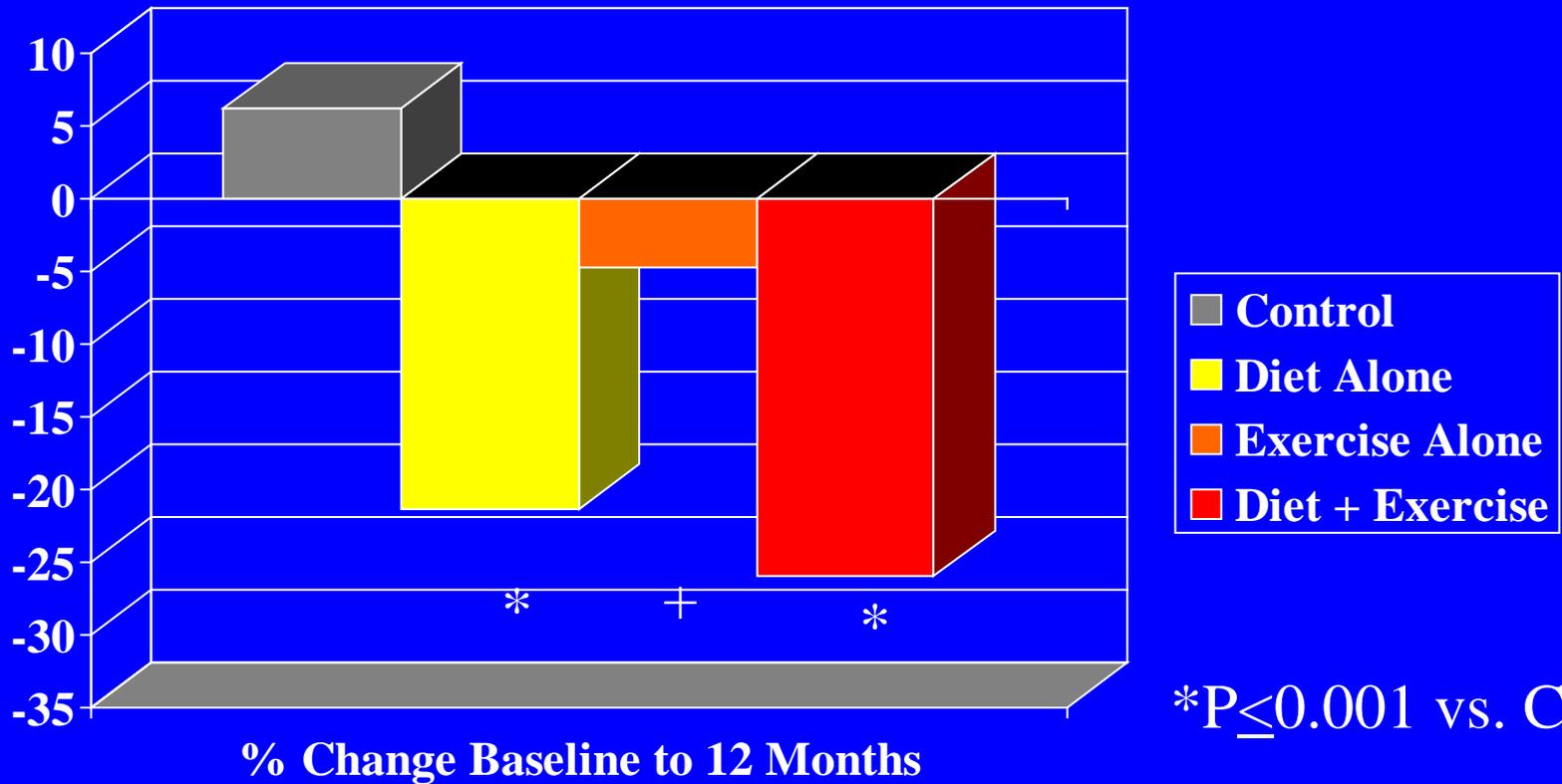
What Intervention Can Best Target Biology Related to Prognosis?

% Weight Change, NEW Trial: Group-Based DPP/Look Ahead, N=438 Postmenopausal Women

(9% missing assumed no change)

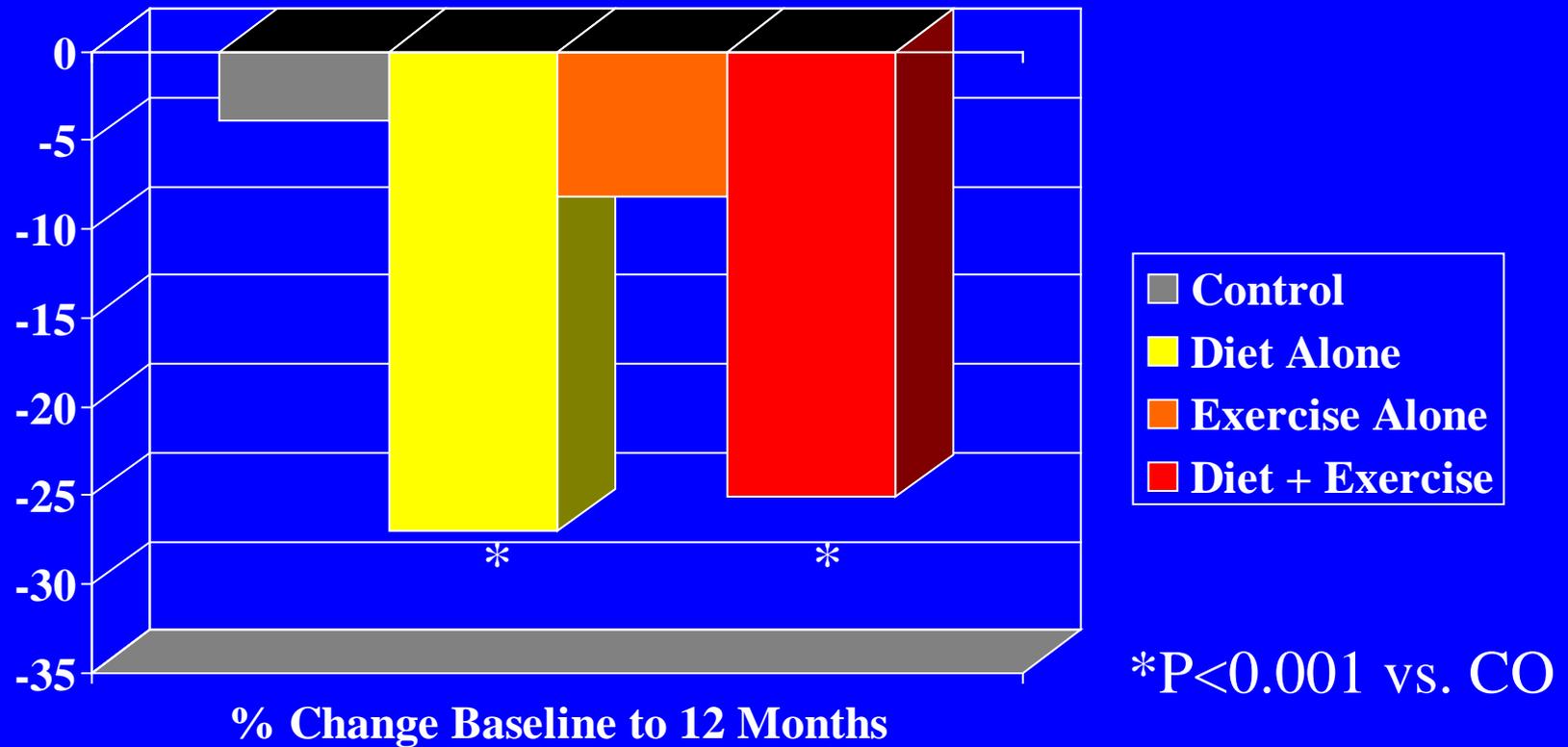Foster-Schubert et al. Obesity 2011 (e-pub)

% Change: Serum Estradiol

% Change Baseline to 12 Months

Legend:
- Control
- Diet Alone
- Exercise Alone
- Diet + Exercise

*P≤0.001 vs. CO

% Free Estradiol Change by Study Arm

% Change Baseline to 12 Months

Control
Diet Alone
Exercise Alone
Diet + Exercise

*P≤0.001 vs. CO
+P=0.08 vs. CO

% Change: Insulin

% Change Baseline to 12 Months

Legend:
- Control
- Diet Alone
- Exercise Alone
- Diet + Exercise

*P<0.001 vs. CO

Mason et al. Am J Prev Med. 2011 Oct;41(4):366-75.

% Change: C-reactive Protein

Imayama et al. The Obesity Society, October 2010

% Change: Interleukin-6

Imayama et al. The Obesity Society, October 2010
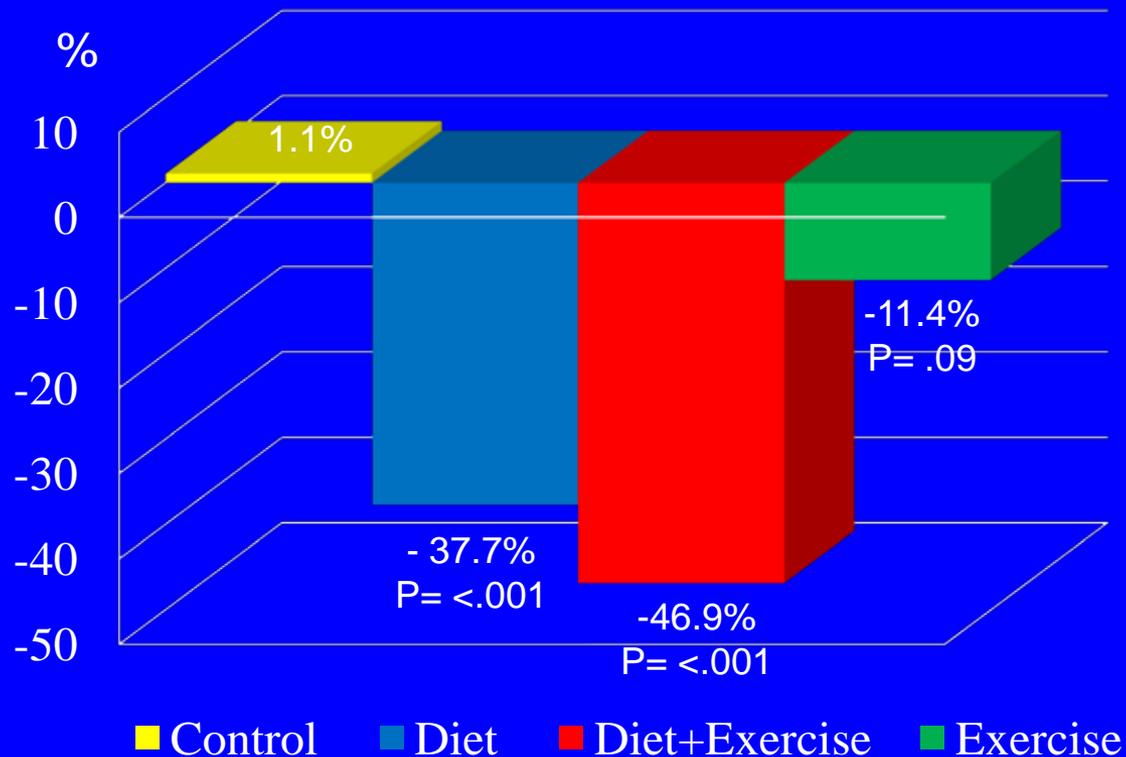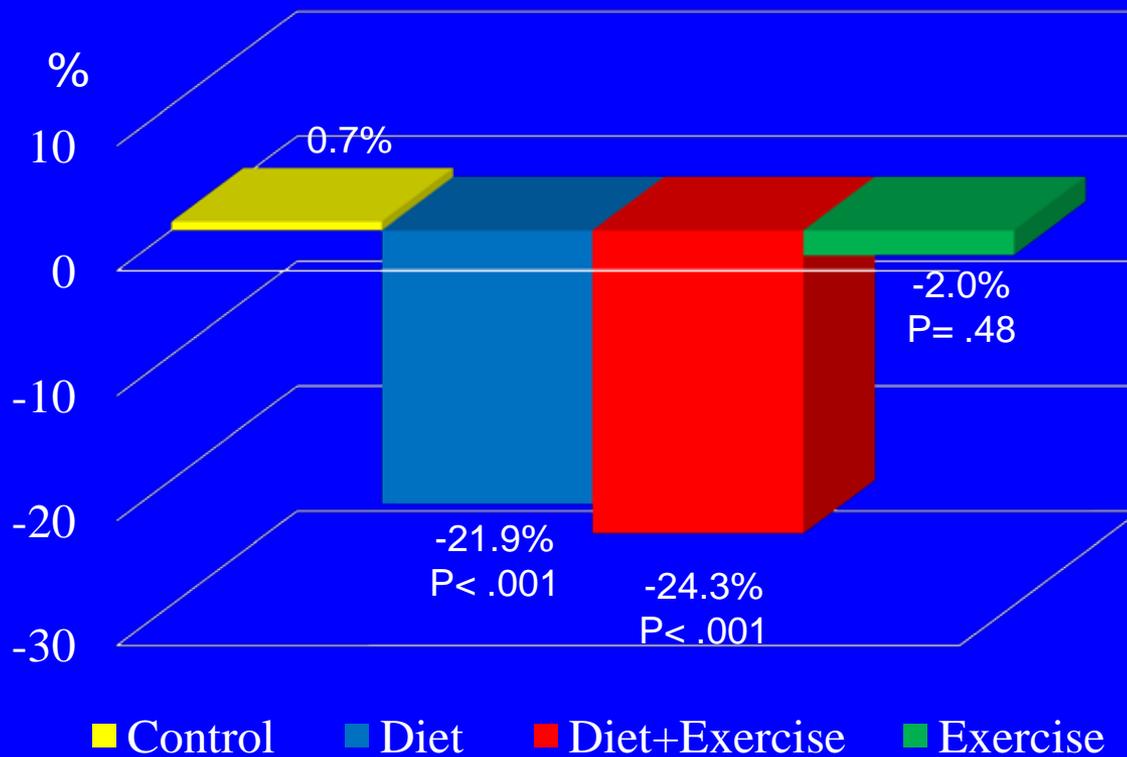
Adverse Effects of Weight Loss in Cancer Survivors?

Weight Change & Prognosis: LACE, 1689 patients, 160 deaths, followed mean 7 years
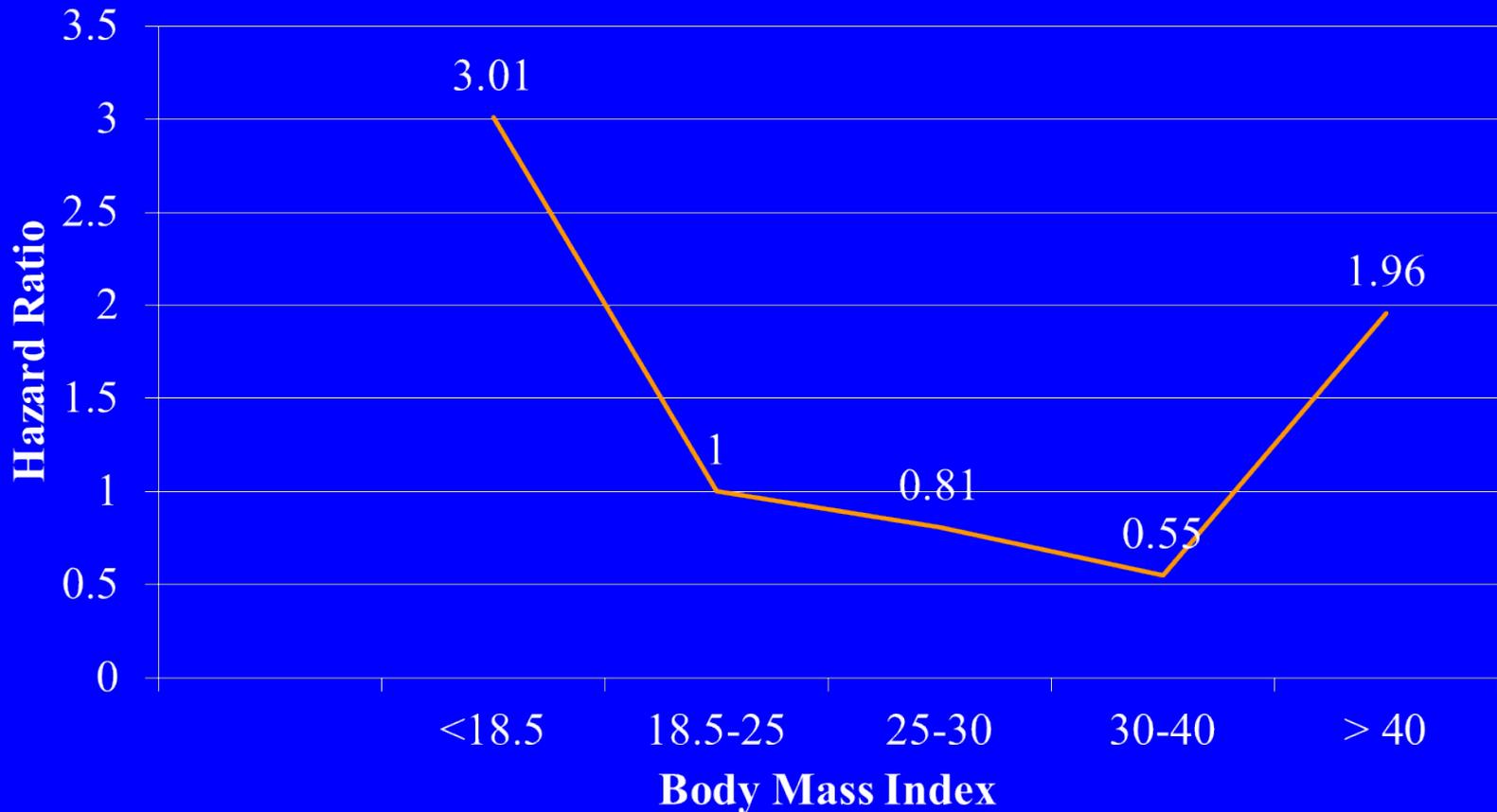
	Recurrences		Deaths	
Wt Change	ER+PR+	ER-PR-	ER+PR+	ER-PR-
↑5-10%	0.7	0.8	1.1	1.3
↑ > 10%	0.6	1.2	0.7	0.8
Stable	1.0	1.0	1.0	1.0
↓5-10%	0.8	1.1	1.1	1.1
↓ > 10%	1.3	2.1*	1.8	2.5*

Caan BJ et al. Ca Causes Cont 2008:19:1319–1328   *p≤0.05

NEW Trial % Change in Leukocytes

Imayama et al. The Obesity Society, October 2010
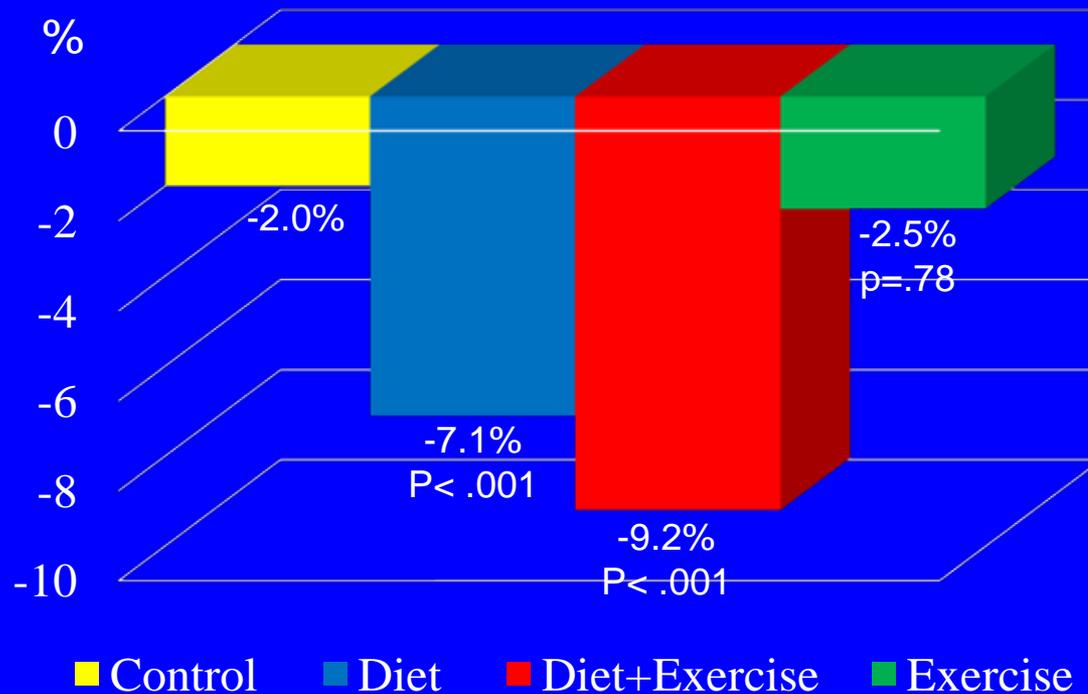
BMI and Risk of Death, HEAL Cohort of Breast Cancer Patients, N=645, Followed Mean 8.5 Years
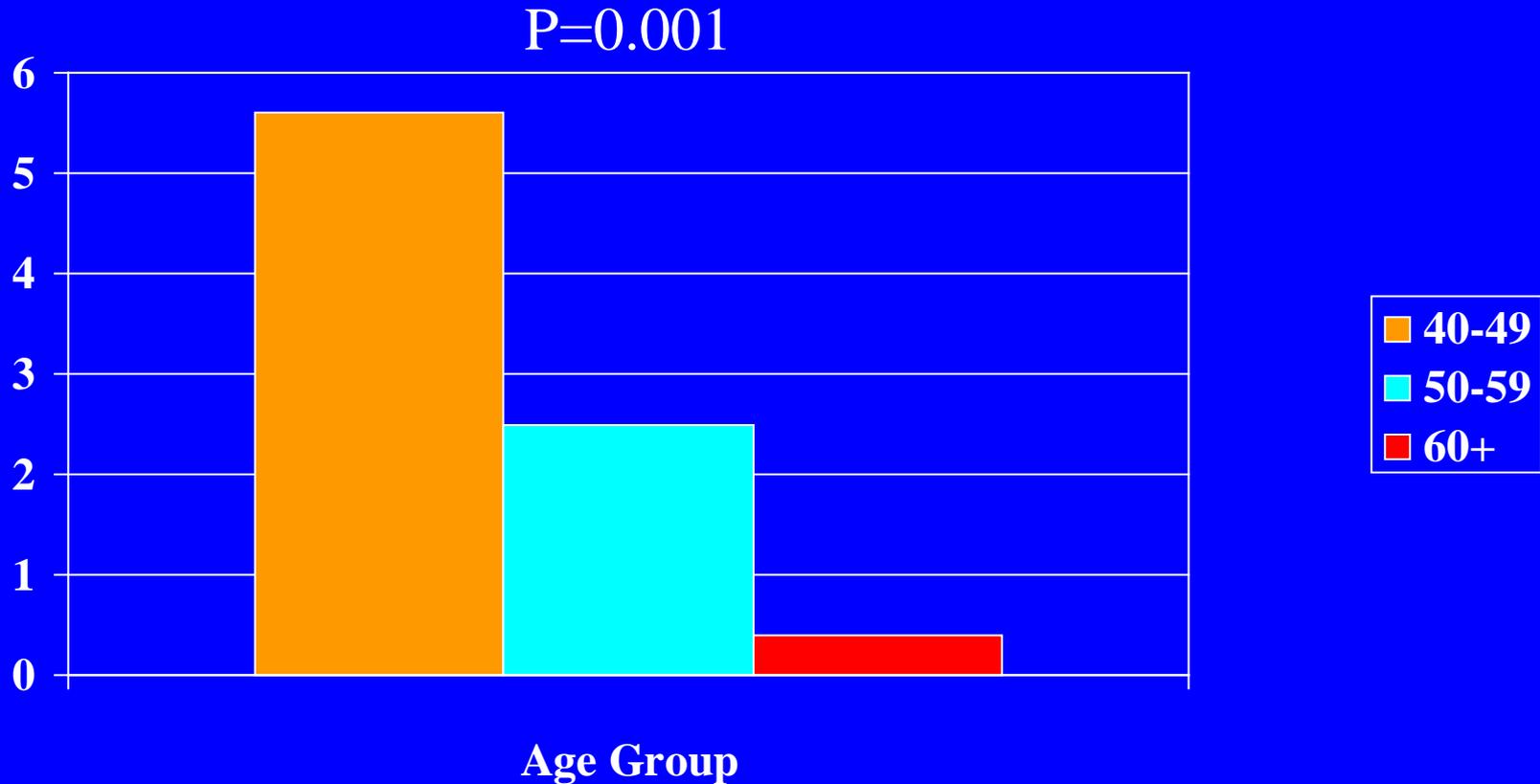
Smith et al, submitted.

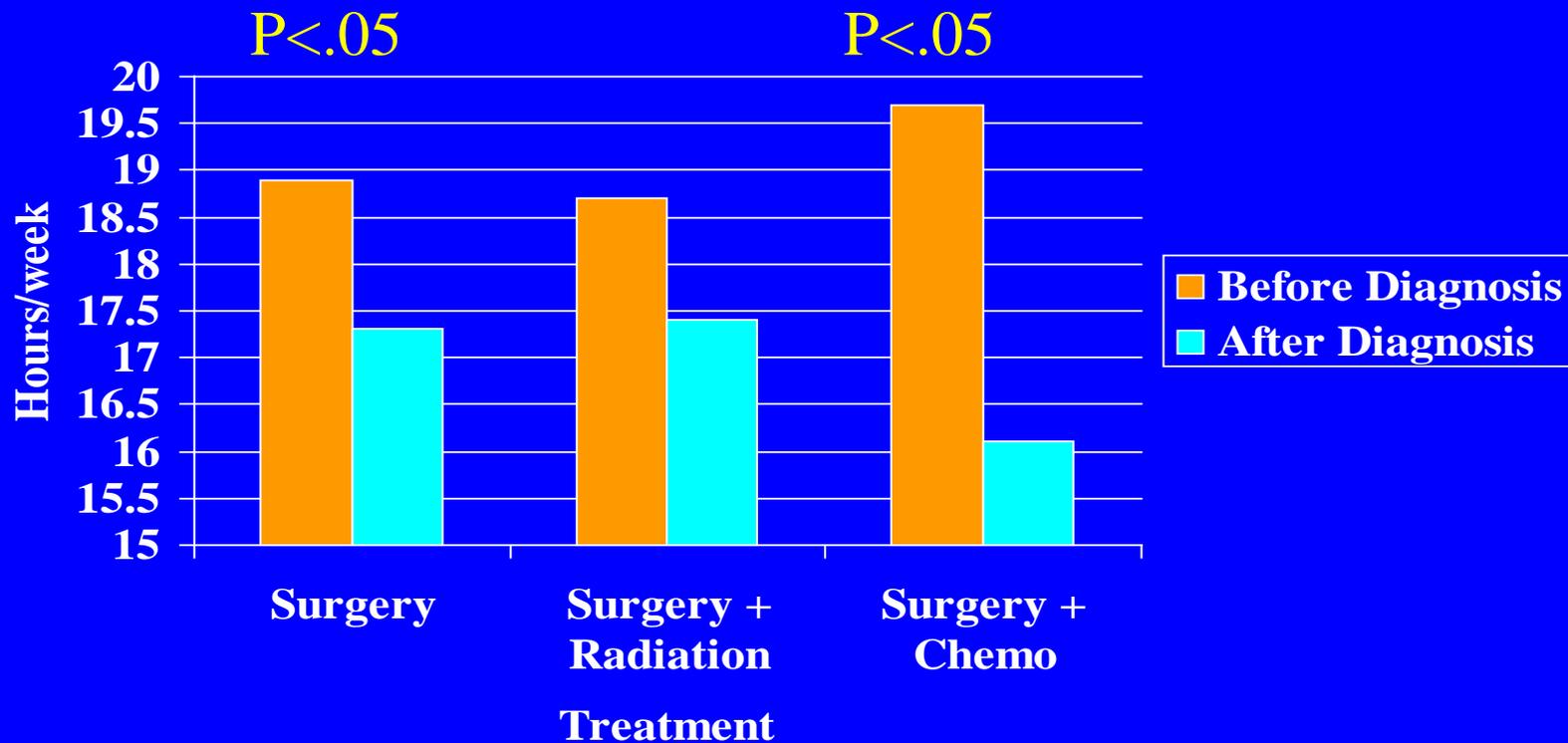# Weight Change (kg) by Stage: HEAL
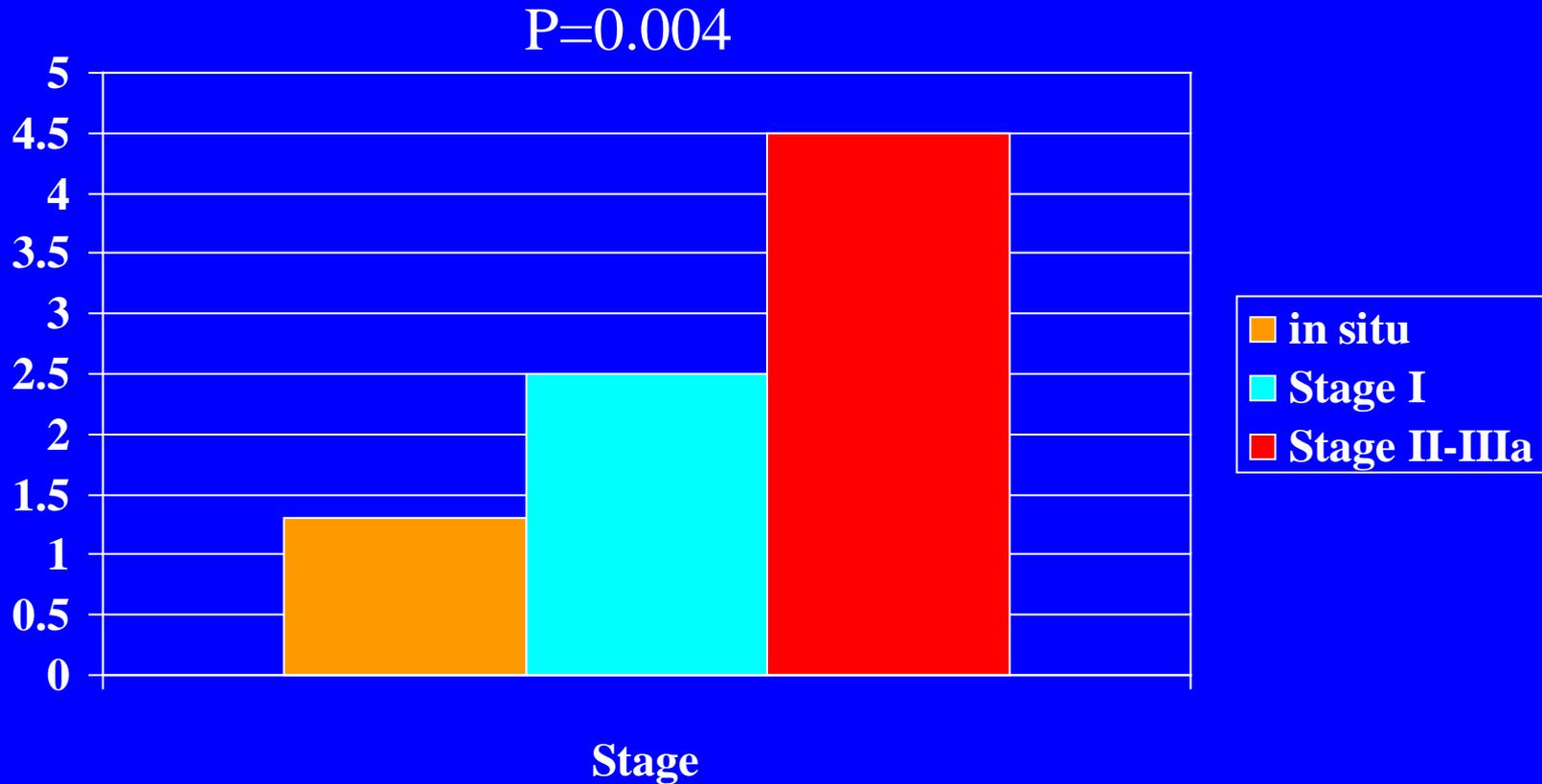
Irwin, M. L. et al. J Clin Oncol; 23:774-782 2005

Weight Change (kg) by Age: HEAL

Irwin, M. L. et al. J Clin Oncol; 23:774-782 2005

Total Physical Activity Before and After Diagnosis in Breast Cancer Survivors by Treatment (HEAL)

Irwin M. et al. Cancer 2003;97:1746-57

What is Not Known in Cancer Survivors: Weight Loss Methods

- Intervention adherence, RCT attrition
- Weight loss maintenance
- Alternate weight loss diets:
  - High protein, high fat, low carb
  - "Mediterranean" (high mono-unsaturated fats, low red meats, high vegetables/fruits)
  - Low glycemic load
  - Prepared meals/meal replacements
- Additive effect of physical activity (resistance and/or aerobic)
- Weight loss medications

What is Not Known in Cancer Survivors: Intervention Costs

- Group plus individual contacts produces most weight loss/exercise adherence effect
- How to deliver "group" experience cheaply
  – Large in-person groups
  – Group phone calls
  – Web
  – Smart phones, other technology
  – Use of existing group structures
- How to deliver individual contacts cheaply
  – Phone
  – Email, IM, smart phone, other technology

What is Not Known in Cancer Survivors: Combination Treatments

- Weight loss diet/exercise + medications targeting same biological pathways:
  - Insulin resistance
    - Metformin
  - Inflammation
    - Statin, NSAIDs, metformin
  - Sex hormones
    - Anti-estrogens, anti-androgens, aromatase inhibitors

What is Not Known in Cancer Survivors: Combination Treatments

- Any combination of:
    - Bariatric surgery
    - Weight loss medications
    - Behavioral weight loss

What is Not Known in Cancer Survivors: Effects in Survivor Groups

- Cancers other than breast
- Children, young adults, older survivors
- Race/ethnicities other than non-Hispanic whites
- High BMI (40+) – usually excluded
- Survivors with:
  - co-morbidities
  - specific treatments
  - disease/treatment sequelae
  - metastatic disease
  - high risk genes

What is Not Known in Cancer Survivors: Dissemination

- RCT participants may have less fatigue, increased vigor, better psychosocial status, better resources, therefore more able to exercise and restrict/change diet

- How to disseminate to the general population of survivors?

- How to incorporate into clinical/community practice

What is Not Known in Cancer Survivors: Adverse Effects

- Are there survivors who should not do vigorous activity?
- Should cancer survivors have functional cardiac screening before starting an exercise program?
- Are there survivors who should not lose weight?
- Is there a maximum safe amount of weight loss?
- Are there clinical markers to follow for adverse effects?
- For some cancers, mortality risk starts at BMI 35+: should weight loss efforts be focused on obese?
- Will intentional weight loss affect chemotherapy efficacy for recurrences?

Recommendations for RCTs

- Use interventions with maximal weight loss effect?
- Individualize goals and choices
- Screen for cancer treatment toxicities
- Power for subgroup analyses or do separate RCTs:
  - Cancer site, subtype, and stage
  - Gender
  - Age group
  - Race/ethnicity
- Determine long-term effects
- Monitor and report adverse effects
- Monitor for other disease endpoints/mortality
- RCTs with survival endpoints must plan for high survival in some cancer populations

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