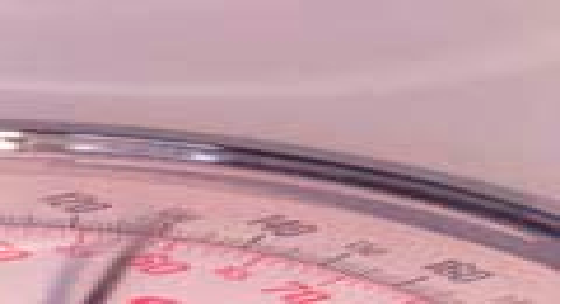
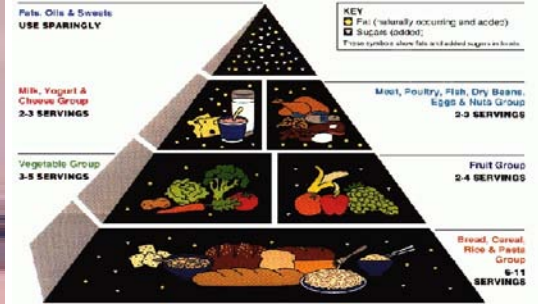




Diet and Weight Influences on Cancer Risk and Progression

Jennifer Ligibel, MD

American Psychosomatic Society Forum

Toward Precision Cancer Care: Biobehavioral Contributions to the Exposome

Chicago, Illinois

October 26, 2012

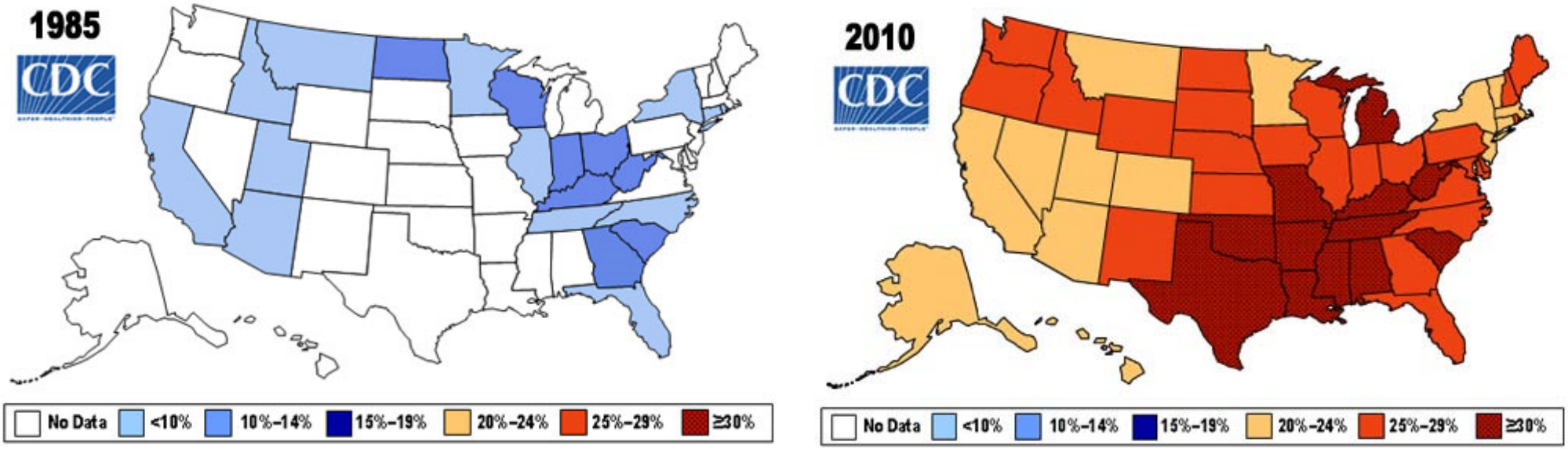
DANA-FARBER/BRIGHAM AND WOMEN'S
CANCER CENTER

Evidence increasingly suggests that adiposity and dietary factors impact cancer prognosis

This session will:

- Review observational evidence linking weight and diet to cancer risk and survival
- Describe randomized trials which have tested the impact of diet and weight loss upon cancer incidence and outcomes
- Explore biologic pathways hypothesized to mediate relationships between energy balance factors and cancer prognosis
- Discuss future directions in energy balance research in cancer survivors

Obesity rates have reached epidemic levels in the US and beyond



Trends in Obesity Prevalence (%), Adults 18 and Older, US, 1985-2010

http://www.cdc.gov/obesity/data/trends.html

Observational studies consistently show increased risk of cancer in obese individuals

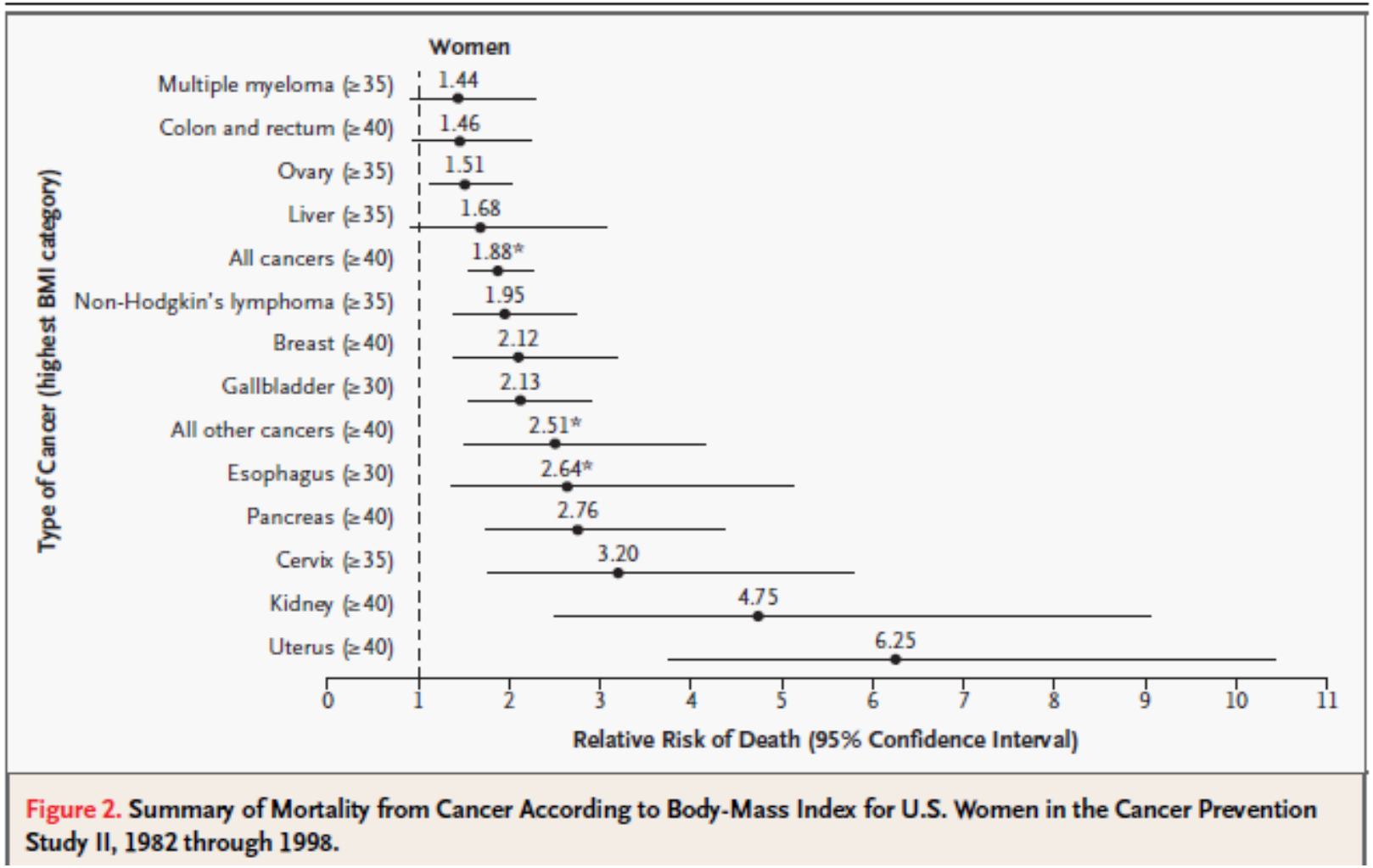


Figure 2. Summary of Mortality from Cancer According to Body-Mass Index for U.S. Women in the Cancer Prevention Study II, 1982 through 1998.

Calle et al. NEJM 2003; 348: 1625-38

Observational studies also show consistent link between obesity and poor prognosis in women with early stage breast cancer

Meta-analysis of obesity and survival in 43 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

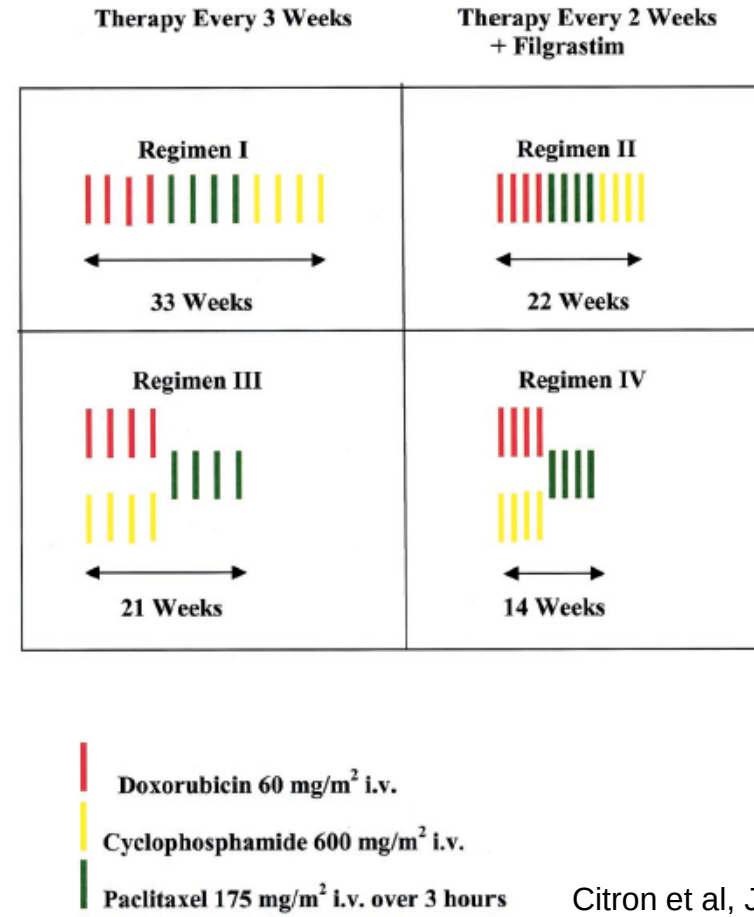
Protani et al. BCRT 2010; 23:627-635

Recent studies show obese patients have poor outcomes after optimization of treatment factors

CALGB 9741

- Enrolled 2005 patients between 1997 and 1999
- Eligibility:
  - Node +
  - Pre and post-menopausal
  - Any HR status
- Median follow-up: 11 years
- **Protocol mandated weight-based chemotherapy dosing**

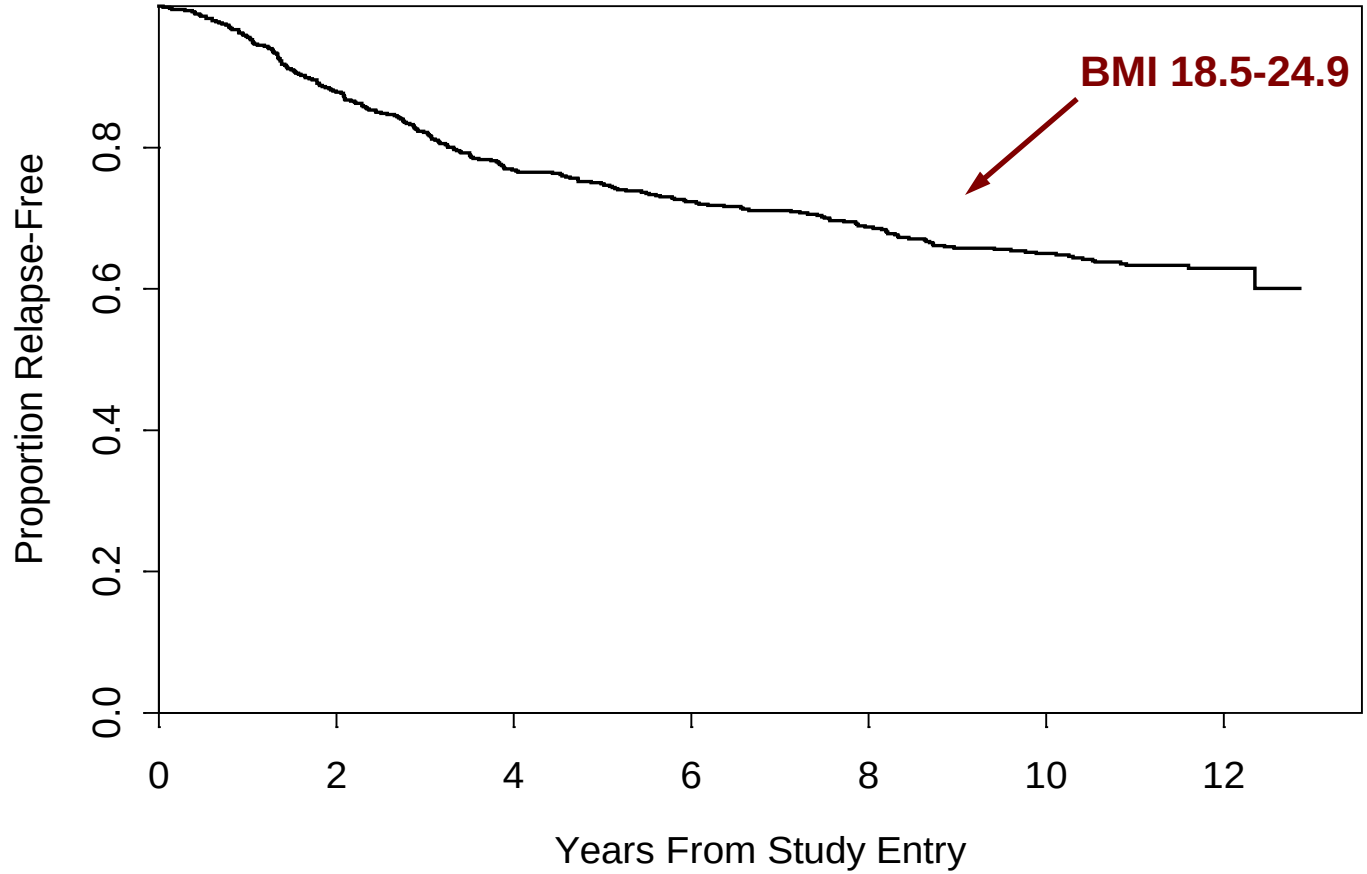
Treatment Schema



Citron et al, JCO 2003

CALGB 40902/9741

Relapse-Free Survival By BMI



.....	<18.5	N= 22	Events= 9	Median= NA	Chi-square=	7.9984
- - - -	18.5-24.9	N= 623	Events= 179	Median= NA	p-value=	0.046
— — —	25-29.9	N= 628	Events= 208	Median= NA		
———	30+	N= 636	Events= 223	Median= NA		

Ligibel et al. EBCC 2012

Multivariate Model for Relapse-Free Survival

Variable	Comparison of Worse : Better for HR	HR	95% CI around HR	P-value
BMI	27 : 22	1.08	1.02 – 1.14	0.010
Nodes	10 : 1	2.29	1.94 – 2.71	<0.0001
Tumor size	5 : 2	1.39	1.22 – 1.60	<0.0001
Menopause	Post : pre	1.11	0.94 – 1.31	0.22
ER	Neg : pos	1.54	1.31 – 1.82	<0.0001
Sequence	Seq : con	1.05	0.89 – 1.23	0.57
Length	q 3 : q 2	1.21	1.03 – 1.43	0.019

Each unit increase in BMI corresponded to a ~1.5% increase in the risk of RFS failure

(eg BMI from 22 to 27: 8% increase in relapse; BMI 22 to 32: 17% increase)

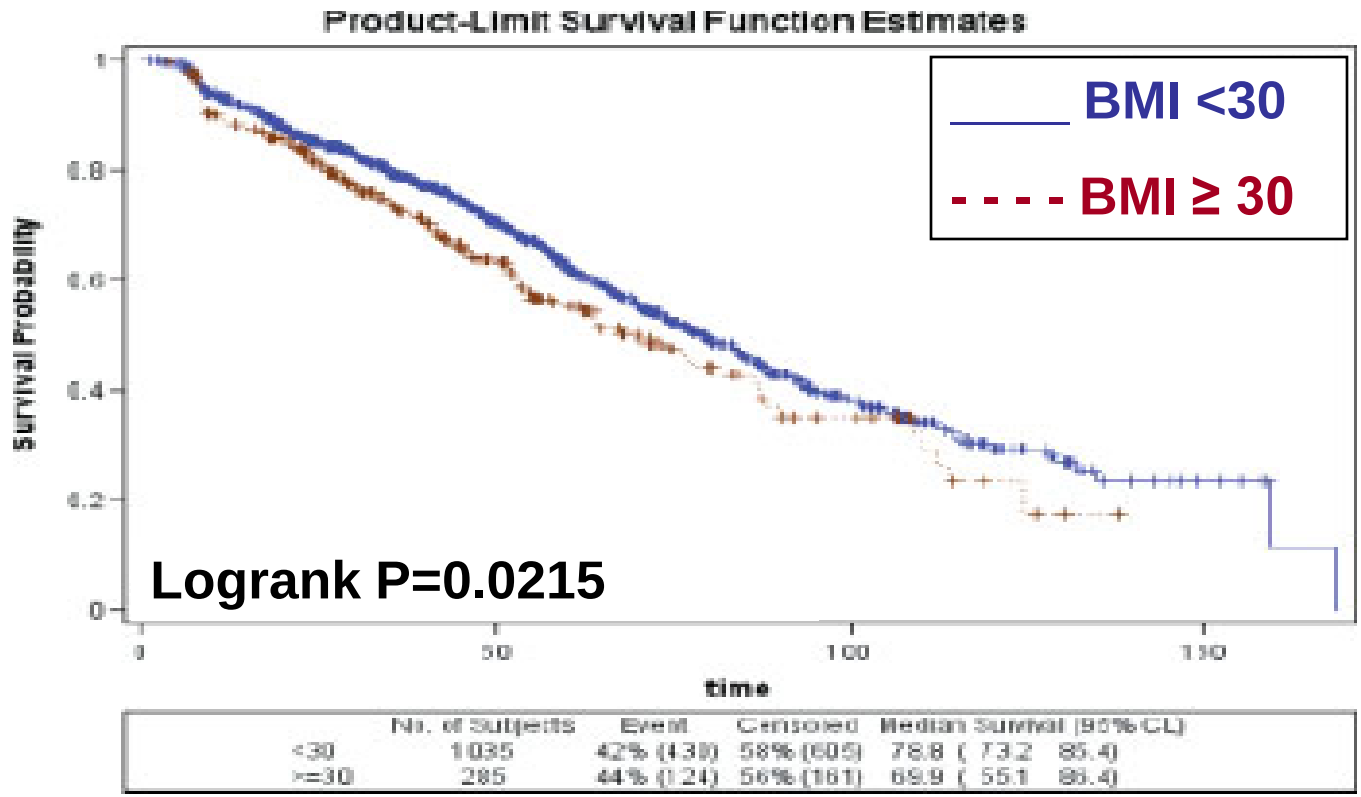
Relationship between obesity and survival has also been studied extensively in prostate cancer

- Obesity associated with more aggressive phenotype and more advanced disease
  - 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.

Obesity and freedom from PSA failure in 1868 men treated with external beam RT for localized prostate CA



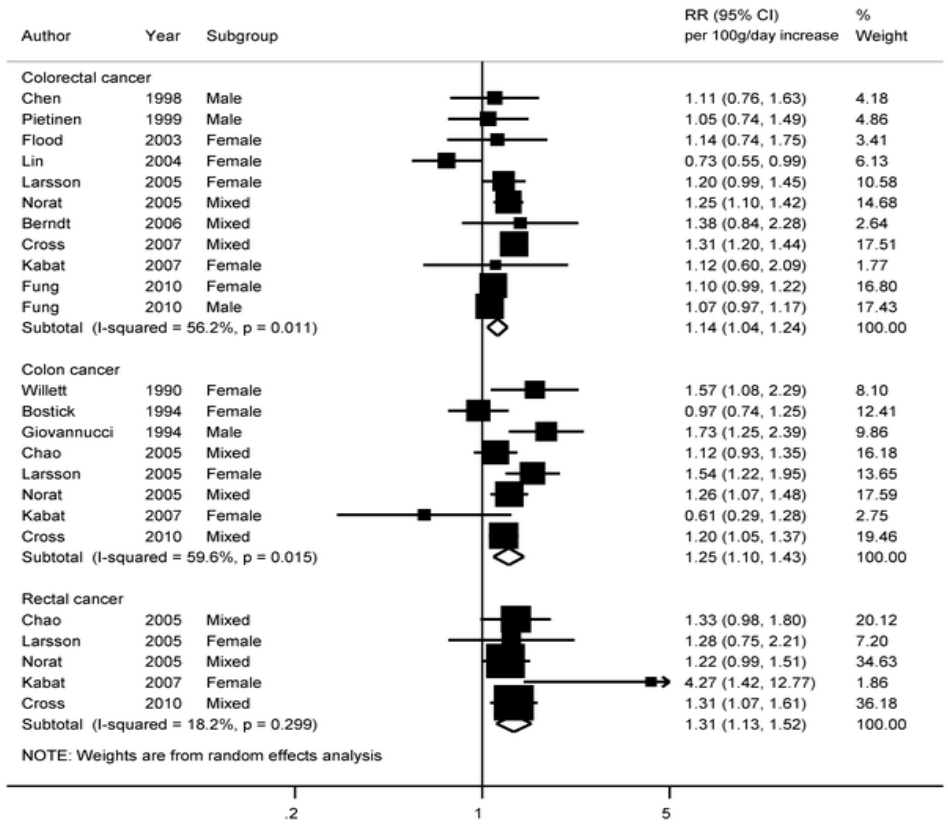
Stroup et al. Cancer, 2007

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

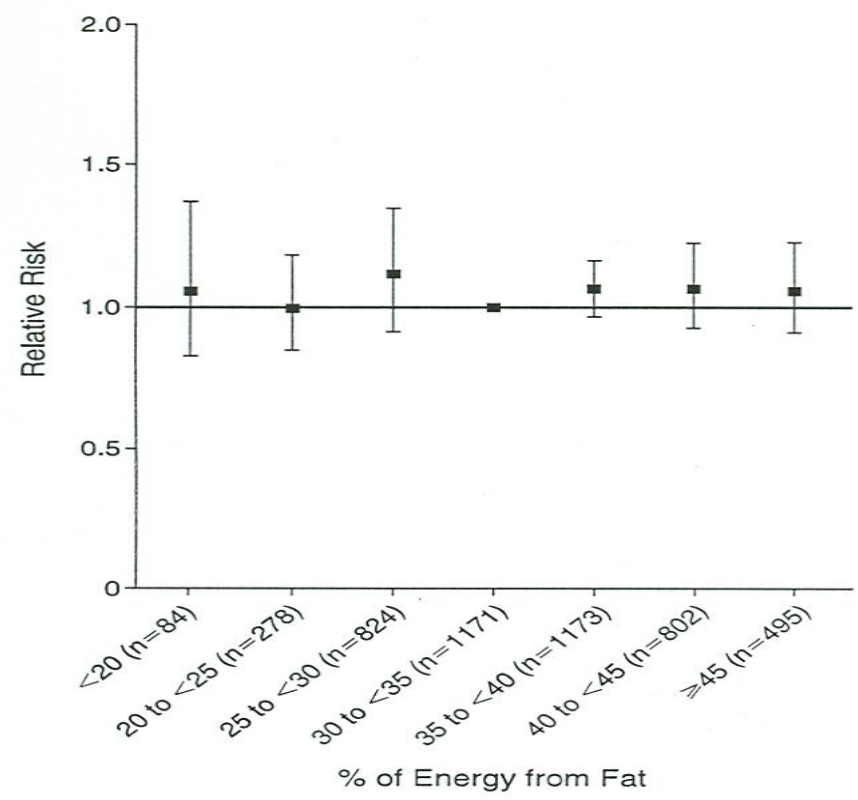
Author	N	Outcome	Hazard Ratio (95% CI) or P value (compared to normal weight)
Tartter	279	Recur Rate	**P = 0.003 for above median weight**
Meyerhardt	3759	DFS	1.11 (0.94-1.30) BMI $\geq$ 30 kg/m^2
Meyerhardt	1792 rectal	DFS	1.10 (0.91-1.32) BMI $\geq$ 30 kg/m^2
		OS	1.09 (0.90-1.33) BMI $\geq$ 30 kg/m^2
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.

Dietary factors also linked to cancer risk, but results not consistent in all malignancies



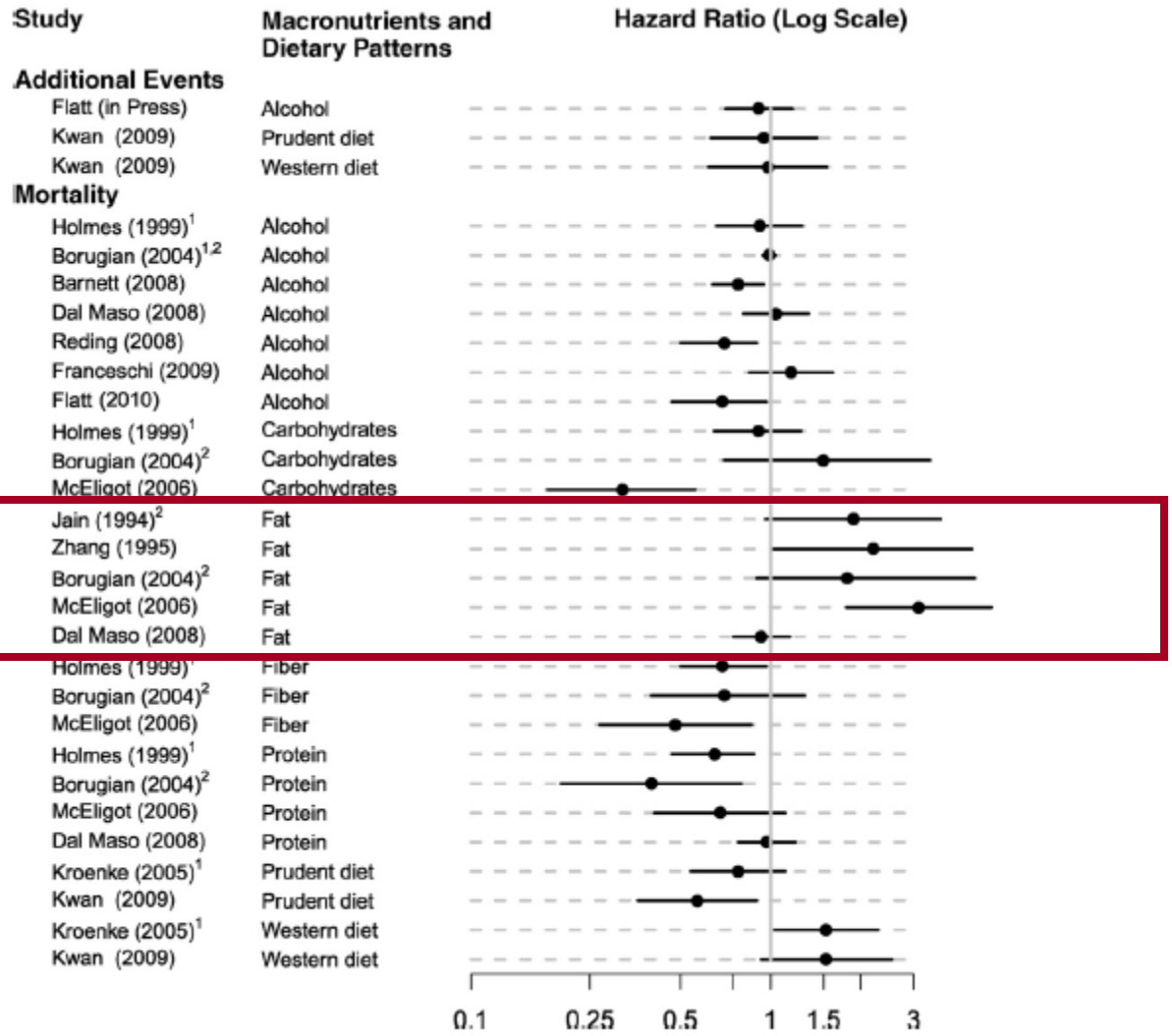
Risk of colon cancer by red meat intake



Risk of breast cancer by fat intake

Chan et al. Plos One, 2011.

Dozens of studies also examine dietary factors and prognosis in breast cancer survivors…



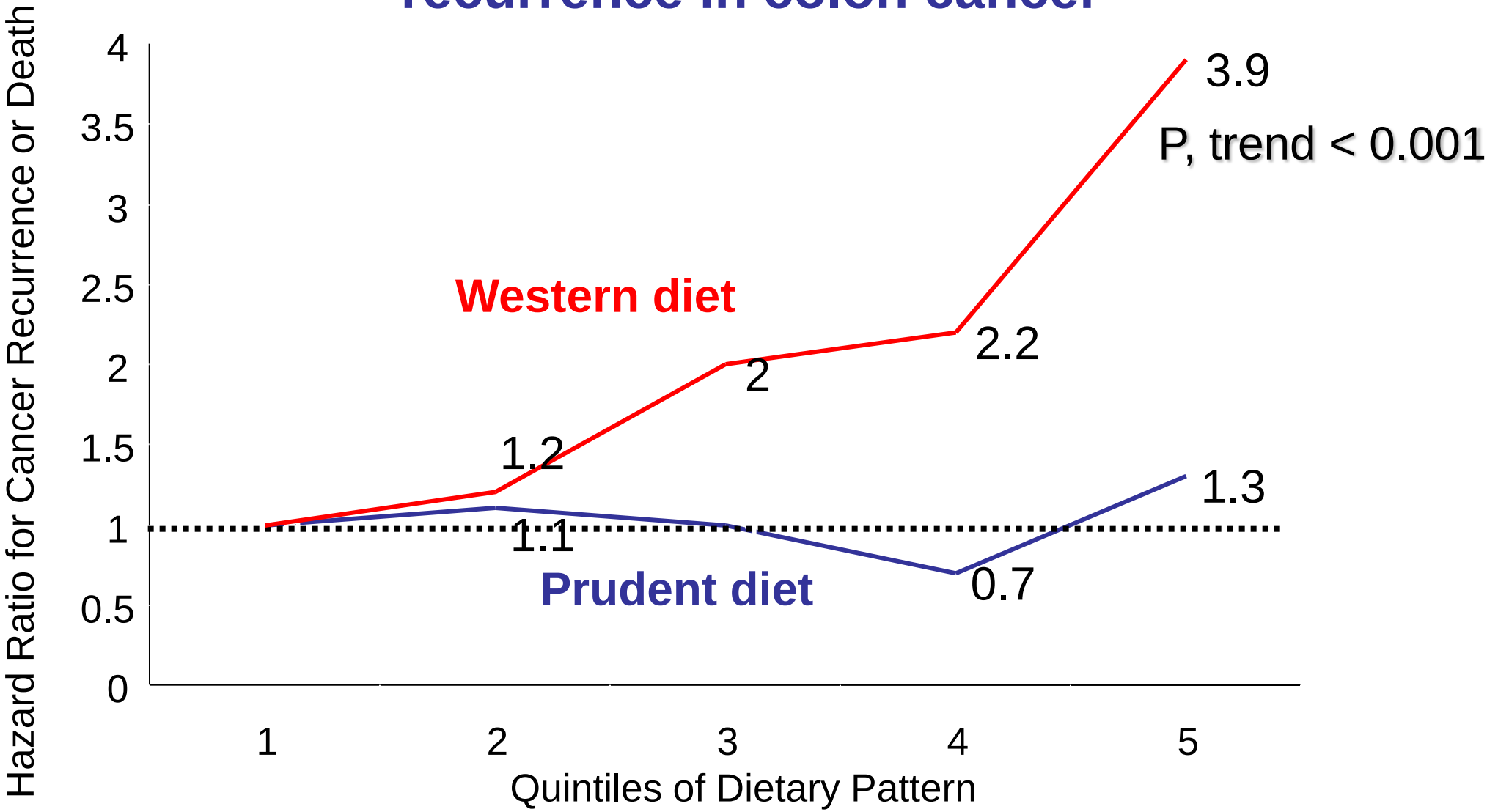
Patterson et al. Maturitas, 2010.

…as well as in prostate cancer

- Some relationship between increased intake of fat, especially saturated, and increased mortality
- Some relationship between lycopene/tomato products and better survival
- But studies largely show mixed results:
  - Many individual studies showing a relationship between a particular micro or macronutrient and disease outcomes
  - Results not reproducible

Berkow et al. Nutrition Reviews 2007; Davies et al. BJC, 2011

One study showed link between dietary pattern and recurrence in colon cancer



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

Do modification of diet and weight impact cancer risk and/or outcomes?

- Few studies have been powered to look at impact of weight loss or dietary change upon cancer risk or prognosis

- Several smaller studies look at impact of changes in diet and weight upon quality of life and other patient-reported outcomes

- A growing number of studies look at the impact of energy balance interventions upon biomarkers linked to cancer risk and prognosis

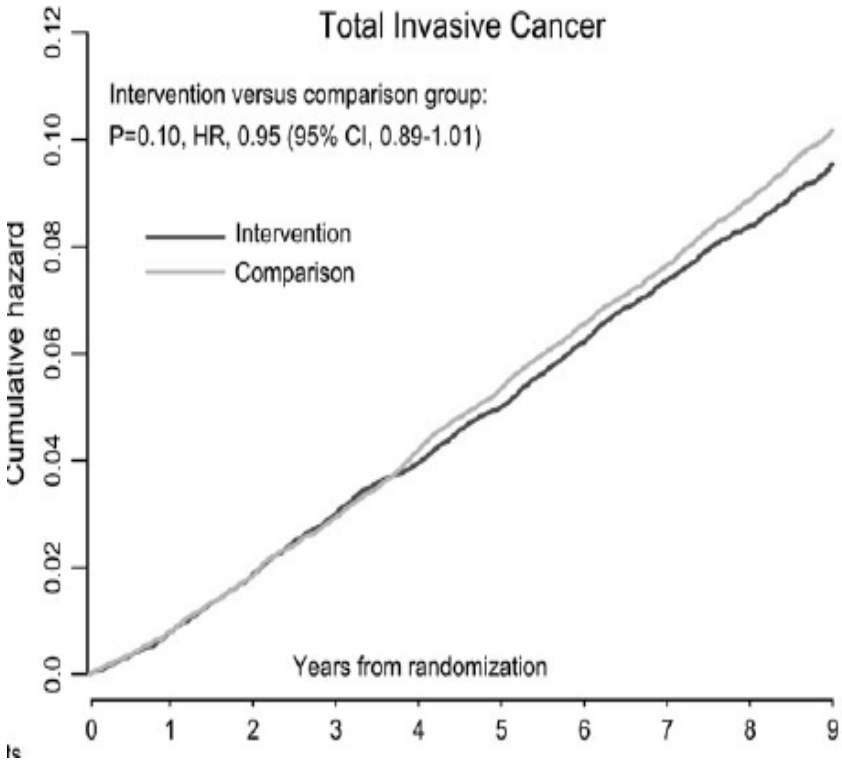
Reducing dietary fat has been tested as a strategy to prevent cancer:

Women's Health Initiative Low-Fat Dietary Intervention Study

- Randomized 48,835 postmenopausal women to a group-based dietary intervention (40%) or control group (60%)
- Intervention goals: decrease dietary fat to 20% of calories, increase fruits, vegetable and grains
- Endpoints:
  - Primary: Incidence of breast and colorectal cancer
  - Secondary: Incidence of ovarian, endometrial and total cancer
- Eligibility: Diet including ≥ 32% of calories from fat

Prentice et al, JNCI 2007.

Results of WHI Low-Fat Diet Intervention Study



Cancer site	Incidence per 1000 person-years (No. of cases) Intervention	Comparison	P†	HR (95% CI)‡
Ovary	0.36 (57)	0.43 (103)	.03	0.83 (0.60 to 1.14)
Endometrium	0.79 (125)	0.71 (170)	.18	1.11 (0.88 to 1.40)
Breast	4.15 (655)	4.52 (1072)	.09	0.91 (0.83 to 1.01)
Colorectal	1.27 (201)	1.18 (279)	.29	1.08 (0.90 to 1.29)
All other sites	4.56 (720)	4.81 (1140)	.30	0.95 (0.86 to 1.04)
Total cancer	10.69 (1687)	11.22 (2661)	.10	0.95 (0.89 to 1.01)

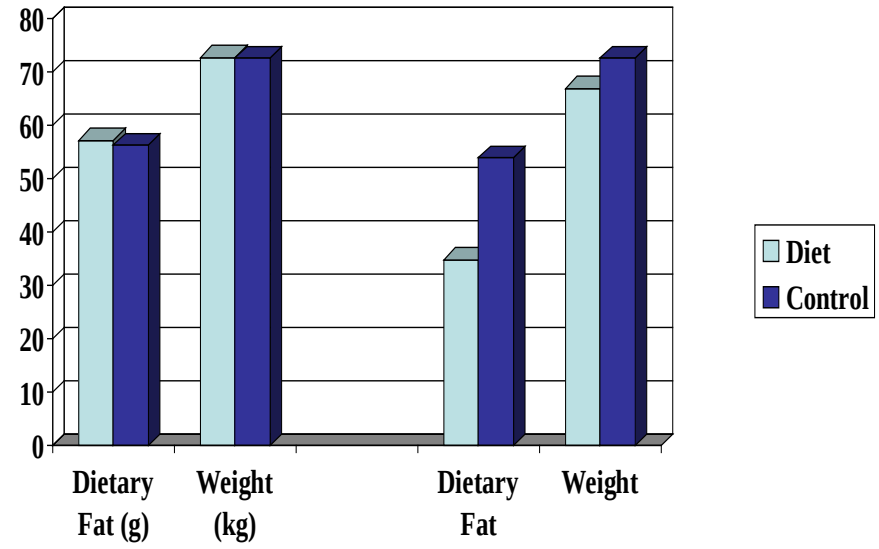
No difference in rates of total cancer…. ? Risk of individual cancers.

Prentice et al, JNCI 2007

Reducing dietary fat has also been studied in breast cancer survivors:

The Women's Interventional Nutrition Study (WINS)

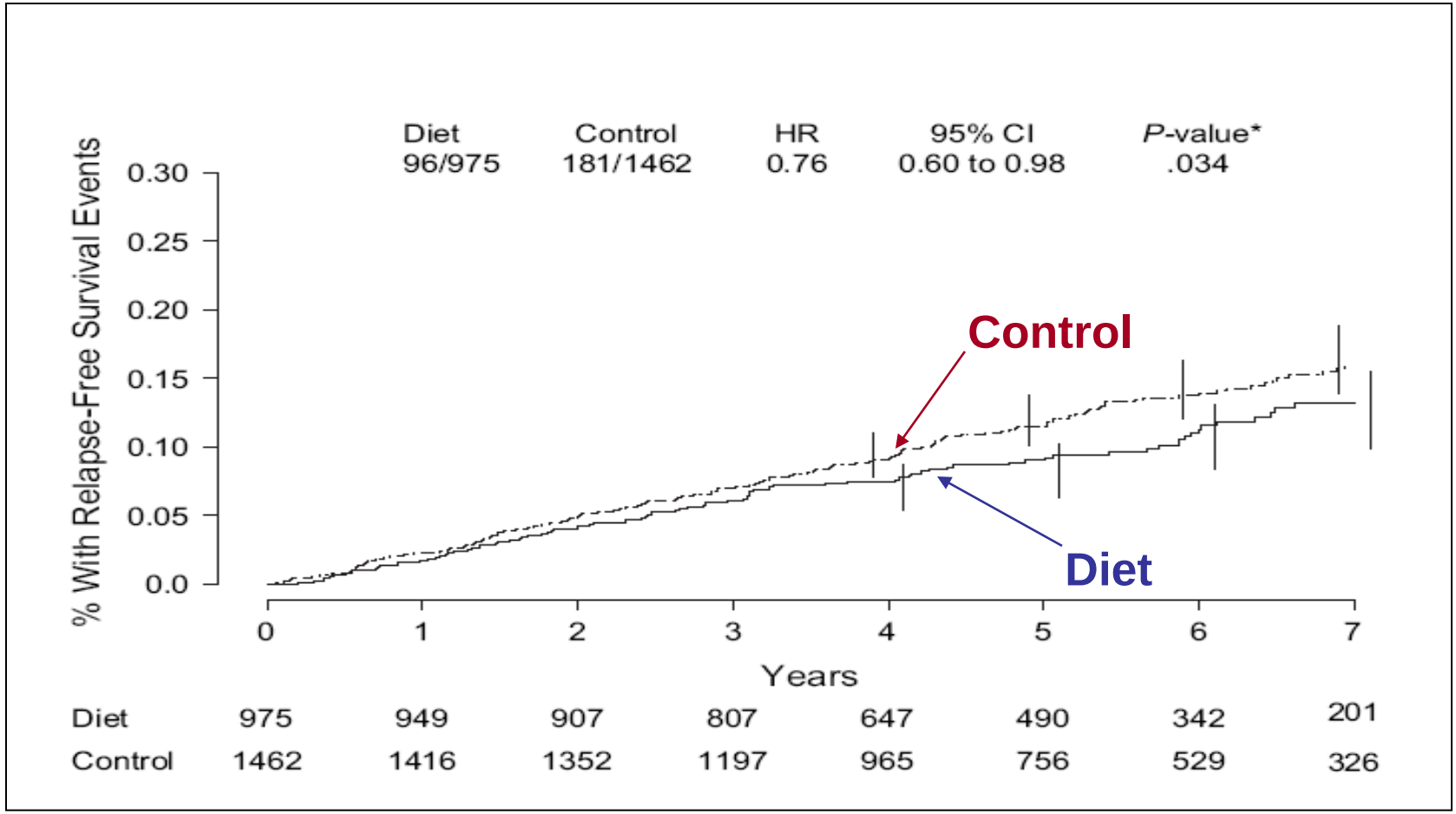
- Randomized 2400 women with early-stage breast cancer to low-fat diet intervention or control group
- Intervention involved one-on-one meetings with dietician, cooking classes
- WINS diet: reduce fat to 15% of total calories



Baseline **5 Years**

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

WINS-Results

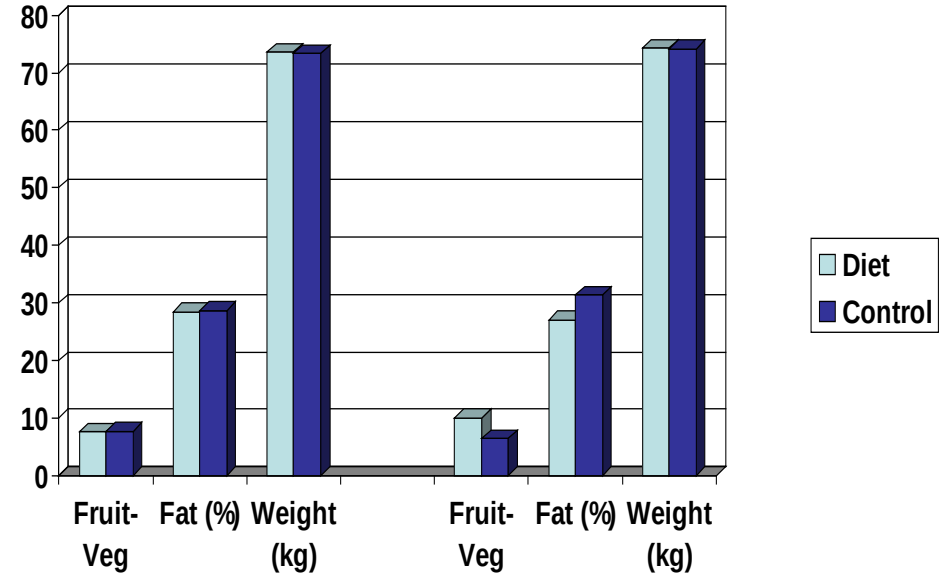


Chlebowski, JNCI 2006: 98: 1767-76

Another study tested the impact of lowering fat and improving dietary quality:

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

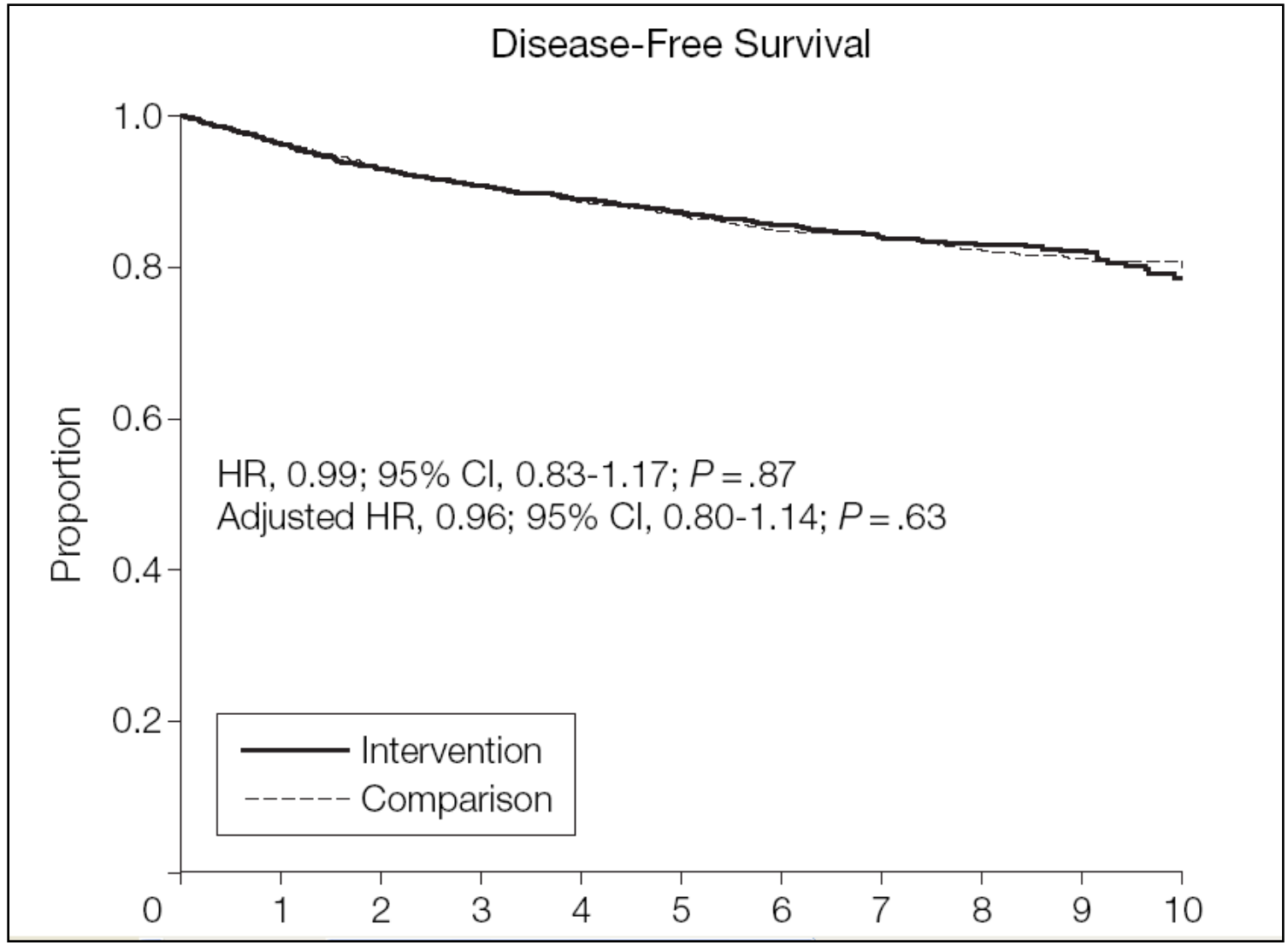
- Included 3088 women with early-stage breast cancer
- Randomized to phone-based diet intervention or control
- WHEL Diet:
  - High fruits and vegetables
  - Low fat
  - High fiber



Baseline **4 Years**

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

Impact of Dietary Intervention on DFS



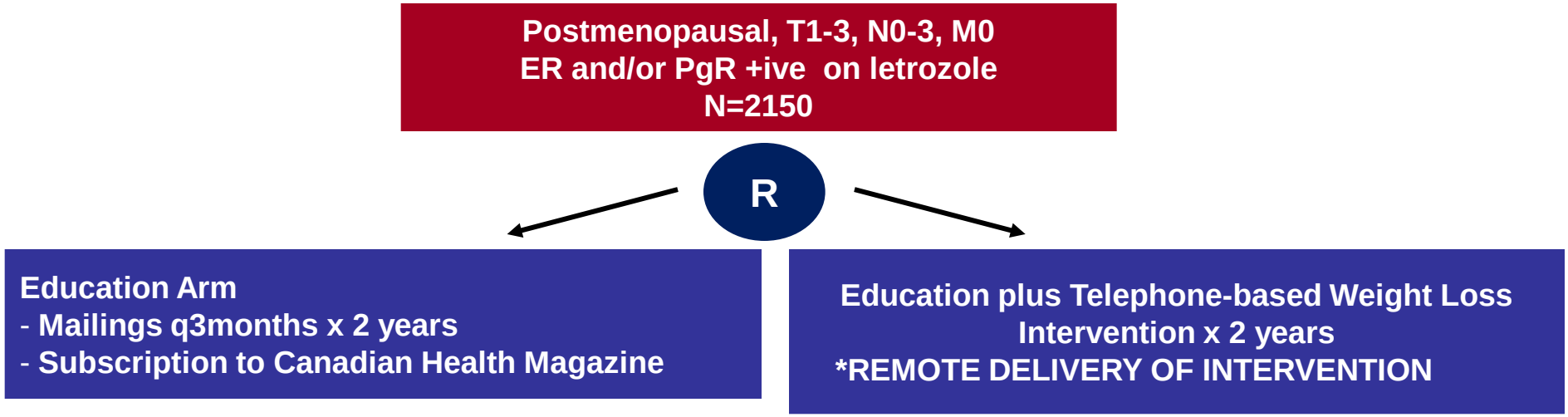
Pierce et al., JAMA 2007; 298: 289-98.

Why are WINS and WHEL different?

	WINS	WHEL
Diet	Low fat	High fruit/vegetables
Weight change	**6 lb weight loss**	**None**
Eligibility	High fat diet	None

One study aimed to study the impact of weight loss on breast cancer prognosis:

Lifestyle Intervention Study Adjuvant

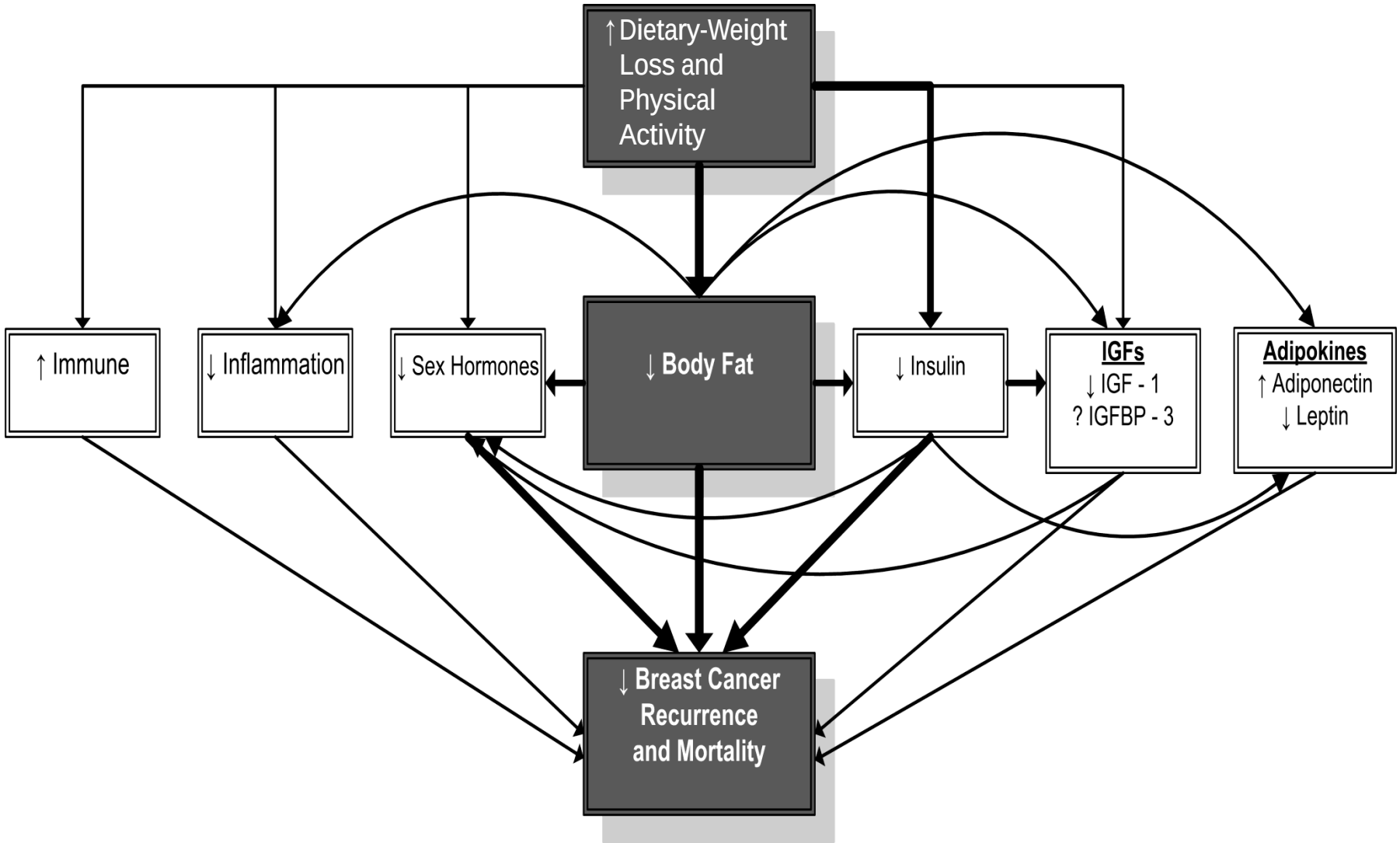


- Study closed after 338 women enrolled due to funding issues
- Intervention participants lost ~4.5kg more than control participants at 6,12,18 months
- 87.5% of protocol mandated calls delivered
- Provides important pilot regarding efficacy of intervention in this population

What do these studies tell us about the links between diet, weight 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
- WHI, WINS and WHEL are the only completed randomized trials looking at changes in energy balance and cancer risk or outcomes
- Is there other evidence that can shed some light on the factors driving the relationship between diet/obesity and cancer?

Interventional studies can also help shed light on the biologic pathways linking energy balance and cancer



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)

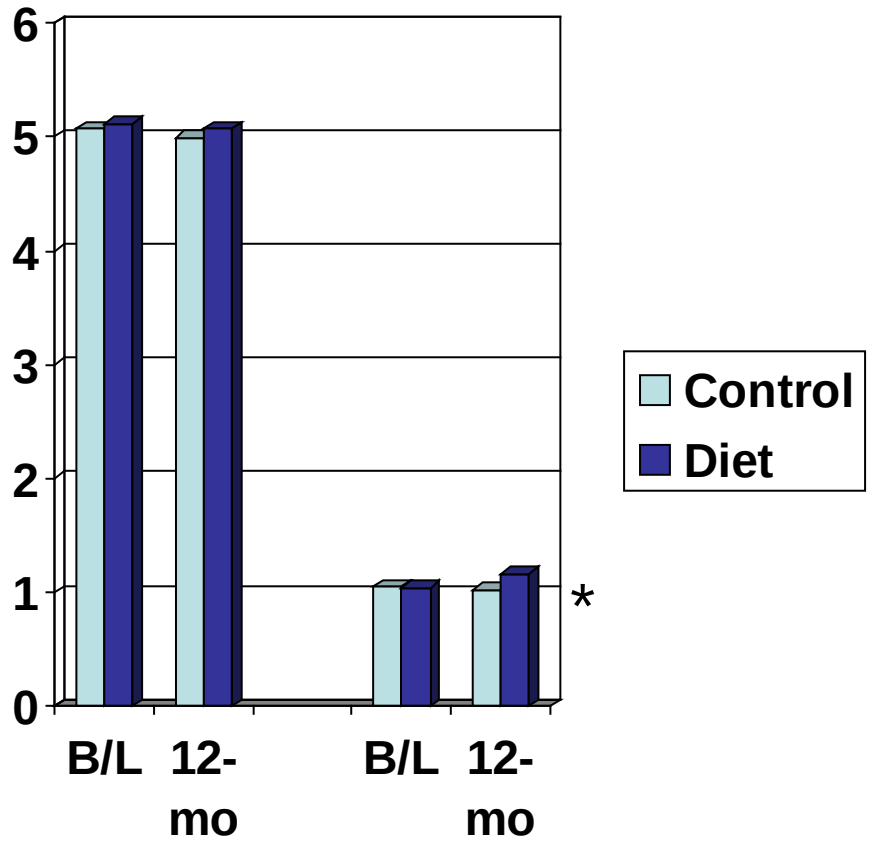
Goodwin et al, JCO 2002; Pasinisi et al, Pritchard et al, JCO 2011; Irwin et al, AACR 2007.

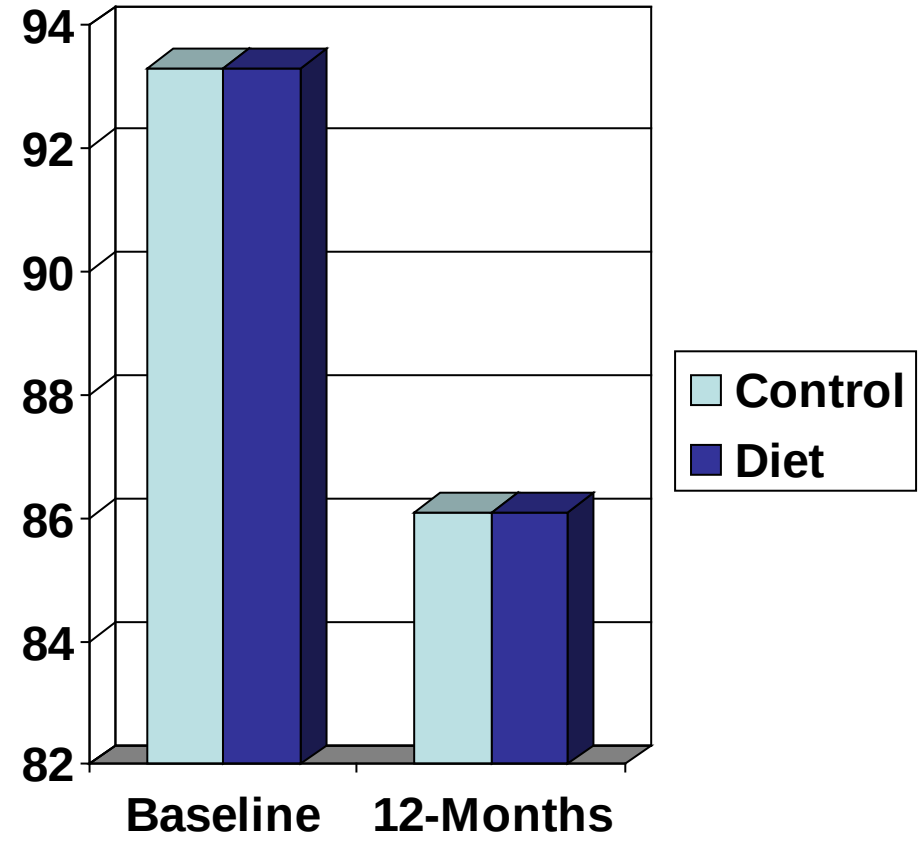
WHEL looked at diet-induced changes in insulin and metabolic biomarkers

- 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

Nutrition and Exercise Study for Women (NEW Trial)

- Designed to evaluate the impact of dietary weight loss and exercise upon hormones linked to breast cancer risk

- Enrolled 439 sedentary, overweight or obese, postmenopausal women

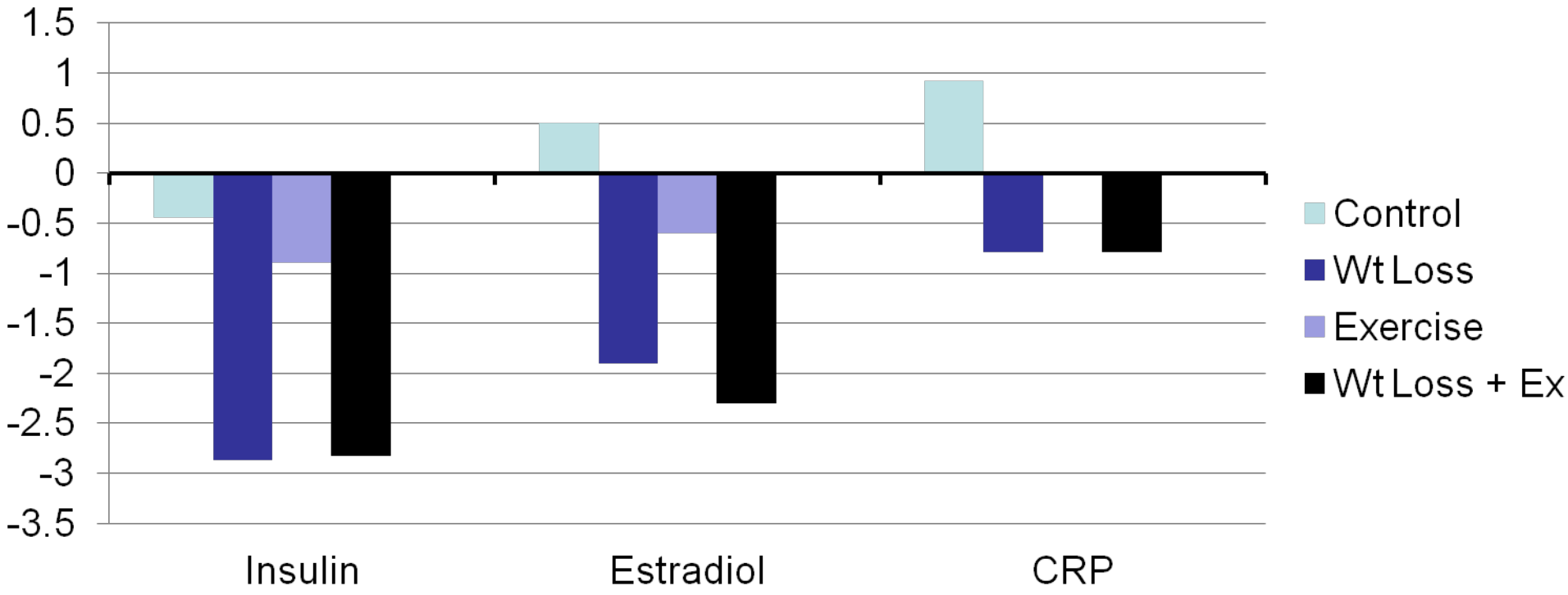
- Participants randomized to 1 of 4 groups:
    - Dietary weight loss
    - Exercise
    - Dietary weight loss + exercise
    - Control

- Endpoints:
    - Primary: change in sex steroids
    - Secondary: change in insulin, metabolic and inflammatory hormones

NEW Study Results

Weight Change:

Diet:	-10.8%
Exercise	-3.3%
Diet + Exercise	-11.9%
Control	-0.6%



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

- Obesity is consistently linked to increased cancer risk and increased risk of poor outcomes in many common malignancies
- The relationship between diet and cancer risk and outcomes is less consistent; may be more significant in some malignancies versus others
- Few randomized trials testing dietary change or weight loss as a strategy for cancer prevention or treatment
- Data from WINS and WHEL suggest that weight loss and/or consuming a diet lower in fat could influence cancer outcomes—at least in breast cancer
- A small number of randomized studies show that changes in weight and potentially diet can impact biomarkers linked to recurrence

Future directions

- 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 prostate and GI malignancies
    - Other factors may be more important in malignancies without the sex steroid-dependence of many breast cancers