Dissecting the Obesity/Cancer Link:

Clinical Evidence

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Role of Obesity in Cancer Survival and Recurrence

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DANA-FARBER/BRIGHAM AND WOMEN'S
CANCER CENTER

Dissecting the Obesity/Cancer Link:

Caloric intake/Diet

Exercise

Weight

Have all been linked to cancer outcomes…

Do we have enough evidence to determine which factor (or factors) is most important?

Dozens of studies show obesity linked to poor prognosis in early stage breast cancer

Meta-analysis of obesity and survival in 45 studies published before 2005

	Breast Cancer-Specific HR [95% CI]	Overall HR [95% CI]
All Studies	**1.33 [1.19-1.50]**	**1.33 [1.21-1.47]**

Adverse prognostic effect of obesity seen regardless of:

- Menopausal status
- Type of study (observational vs. treatment cohort)
- Weight measure
- Year of report

Protani et al. BCRT 2010; 23:627-635

Several studies evaluate weight and outcomes in colorectal cancer; results are less consistent

Author	N	Outcome	Hazard Ratio (95% CI) or P value (compared to normal weight)
Tartter	279	Recur Rate	**P = 0.003 for above median weight**
Meyerhardt	3759	DFS	1.11 (0.94-1.30) BMI $\geq$ 30 kg/m^2
Meyerhardt	1792 rectal	DFS	1.10 (0.91-1.32) BMI $\geq$ 30 kg/m^2
		OS	1.09 (0.90-1.33) BMI $\geq$ 30 kg/m^2
Dignam	4288	DFS	1.06 (0.93-1.21) BMI 30-34.9 kg/m^2 **1.27 (1.05-1.53) BMI $\geq$ 35 kg/m^2**
Meyerhardt	1053	DFS	1.00 (0.72-1.40) BMI 30-34.9 kg/m^2 1.24 (0.84-1.83) BMI $\geq$ 35 kg/m^2
Hines	496	OS	**0.77 (0.61-0.97) BMI $\geq$ 25 all stages** 0.92 (0.65-1.30) stage I-II 0.92 (0.59-1.45) stage III 0.58 (0.37-0.90) stage IV

Meyerhardt et al. J Clin Onc 2010; 28.

Obesity associated with worse outcomes in men undergoing prostatectomy for prostate Ca

- Obesity associated with more aggressive phenotype
  - Higher gleason scores
  - More likely to extend beyond prostate
- Higher rates of biochemical (PSA) failure in obese men after radical prostatectomy (RP)
  - Amling et al: BMI ≥ 30 associated with significantly increased rates of PSA ≥0.2 ng/ml after RP (P=0.027)
  - Freedland et al: BMI ≥35 associated with increased risk of PSA failure after RP (p=0.002)

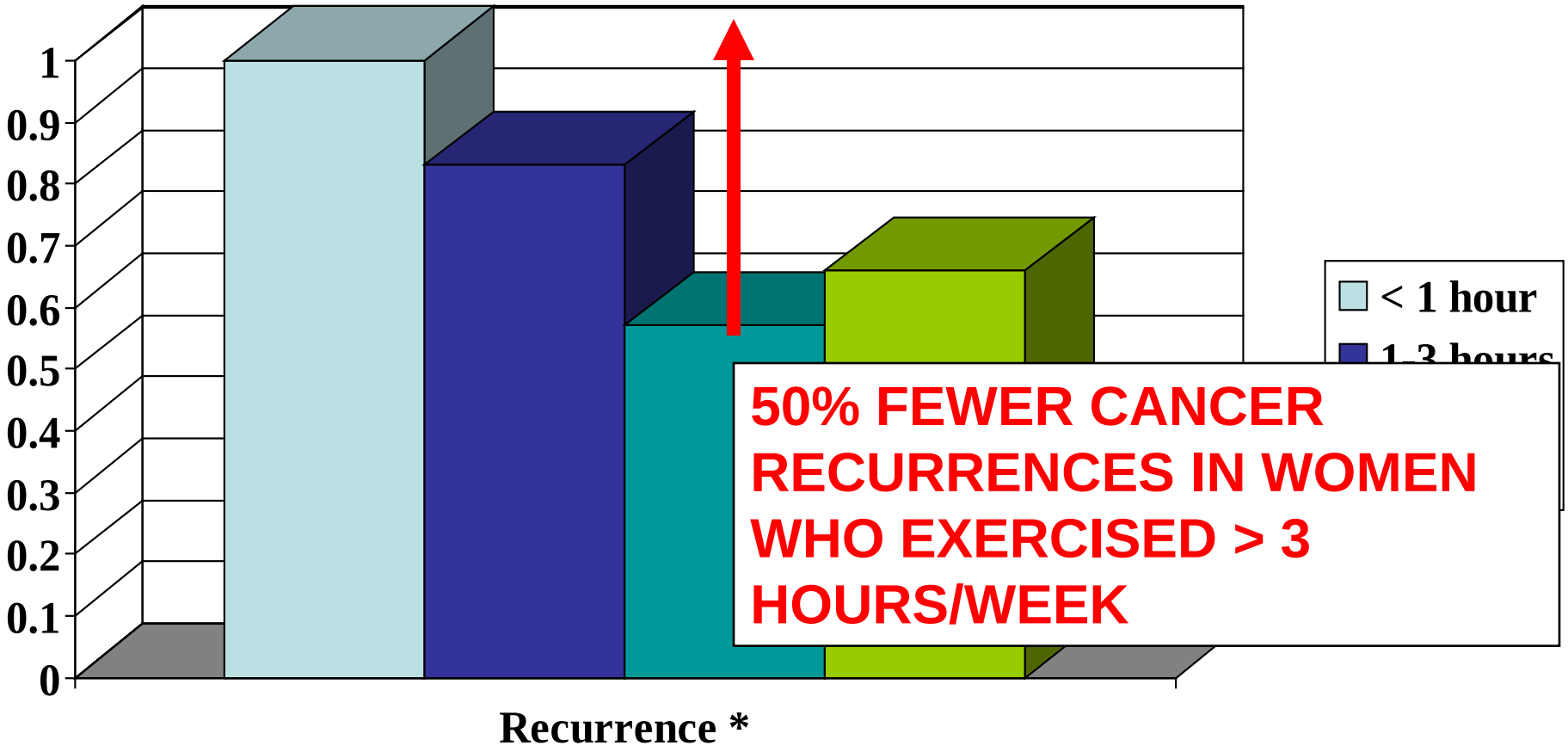
Amling et al. JCO, 2004. Freedlander et al, JCO, 2004.

Observational evidence also suggests link between physical activity and breast cancer prognosis

Study	N	Patient population	Timing of exercise
NHS	2987	Pre- and post	2+ yrs post-dx
CWLS	4482	Pre- and post-	5+ yrs post-dx
HEAL	933	Pre and Post-	Pre- and post-dx
Shanghai	4826	Pre and post	Post-dx
Abrahmson et al	1264	Pre-	Pre-dx

Holmes M et al JAMA 2005; Holick C et al. CEBP 2008; Chen et al. 2011, Canc Prev Res; Irwin ML et al JCO, 2008.

Nurses' Health Study: Physical activity after breast cancer diagnosis



*p=0.05

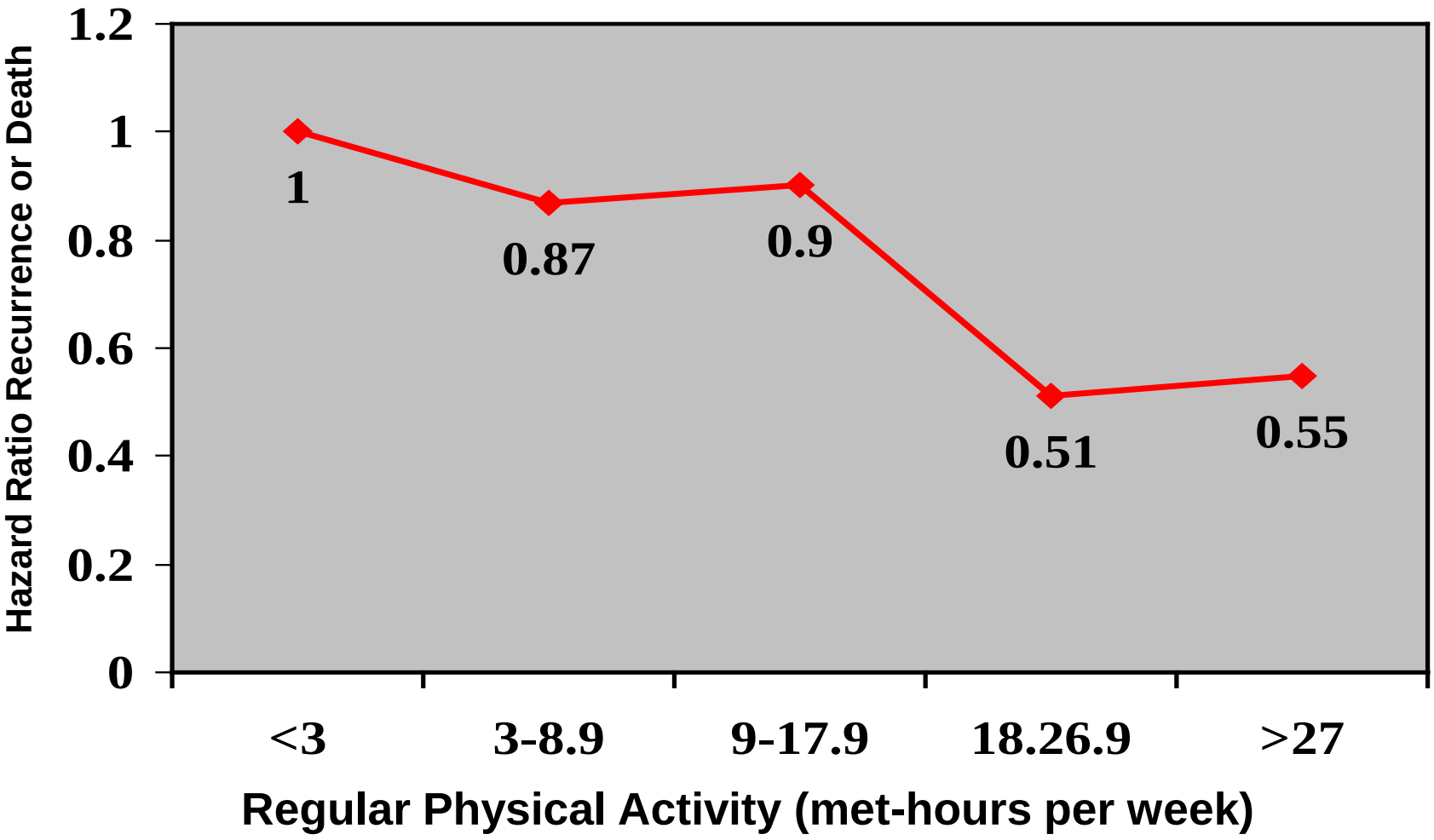
Holmes et al. JAMA 2005; 293: 2479-2486

Several studies also show a link between PA and outcomes in colorectal cancer

- CALGB 89803: Prospective study of 832 patients with Stage III colon CA enrolled in adjuvant chemotherapy trial
- Looked at relationship between recreational exercise 6 months post therapy and risk of recurrence and death
- Calculated weekly MET-hrs of weekly activity
  - One MET-hr = amount of energy expended sitting quietly for one hour
  - Twelve MET-hrs = energy required to run for one hour

Meyerhardt, J. A. et al. J Clin Oncol; 24:3535-3541 2006

89803 and Exercise: Disease-Free Survival in Stage III Colon Cancer Survivors

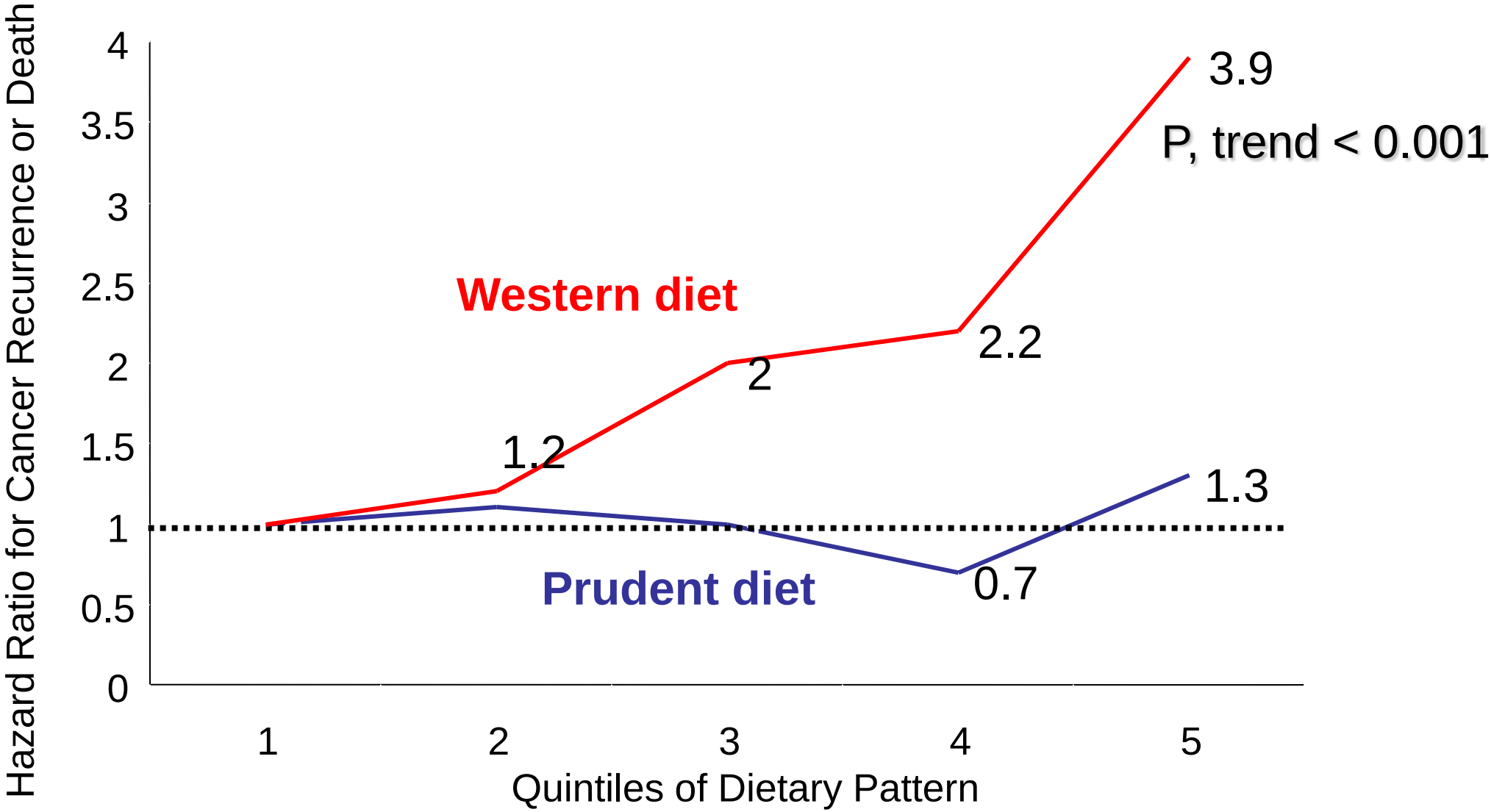


Meyerhardt, J. A. et al. J Clin Oncol; 24:3535-3541 2006

Dietary patterns also linked to prognosis in colorectal cancer

- Western and prudent pattern diets predictive of heart disease, diabetes, colorectal cancer
- Prudent pattern: high intakes of vegetables, fruit, legumes, whole grains, fish, and poultry
- Western pattern: high intakes of red meat, processed meat, refined grains, sweets and dessert, French fries, and high-fat dairy products

CALGB 89803: DFS By Dietary Pattern



Meyerhardt, J. et al. JAMA 2007298(7):754-764.

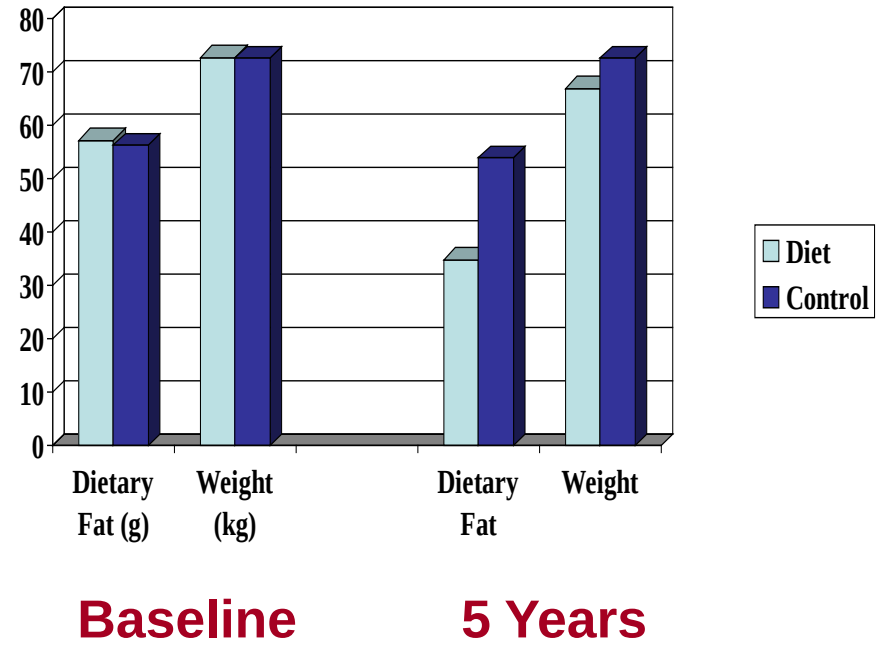
Dissecting the Obesity/Cancer Link

- Observational evidence show relationships between cancer and individual aspects of energy balance:
  - Weight
  - Physical activity
  - Diet

- How do we determine which factors are most important?
  - Optimal data:
    - Randomized trials testing the impact of different energy balance factors on cancer risk and outcomes *(not available)*
  - Available data:
    - RCT's testing impact of one factor on cancer risk/outcomes
    - Studies looking at the impact of energy balance interventions upon biomarkers linked to cancer risk/outcomes

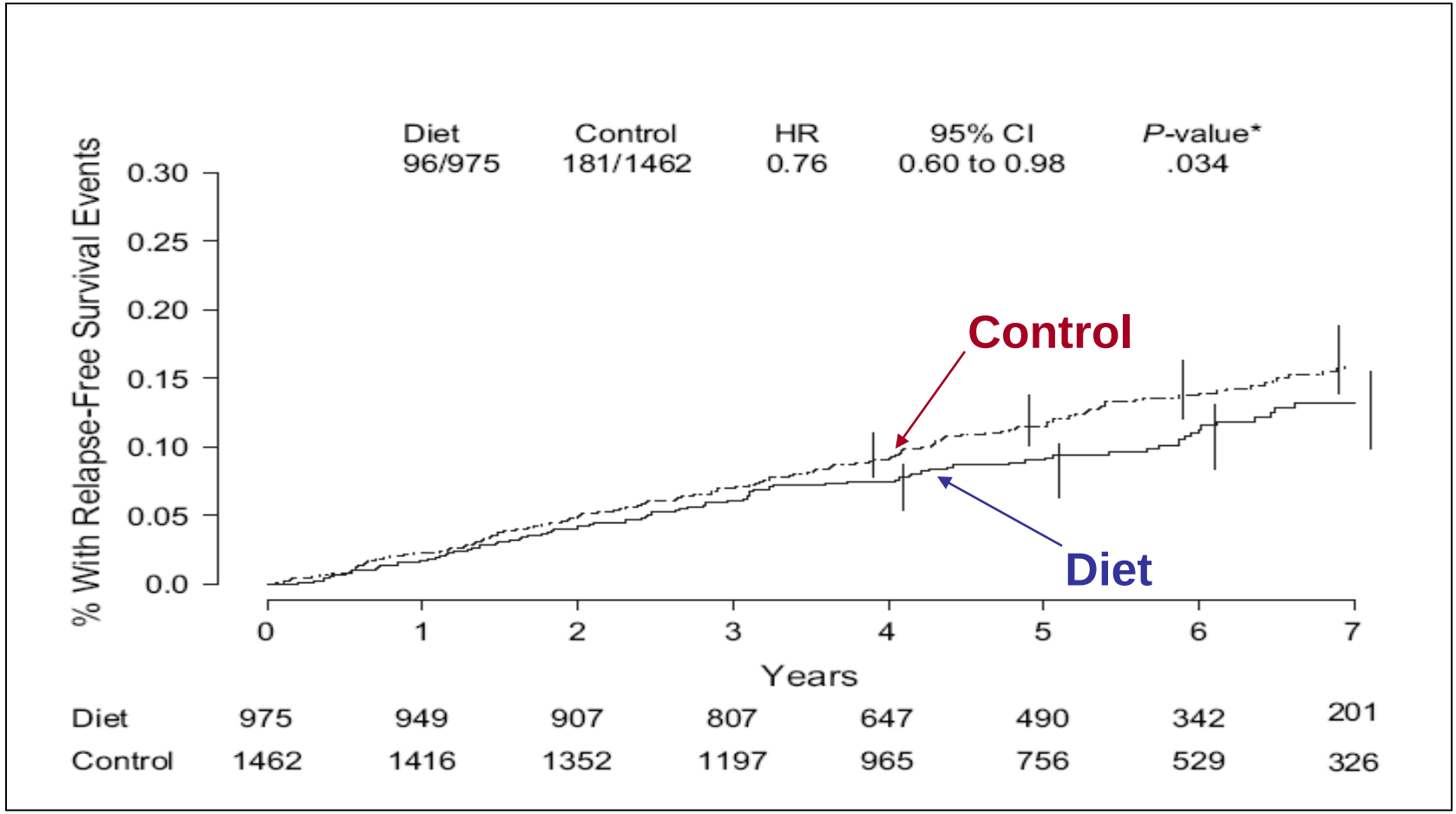
The Women's Interventional Nutrition Study (WINS)

- Randomized 2400 women with early-stage breast cancer to low-fat diet intervention or control group
- Intervention involved one-on-one meetings with dietician, cooking classes
- WINS diet: reduce fat to 15% of total calories



Chlebowski et al, JNCI 2006: 98: 1767-76.

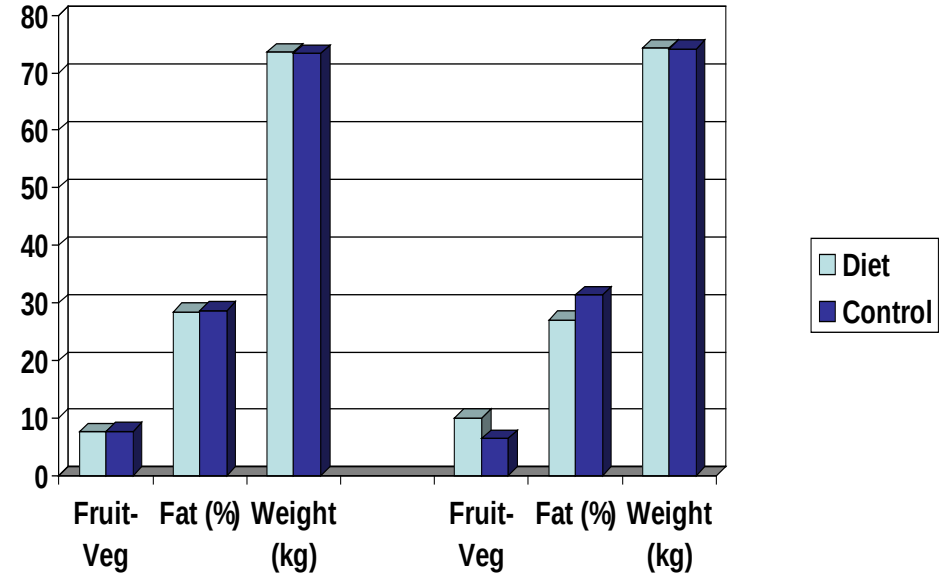
WINS-Results



Chlebowski, JNCI 2006: 98: 1767-76

The Women's Healthy Eating and Living Study (WHEL)

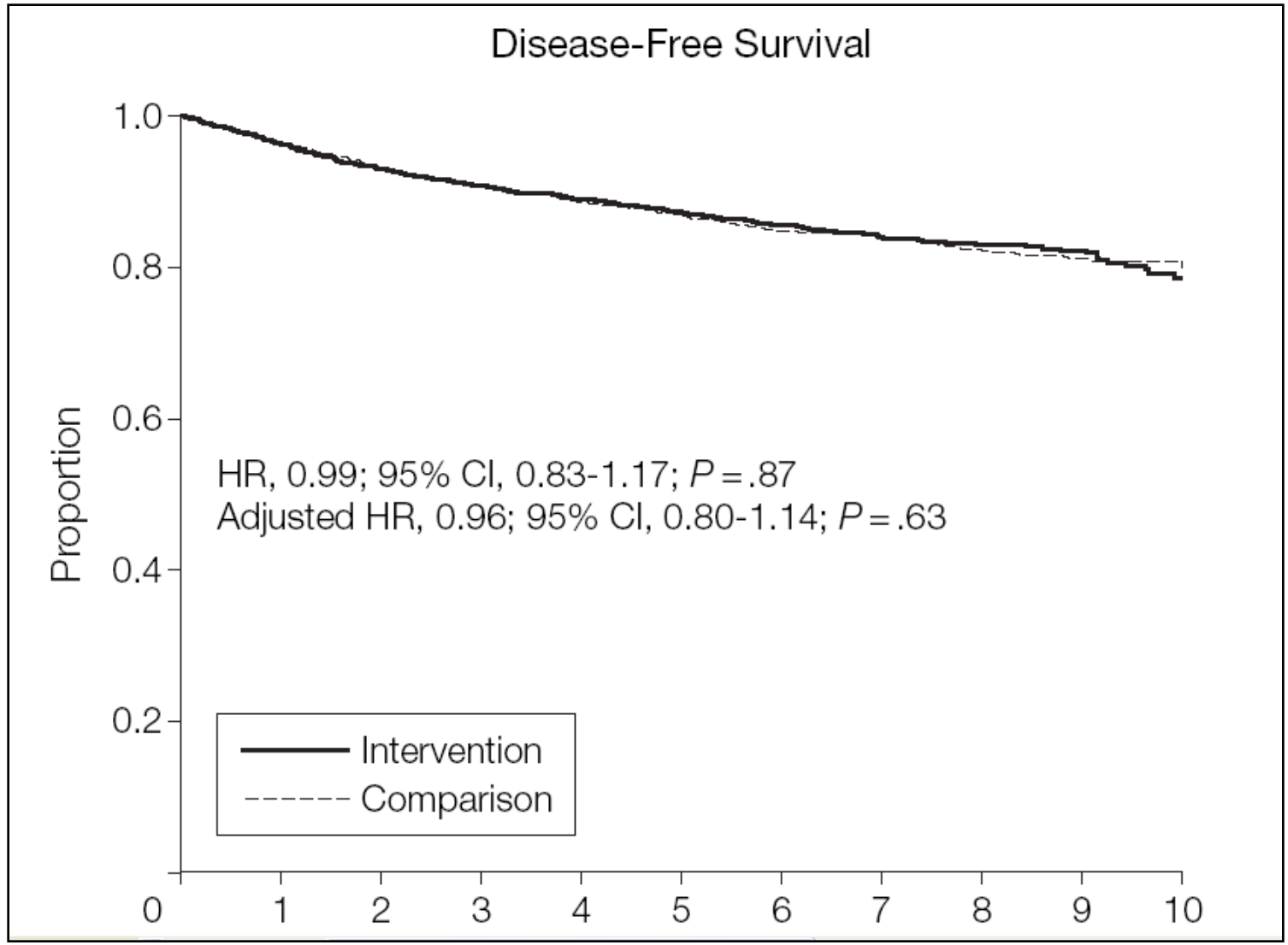
- Included 3088 women with early-stage breast cancer
- Randomized to phone-based diet intervention or control
- WHEL Diet:
  - High fruits and vegetables
  - Low fat
  - High fiber



Baseline **4 Years**

Pierce et al., JAMA 2007; 298: 289-98.

Impact of Dietary Intervention on DFS



Pierce et al., JAMA 2007; 298: 289-98.

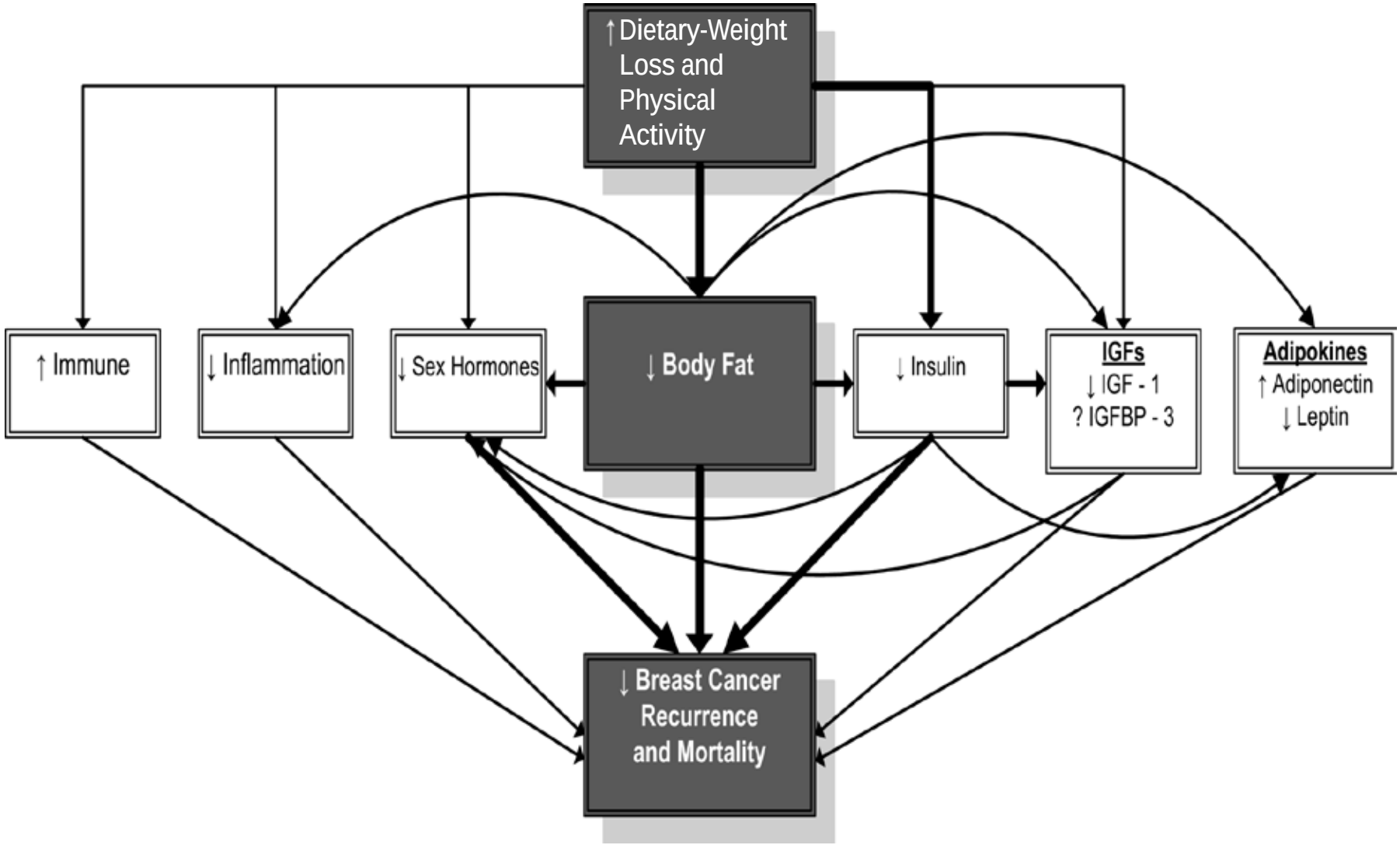
Possible explanations for the different outcomes of WINS and WHEL

- Fat intake was not sufficiently decreased in WHEL
- Study design factors influenced the results
  - Eligibility criteria
  - Timing of enrollment
- Weight loss seen in WINS and not WHEL

What do WINS and WHEL tell us about the link between energy balance and cancer?

- WINS and WHEL offer the most direct evidence we have that weight impacts risk of cancer recurrence
- Also suggests that weight change after diagnosis could impact risk of recurrence
- WINS and WHEL are the only completed randomized trials looking at changes in energy balance and cancer outcomes
- Is there other evidence that can shed some light on the factors driving the relationship between obesity and cancer?

Link between energy balance and cancer likely mediated via a number of interrelated pathways



Irwin ML. Exerc. Sport Sci. Rev. 2006; 34(4): 182-93

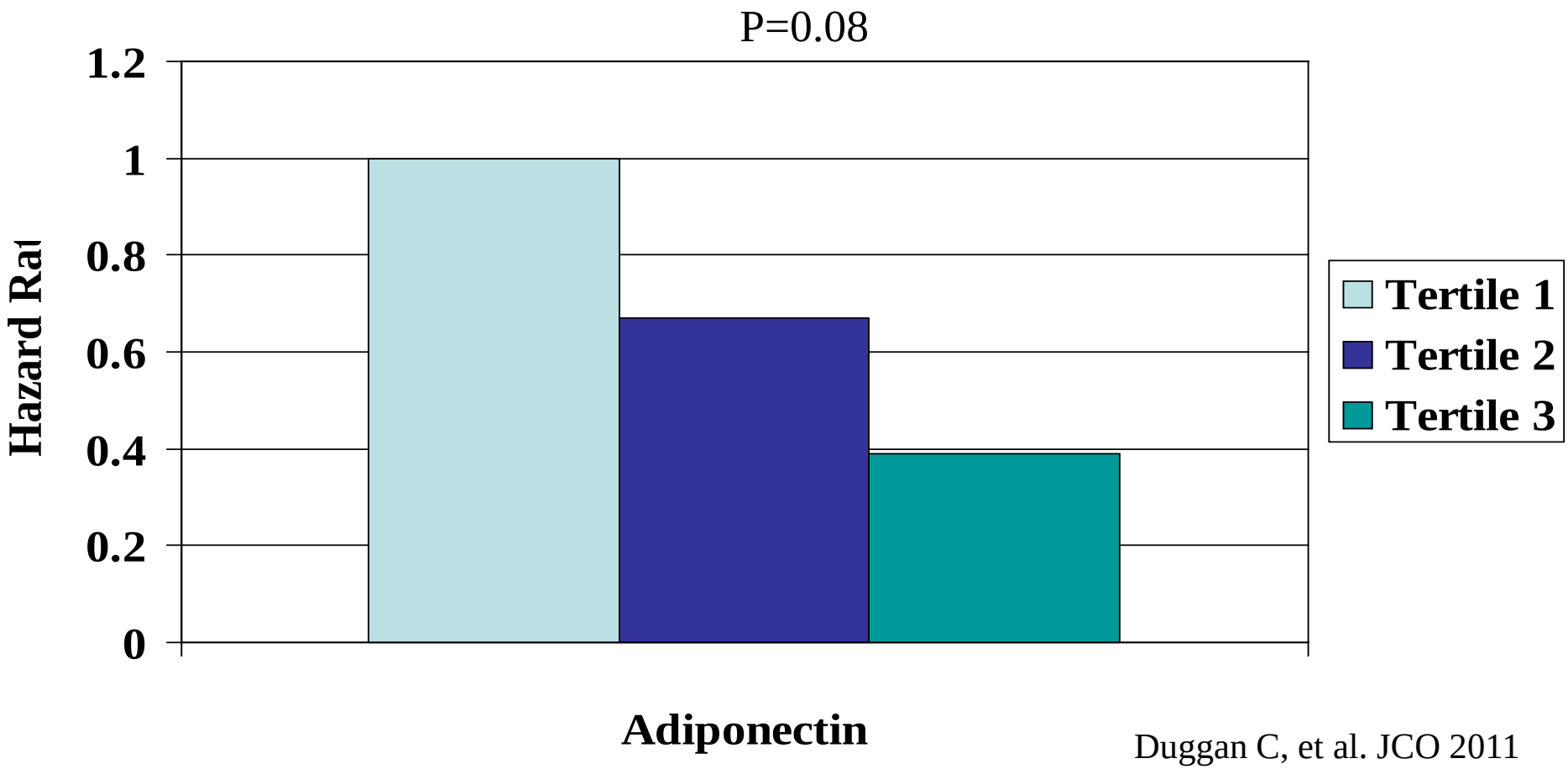
Prognostic Effects of Insulin in Breast Cancer

		n	Factor Measured	Recurrence	Death
Goodwin	**2002**	512	Fasting Insulin	HR=2.0	HR=3.1
Pasanisi	**2006**	110	Fasting Insulin IRS	HR=2.42 HR=3.0	
Pritchard	**2011**	667	Non-fasting C-peptide	$p < 0.05$*	
Irwin (HEAL)	**2010**	689	Fasting C-peptide		HR=3 (significant)
Duggan (HEAL)	**2010**	527	HOMA		HR=4.3 (BC death) HR=1.6 (overall mortality)
Emaus	**2010**	1364	IRS Components: BMI, cholesterol, BP, exercise		HR 1.3-3.0 (significant)

Goodwin et al, JCO 2002; Pasinisi et al, Pritchard et al, JCO 2011; Irwin et al, AACR 2007.

Other Metabolic Hormones Also Linked to Breast Cancer Outcomes:

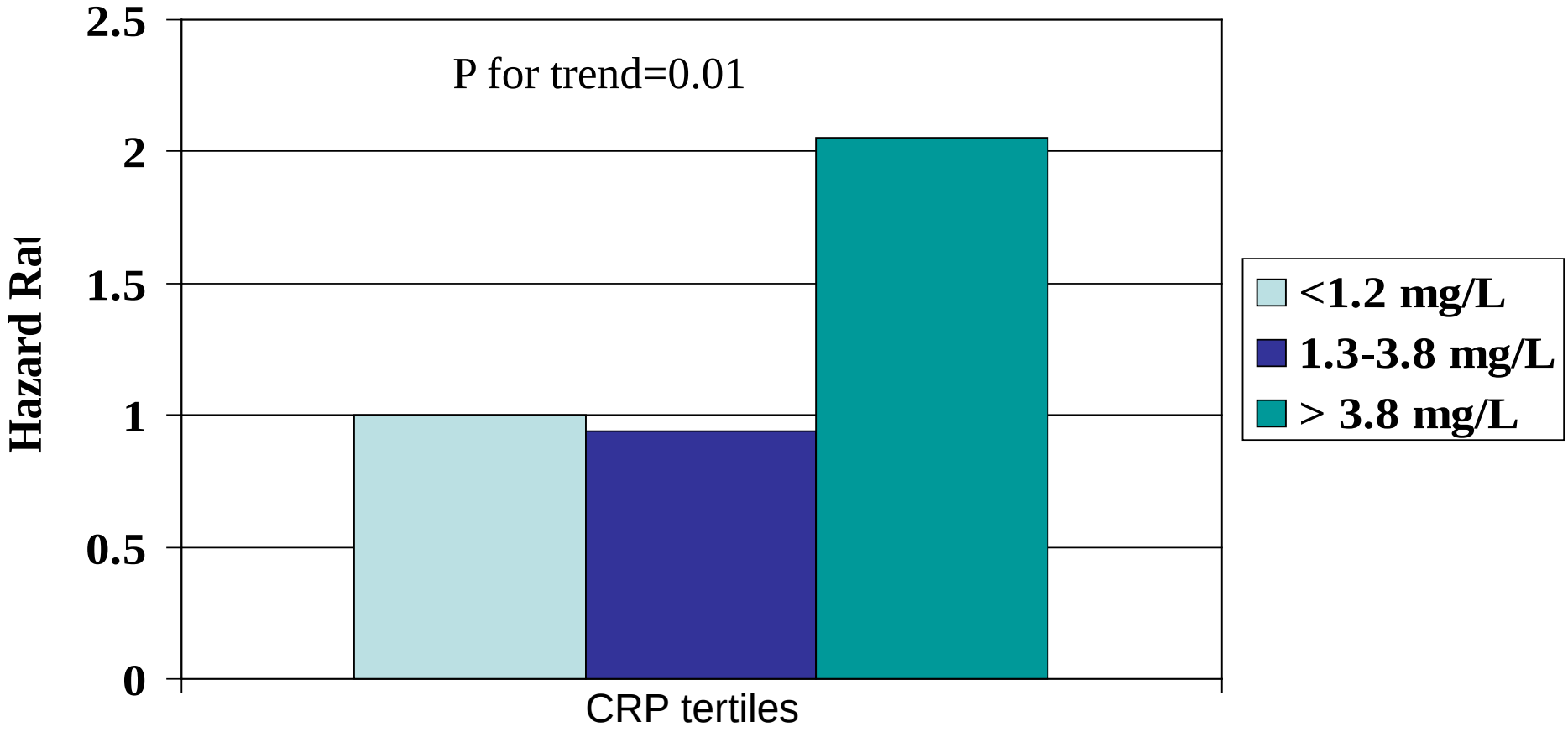
Adiponectin Levels and Breast Cancer Death in the HEAL Study



Duggan C, et al. JCO 2011

Inflammatory Biomarkers also linked to breast cancer prognosis:

CRP and Risk of Total Death in the HEAL study



Pierce, et al. JCO, 2009

Observational studies show relationship between components of energy balance and biomarkers linked to breast cancer prognosis

Health Eating Activity and Lifestyle Study of 710 breast cancer survivors

Table 2. Association between BMI and hormones/peptides (mean ±SE) among a sample of 710 women with breast cancer

	BMI < 25 (n = 284)	BMI = 25-29.9 (n = 216)	BMI > 30 (n = 210)	P for trend
C-peptide (ng/mL)				
Unadjusted	1.83 ± 0.06	2.37 ± 0.07*	2.82 ± 0.07†,‡	0.0001
Adjusted§	1.79 ± 0.06	2.34 ± 0.06*	2.91 ± 0.07†,‡	0.0001
Adjusted‖	1.81 ± 0.06	2.34 ± 0.06*	2.88 ± 0.07†,‡	0.0001
Leptin (ng/mL)				
Unadjusted	12.5 ± 0.8	23.5 ± 0.9*	42.2 ± 0.9†,‡	0.0001
Adjusted§	12.8 ± 0.8	23.6 ± 0.9*	41.6 ± 0.9†,‡	0.0001
Adjusted‖	13.0 ± 0.8	23.7 ± 0.9*	41.3 ± 0.9†,‡	0.0001
IGF-I (ng/mL)				
Unadjusted	144.1 ± 3.4	137.8 ± 3.9*	114.9 ± 3.9†,‡	0.0001
Adjusted§	142.5 ± 3.1	136.5 ± 3.5*	118.4 ± 3.6†,‡	0.0001
Adjusted‖	142.3 ± 3.4	136.5 ± 3.5*	118.7 ± 3.6†,‡	0.0001

- BMI significantly associated with c-peptide, leptin and IGF-1
- Relationship independent of self-reported physical activity levels

Irwin et al. CEBP 2005

HEAL: physical activity and biomarkers linked to breast cancer prognosis

Table 3. Association between sports/recreational physical activity and hormones/peptides (mean ± SE) among a sample of 710 women with breast cancer

	Tertile 1 (<2.6 MET-h/wk; n = 236)	Tertile 2 (2.6-13.2 MET-h/wk; n = 238)	Tertile 3 (>13.3 MET-h/wk; n = 236)	P for trend
C-peptide (ng/mL)				
Unadjusted	2.49 ± 0.07	2.34 ± 0.07	2.04 ± 0.07*,†	0.001
Adjusted‡	2.48 ± 0.07	2.35 ± 0.07	2.04 ± 0.07*,†	0.001
Adjusted§	2.33 ± 0.06	2.35 ± 0.06	2.19 ± 0.06	0.13
Leptin (ng/mL)				
Unadjusted	30.5 ± 1.1	24.5 ± 1.1‖	18.9 ± 1.1*,†	0.001
Adjusted‡	30.0 ± 1.1	24.5 ± 1.1¶	19.4 ± 1.1*,†	0.001
Adjusted§	26.1 ± 0.8	24.3 ± 0.8	23.4 ± 0.8*	0.020
IGF-I (ng/mL)				
Unadjusted	119.7 ± 3.7	136.1 ± 3.7‖	144.7 ± 3.7*	0.0001
Adjusted‡	125.8 ± 3.4	134.9 ± 3.3‖	140.0 ± 3.4*	0.0037
Adjusted§	129.5 ± 3.4	135.0 ± 3.3	136.2 ± 3.4*	0.018

- Physical activity significantly associated with c-peptide, leptin and IGF-1
- Adjusting for BMI weakened association, but relationship between PA and both leptin and IGF-1 remained significant

Irwin et al. CEBP 2005

Women's Health Initiative also looked at energy balance factors and insulin in at-risk women

- Study looked at insulin levels in 2996 postmenopausal women taking part in WHI
- More than 70% of participants overweight or obese
- BMI, caloric intake and physical activity all significantly related to fasting insulin levels
- Regression modeling showed associations remained significant with adjustment for the other 2 factors

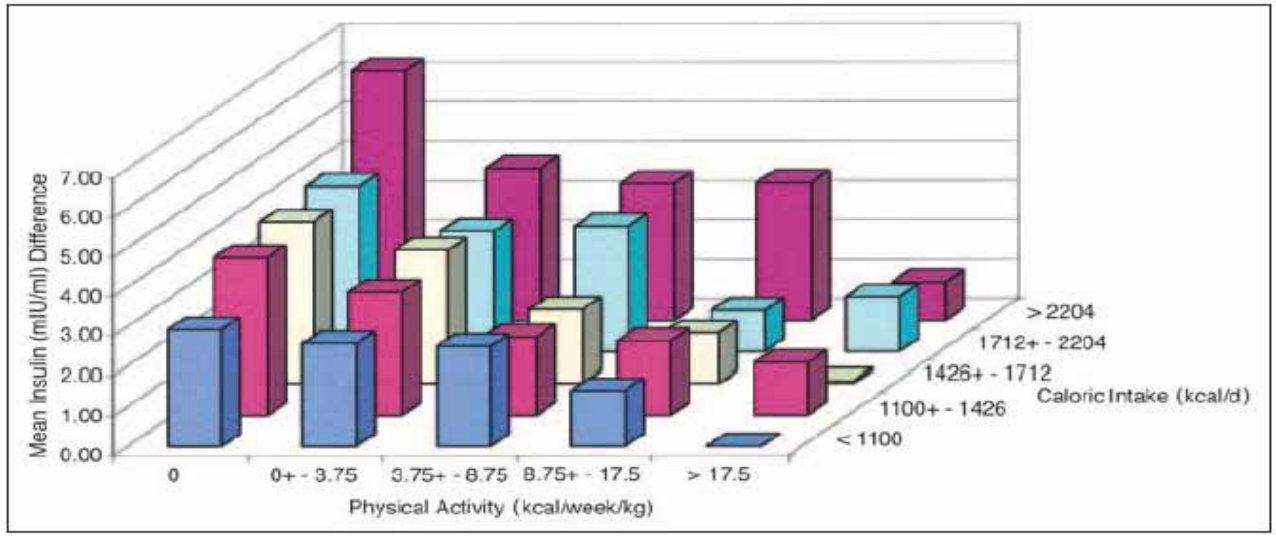
Table 3. Fasting Insulin Levels by BMI and Physical Activity and Caloric Intake Quintiles

Parameter	Mean (μU/mL)	SD	P*
BMI			
< 25	8.10	4.14	< .0001
25-29	10.40	6.93	
≥ 30	14.45	7.49	
Total recreational and physical activity, kcal/wk/kg			
0	13.03	9.90	< .0001
> 0-3.75	11.94	6.05	
> 3.75-8.75	11.33	6.64	
> 8.75-17.5	10.56	5.69	
> 17.5	9.48	5.31	
Caloric intake, kcal/d			
< 1,100	10.62	6.00	< .0001
> 1,100-1,426	11.08	6.38	
> 1,426-1,712	10.79	5.91	
> 1,712-2,204	11.28	6.44	
> 2,204	12.49	9.55	

Abbreviations: BMI, body mass index; SD, standard deviation; WHI, Women's Health Initiative.
*From linear regression models adjusted for race or ethnicity, age, current smoking, alcohol intake, and WHI study component.

Chlebowski et al. JCO 2004; 22, 4507-13

Insulin levels by quartiles of physical activity and caloric intake



- Relationship between insulin levels and PA/caloric intake was the same for each quartile
- No interaction in relationship between lower insulin levels and higher PA or lower caloric intake

Chlebowski et al. JCO 2004; 22: 4507-13

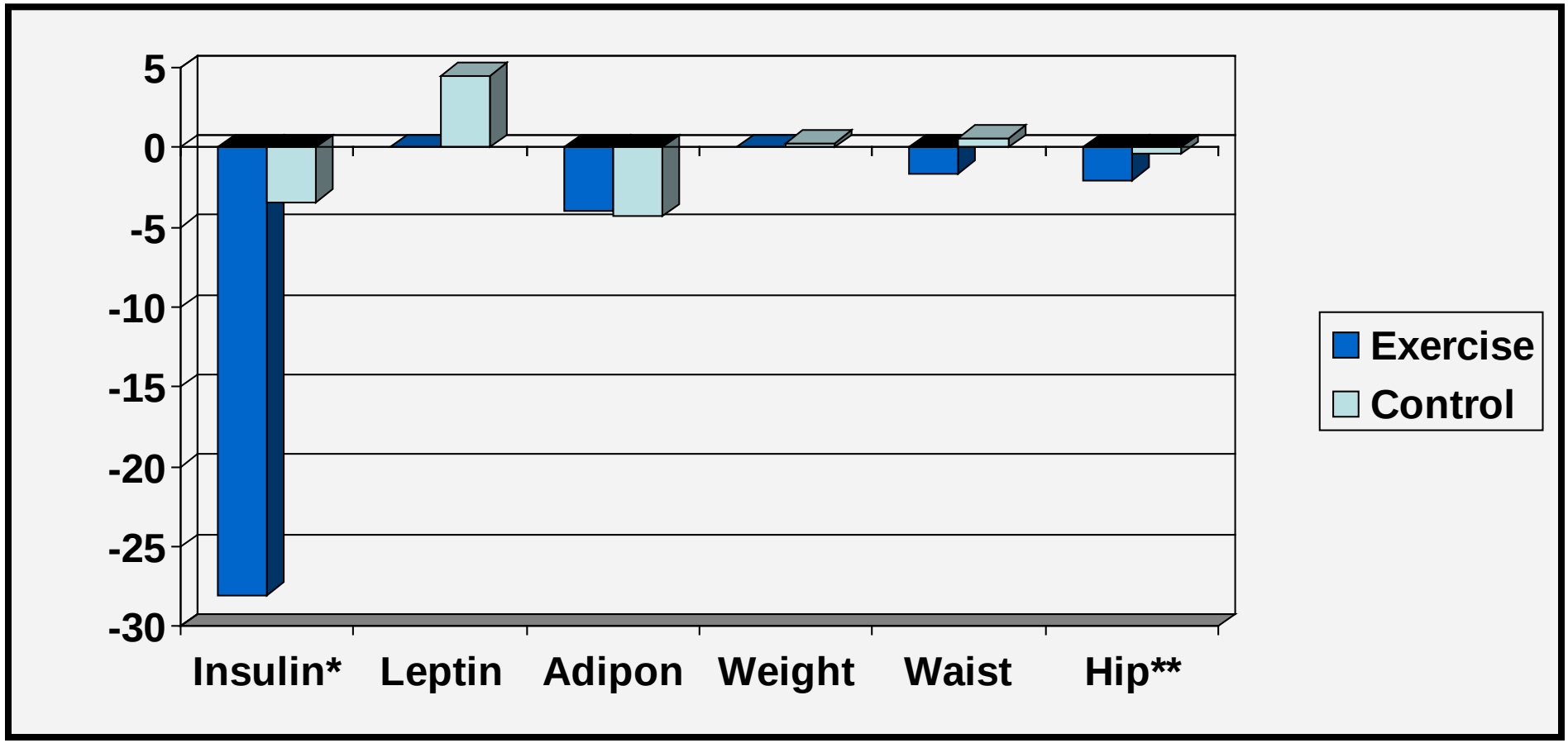
Interventional studies show changes in diet/weight/exercise favorably affect biomarkers linked to breast cancer prognosis

Exercise and Insulin Study in Breast Cancer Survivors

- Enrolled 101 overweight, sedentary breast cancer survivors (average BMI 30.0 kg/m2)
- Randomized to 16-week mixed strength and aerobic training intervention vs. usual care
- Intervention group significantly increased physical activity:
  - Aerobic activity increased from 11 minutes/week to 110
  - Strength increased on all tested exercises (average time spent in strength training: 100 minutes/week)

Ligibel et al. JCO 2008; 26: 907-912

Exercise and % change in metabolic hormones over 16 weeks

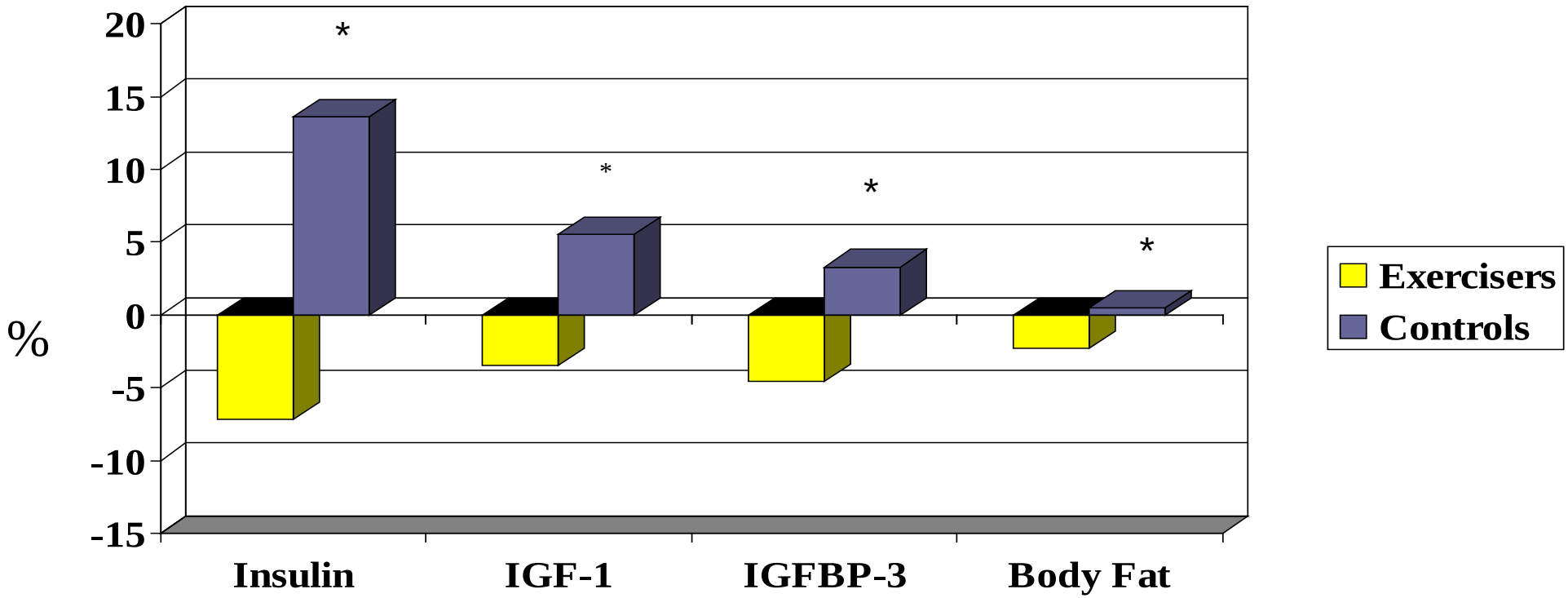


*P=0.07, ** p=0.02

Ligibel et al. JCO 2008; 26: 907-912.

Yale Exercise and Survivorship Study

75 sedentary, overweight breast cancer survivors randomized to exercise vs. control



* P < .05

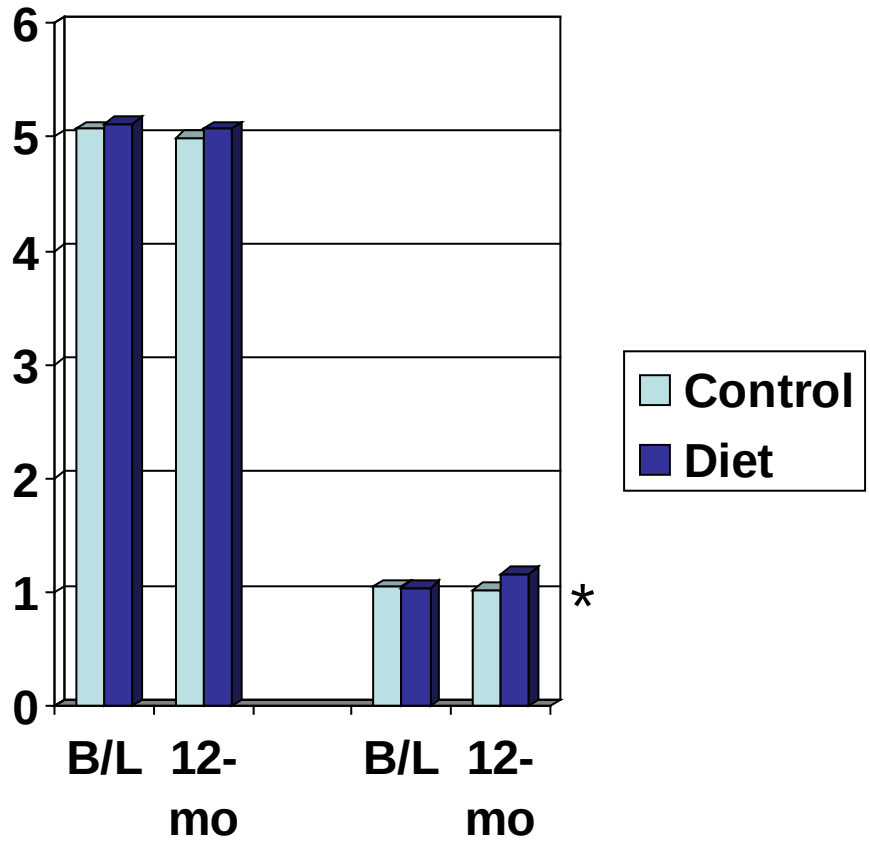
Irwin ML, et al. CEBP, 2009, Irwin ML, et al. Obesity, 2010

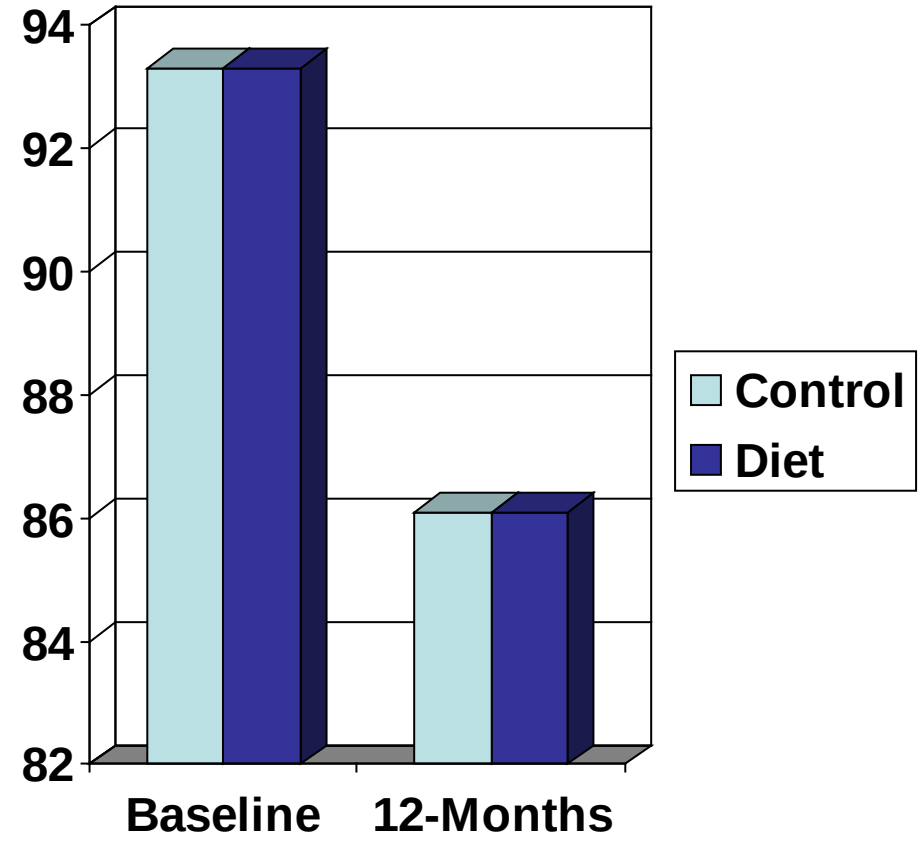
WHEL looked at diet-induced changes in insulin and metabolic biomarkers

- Included 393 intervention and control patients
- Fasting blood samples obtained at baseline and 1 year
- 24-hour dietary recalls demonstrated changes in diet between baseline and 12-months:
  - Both groups sig decreased caloric intake (~250-350kcal/d)
  - Both groups sig decreased % calories from fat
    - » Control: 28.1% to 27%
    - » Intervention: 28.1% to 21.8%
  - Intervention group also sig increased % cal from carbohydrates and increased fiber

Rock et al. J. Nutr. 134: 342–347, 2004

Impact of dietary intervention upon insulin and metabolic biomarkers





Cholesterol **Triglycerides** **Insulin**

* $p<0.05$

Rock et al. J. Nutr. 134: 342–347, 2004

Transdisciplinary Research on Energetics and Cancer

- Several projects that will explore impact of weight loss, diet and physical activity on biomarkers linked to cancer recurrence:
    - Harvard: Impact of exercise and metformin on insulin, metabolic hormones and inflammatory mediators in colorectal cancer survivors
    - UCSD: Impact of weight loss and metformin on insulin, sex steroids, inflammatory mediators in breast cancer survivors
    - Penn: Impact of exercise and weight loss upon lymphedema and biomarkers in breast cancer survivors

Conclusions

- Observational evidence shows links between all aspects of energy balance and cancer outcomes
- Randomized data testing the impact of individual factors on cancer outcomes not available
- The WINS and WHEL data suggest that weight may influence cancer outcomes—at least in breast cancer
- Biomarker data show caloric intake, BMI and physical activity all linked to markers linked to cancer recurrence
- A small number of randomized studies show that changes in weight and activity can impact biomarkers linked to recurrence

Next steps

- Randomized trials testing the impact of weight loss and other aspects of energy balance on cancer outcomes are needed
- Ongoing and future trials should include biomarker measurements to validate surrogate markers of cancer recurrence
- Data are needed in malignancies other than breast cancer; relationships may be different
    - Diet may play a greater role in GI malignancies
    - Other factors may be more important in malignancies without the sex steroid-dependence of many breast cancers