Diet, Exercise and Weight: Could Lifestyle Modifications Improve Breast Cancer Outcomes?

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Cancer Outcomes Research Program Seminar

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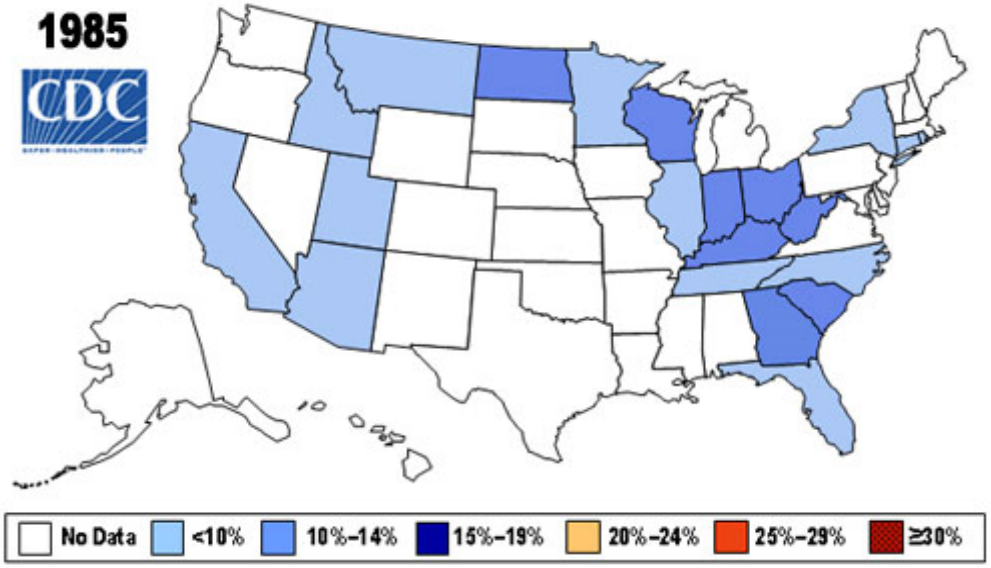
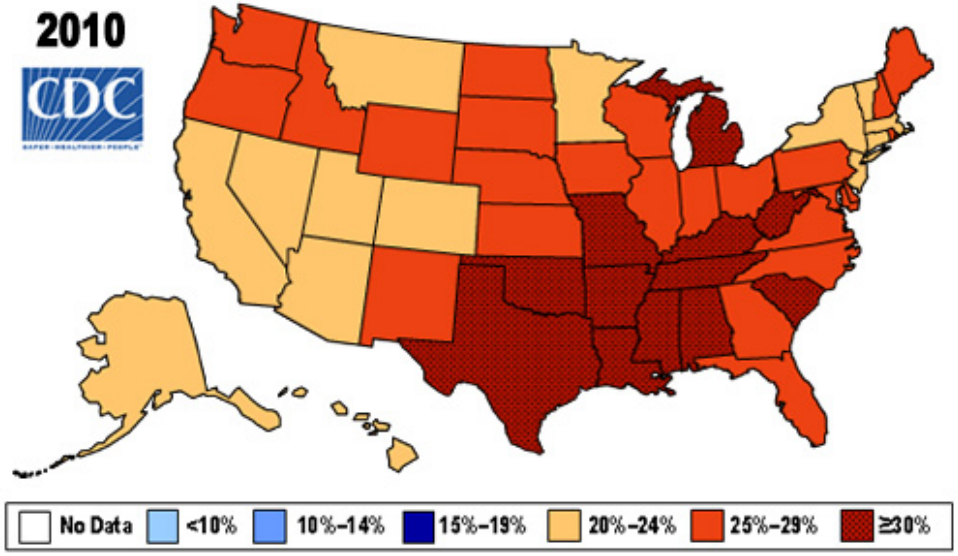
Objectives

- Review the observational data linking lifestyle factors and breast cancer risk and outcomes
- Discuss the (limited) data that changes in lifestyle factors could lower the risk of breast cancer recurrence
- Explore the biology underlying the connection between lifestyle factors and breast cancer
- Discuss next steps in lifestyle research in breast cancer
- Discuss the ASCO Obesity Initiative

Obesity rates have reached epidemic levels in the US

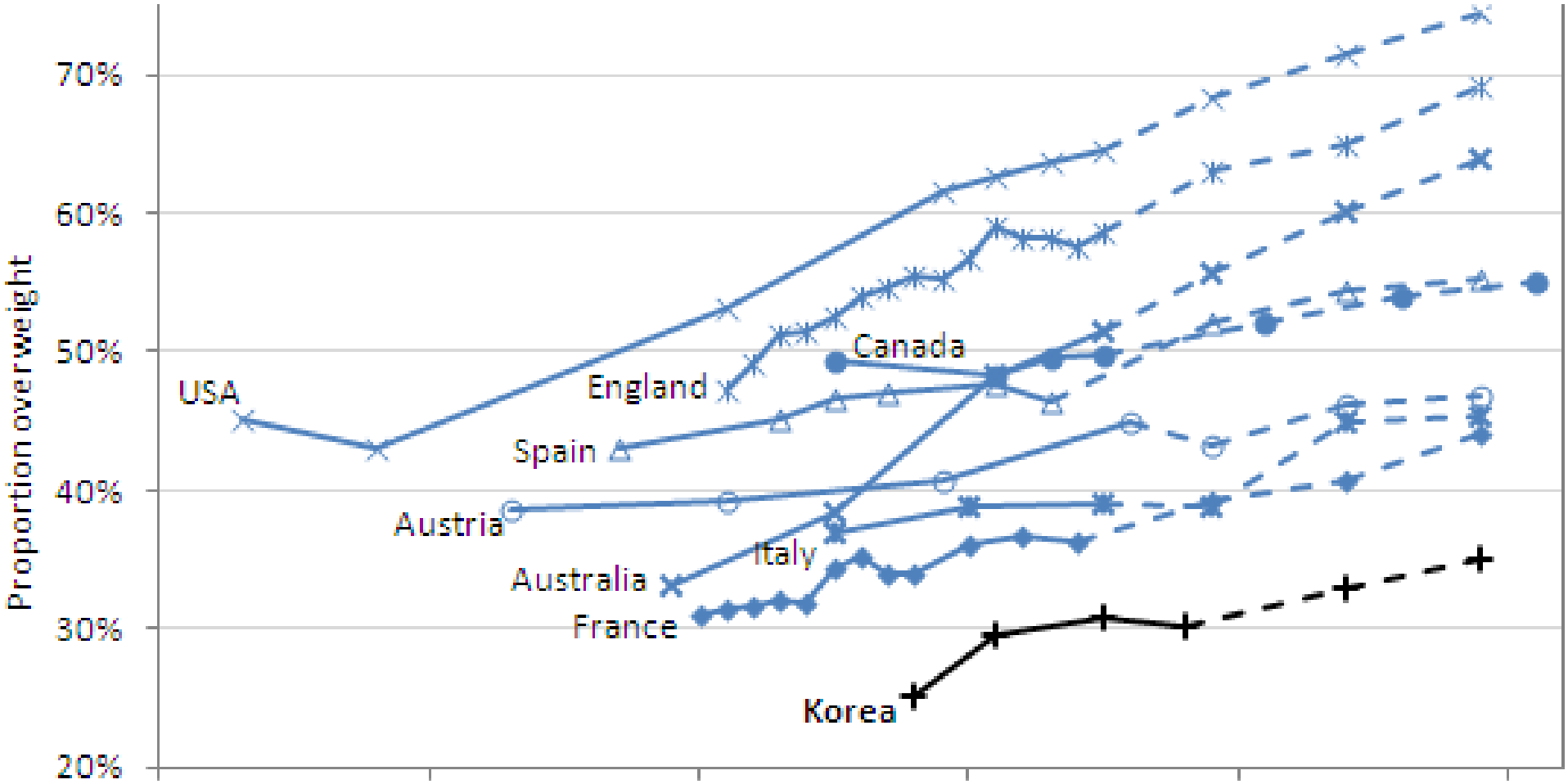




Trends in Obesity Prevalence (%), Adults 18 and Older, US, 1985-2010

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

Proportion adults who are overweight or obese, 1970-2020



www.oecd.org

In addition to increased risk of heart disease and diabetes, obesity also linked to increased risk of cancer

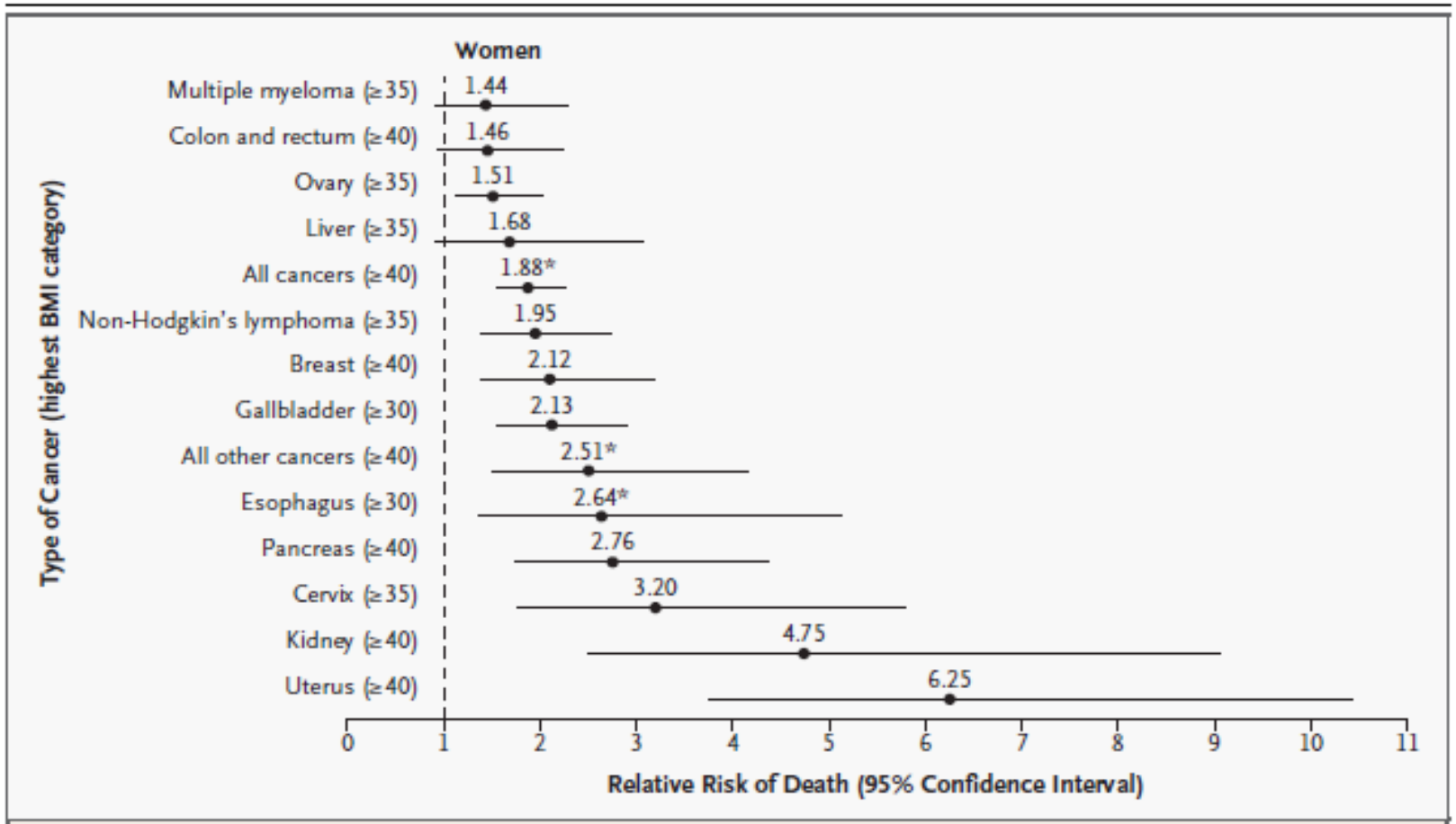


Figure 2. Summary of Mortality from Cancer According to Body-Mass Index for U.S. Women in the Cancer Prevention Study II, 1982 through 1998.

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

How does the rising prevalence of obesity impact cancer?

- Average person in US and UK weighed 9-18kg more in 2007 than 1990

- Using SEER data to calculate attributable risk percent of cancers due to obesity, in 2007 obesity led to:
  - 4% of all cancers in men (38,000 cancers/year)
  - 7% of all cancers in women (50,500 cancers/year)

Polednak et al. *Cancer Detection and Prevention* 2008; 32;190-9. Wang et al. *Lancet* 2011; 378:815-25.

Studies suggest that weight at diagnosis also linked to prognosis in breast cancer

Meta-analysis of 82 studies looking at obesity and survival in breast cancer

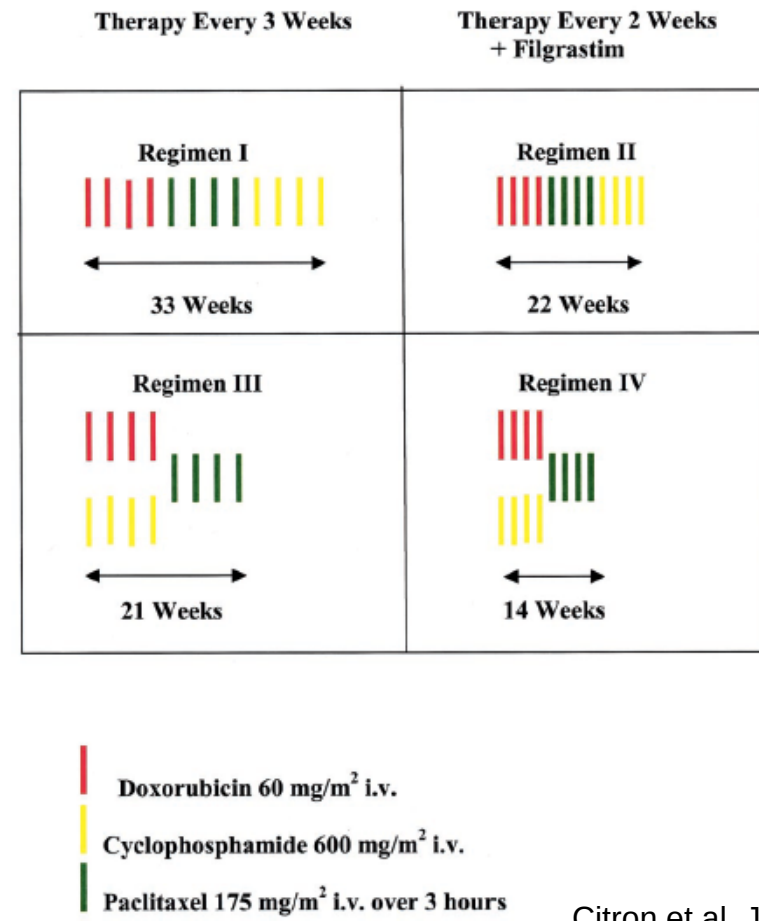
	Breast Cancer-Specific HR [95% CI]	Overall HR [95% CI]
All patients	**1.35 [1.24-1.47]**	**1.41 [1.29-1.53]**
Premenopausal		1.75 [1.26-2.41]
Postmenopausal		1.34 [1.18-1.53]

Chan et al. Annals of Oncology 2014

CALGB 9741

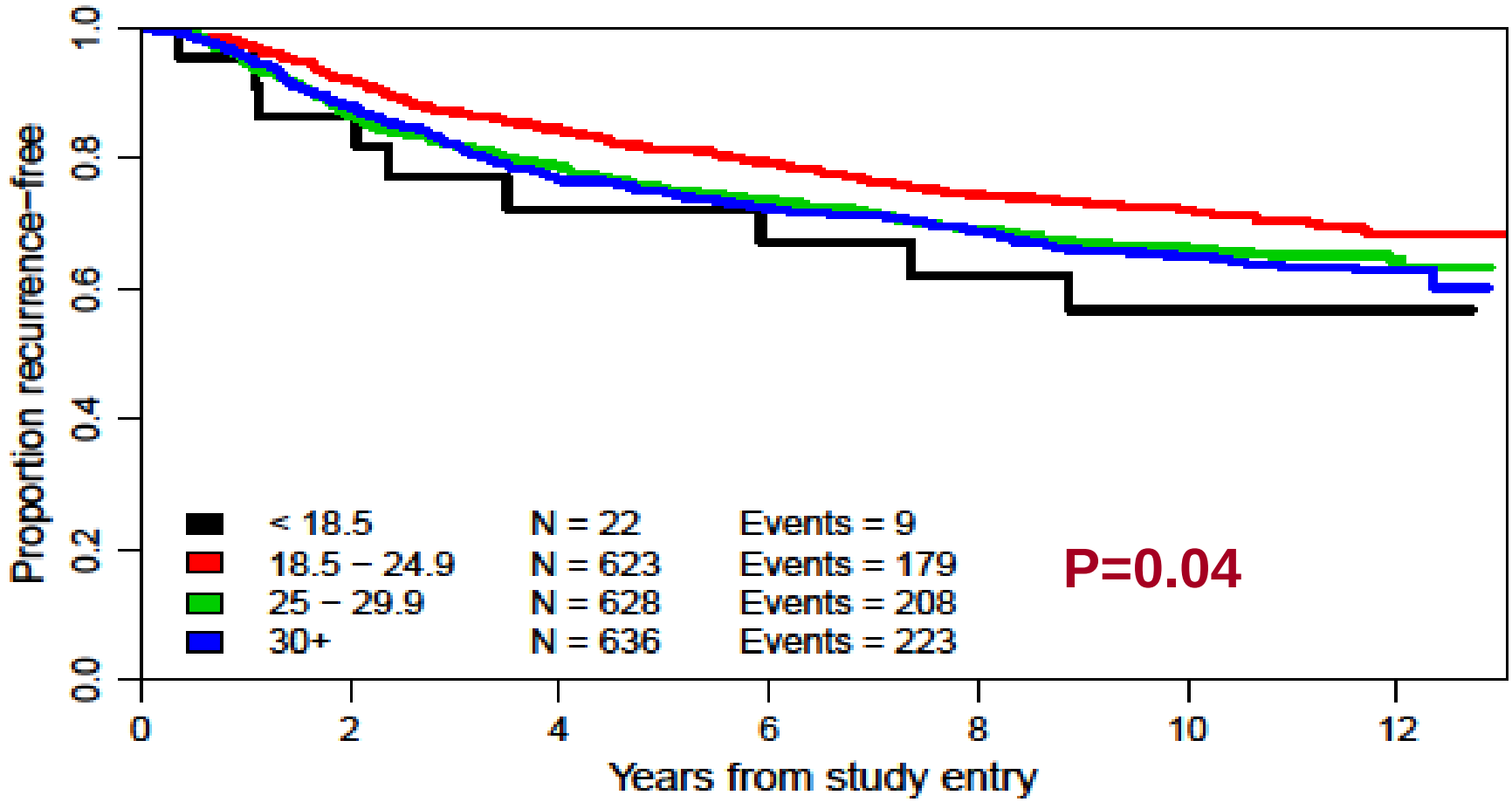
- Enrolled 2005 patients between 1997 and 1999
- Eligibility:
  - Node +
  - Pre and post-menopausal
  - Any HR status
- Protocol mandated weight-based chemotherapy dosing
- Median follow-up: 11 years

Treatment Schema



Citron et al, JCO 2003

Recurrence Free Survival by BMI



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)

Do obese patients develop different tumors than leaner patients?

- In 9741, no differences in histology between obese and normal weight patients
  - ER and PR
  - Tumor grade

- BMI and tumor biologic subtype (PAM50)

	Normal BMI (n=409)	Overweight (n=409)	Obese (n=437)
Luminal A	34%	34%	27%
Luminal B	21%	28%	30%
Basal-like	25%	18%	24%
HER-2 Enriched	20%	20%	19%

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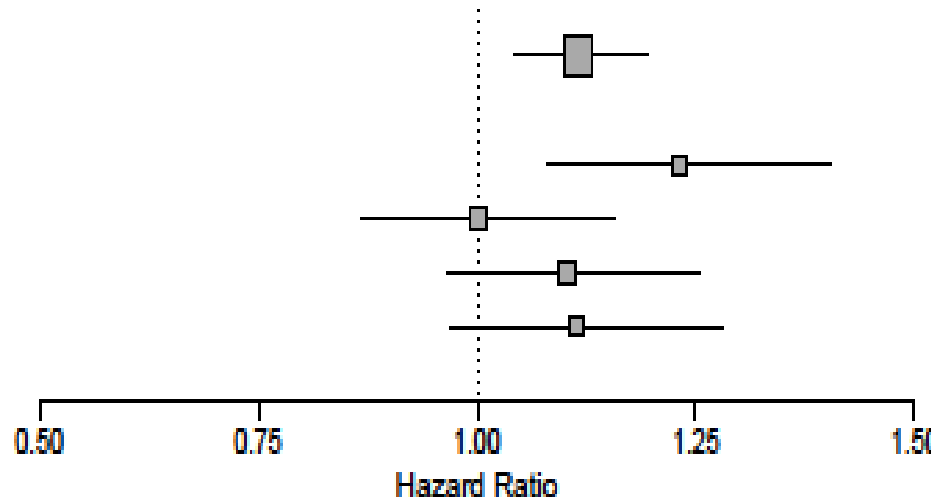
Relationship between BMI and recurrence by PAM 50 subtype

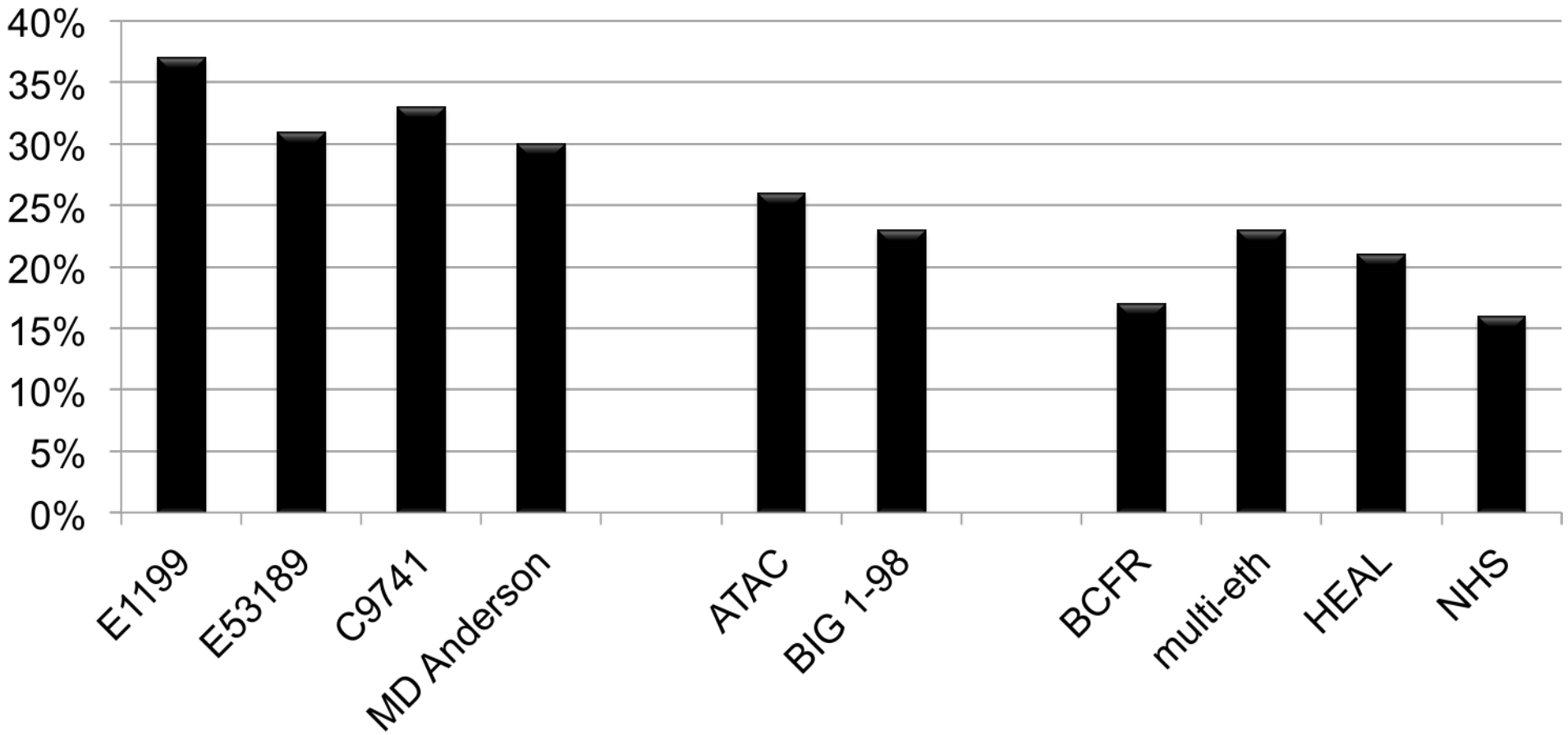
*

	N	HR (95% CI)
PAM50 subset	**1272**	**1.12 (1.04, 1.19)**
Luminal A	403	1.23 (1.08, 1.40)
Luminal B	334	1.00 (0.87, 1.16)
HER2−enriched	251	1.10 (0.97, 1.26)
Basal−like	284	1.11 (0.97, 1.28)



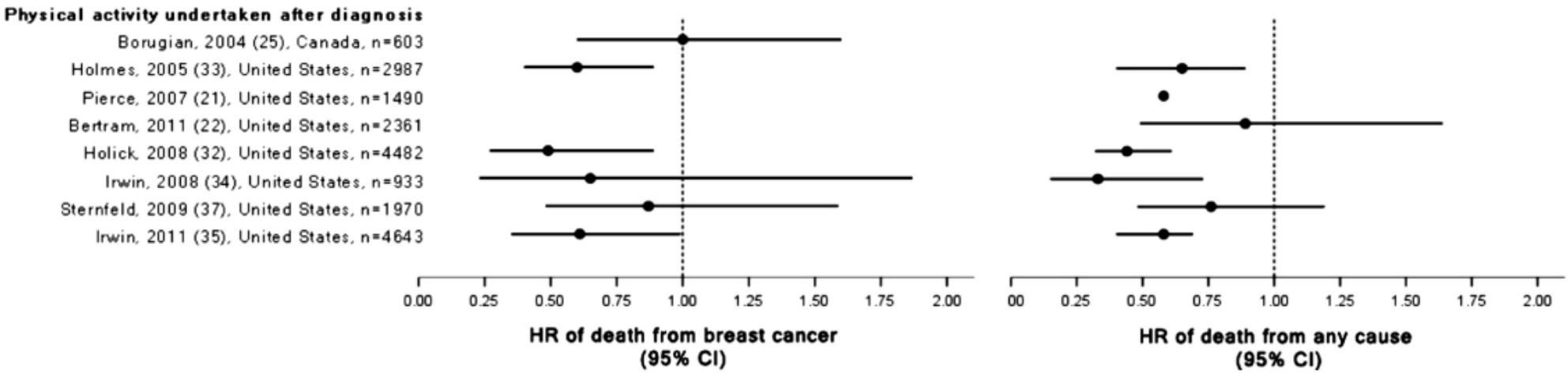
* HR for a 5-unit increase in BMI

Prevalence of obesity at diagnosis in breast cancer patients



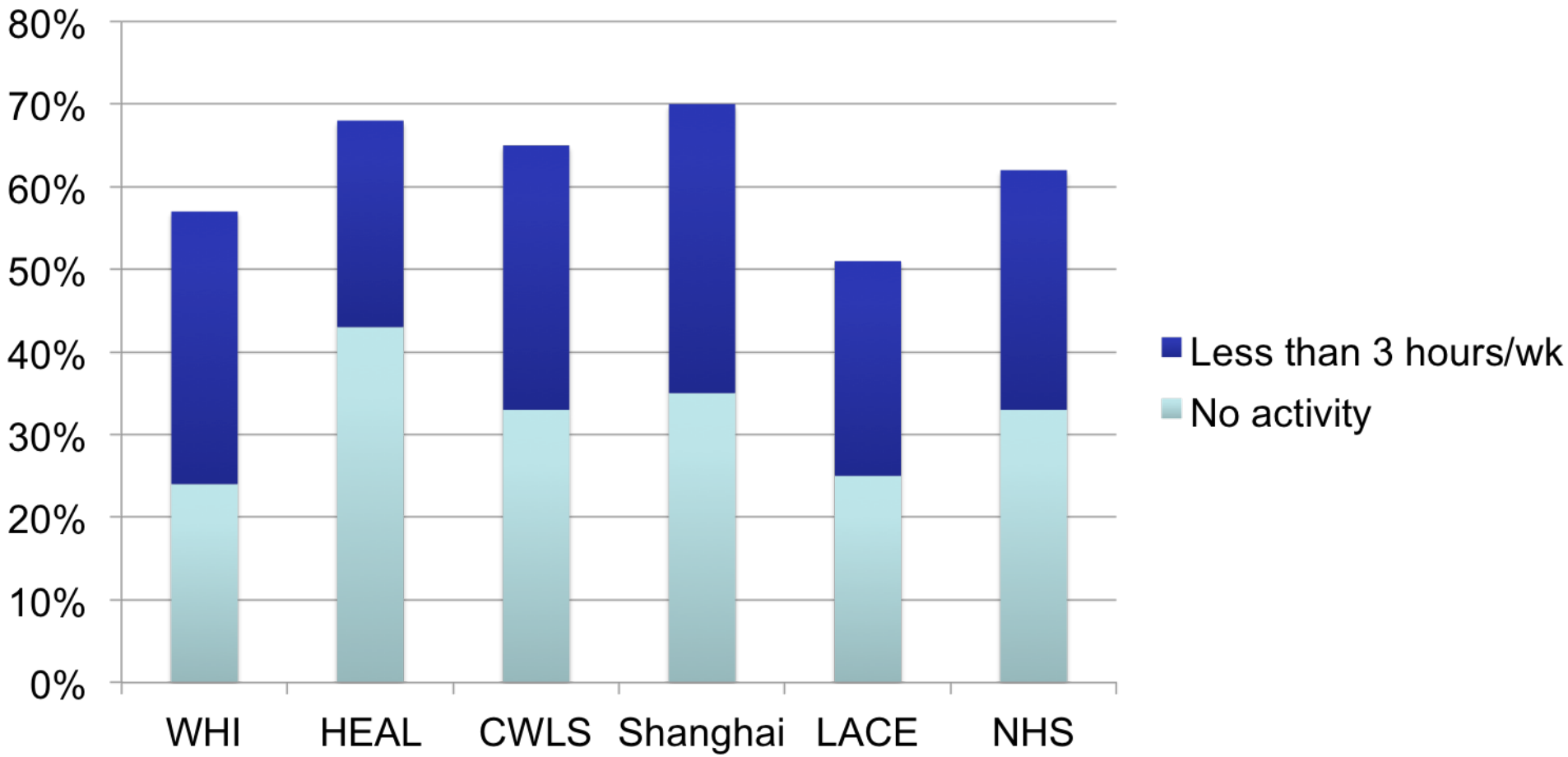
Inactivity after diagnosis also linked to risk of mortality

Post-diagnosis physical activity and breast cancer prognosis



Ballard-Barbash et al. JNCI 2012;104:815-840

Physical activity patterns in breast cancer survivors



Irwin Canc Prev Res 2011; Irwin JCO 2008; Holick CEBP 2008; Chen Canc Prev Res 2011; Sternfeld CEBP 2009; Holmes JAMA 2005.

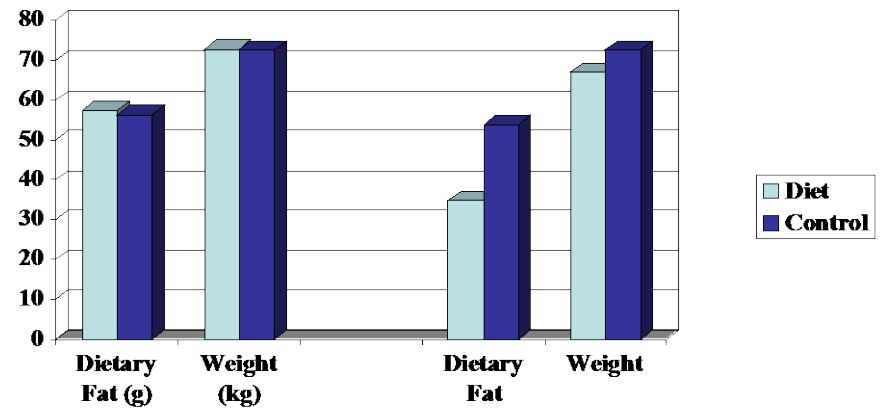
So obesity and inactivity are linked to poor outcomes in breast cancer and are common in cancer survivors

But does Lifestyle Change after breast cancer diagnosis improve prognosis?

Few studies have evaluated impact of lifestyle change on breast cancer outcomes

Women's Interventional Nutrition Study (WINS)

- Randomized 2437 women to low-fat diet intervention or control group
- Eligibility:
  - Stage I-III breast cancer
  - At least 20% calories from fat
- Intervention: one-on-one meetings with dietician, cooking classes
- WINS diet: reduce fat to 15% of total calories



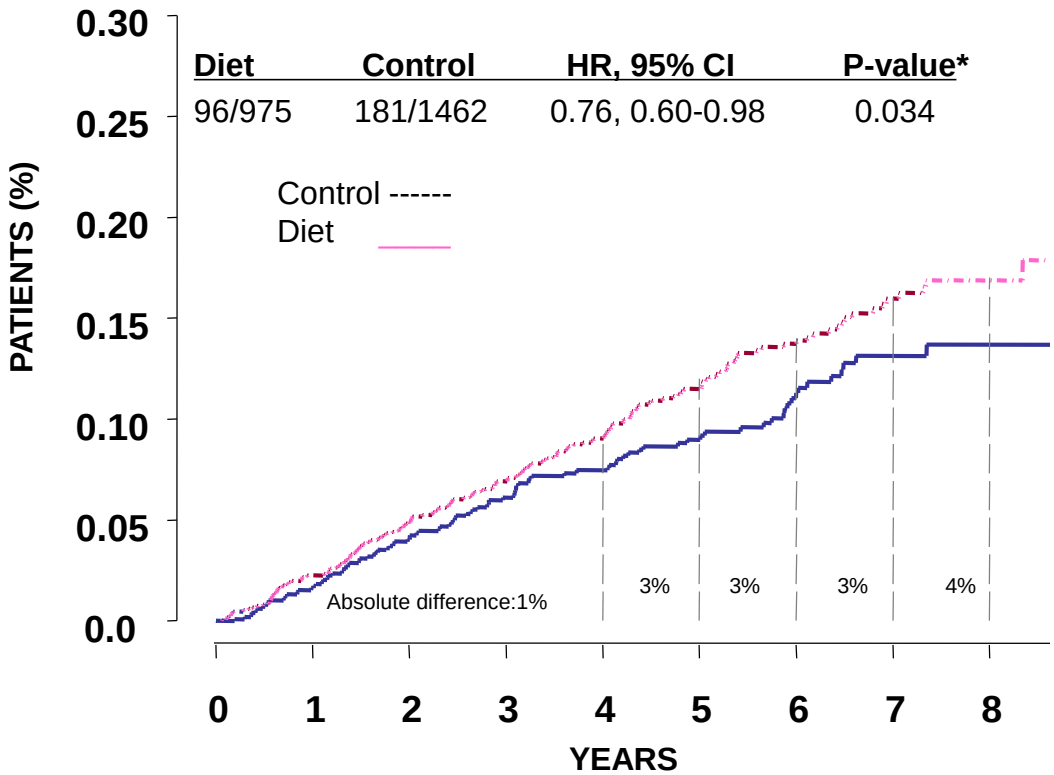
Baseline **5 Years**

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

WINS: Relapse-free survival

ALL PATIENTS

Diet	Control	HR, 95% CI	P-value*
96/975	181/1462	0.76, 0.60-0.98	0.034



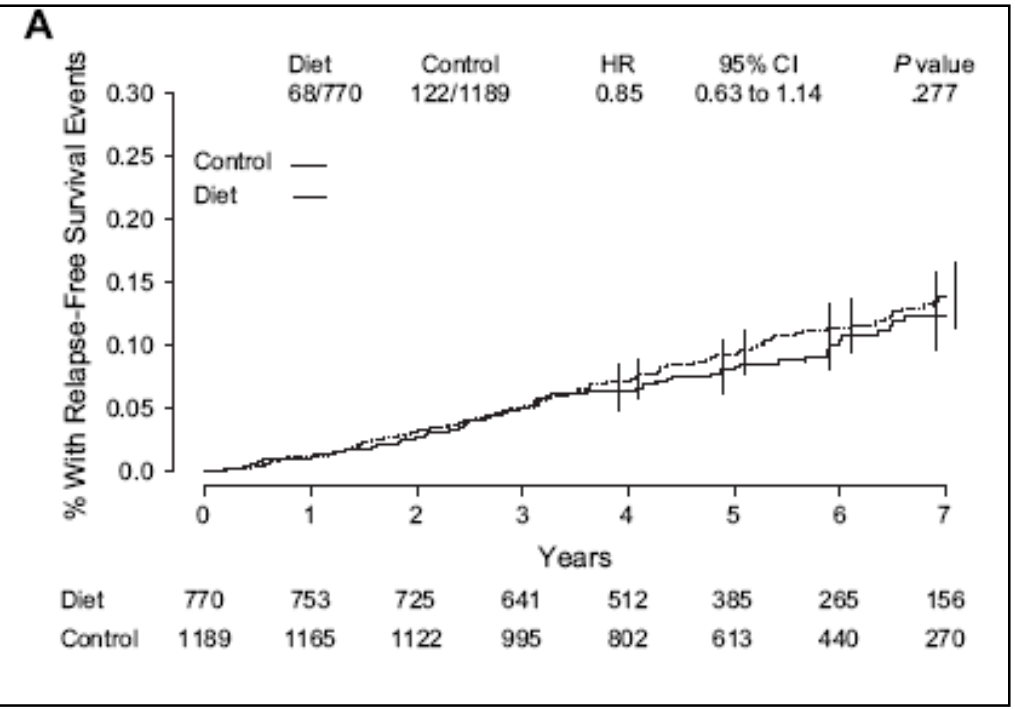
* From adjusted Cox proportional hazard model;

SUBGROUPS

	HR, 95% CI
BMI	
< 25	0.83, 0.54-1.27
25-30	0.77, 0.51-1.18
≥ 30	0.66, 0.42-1.04

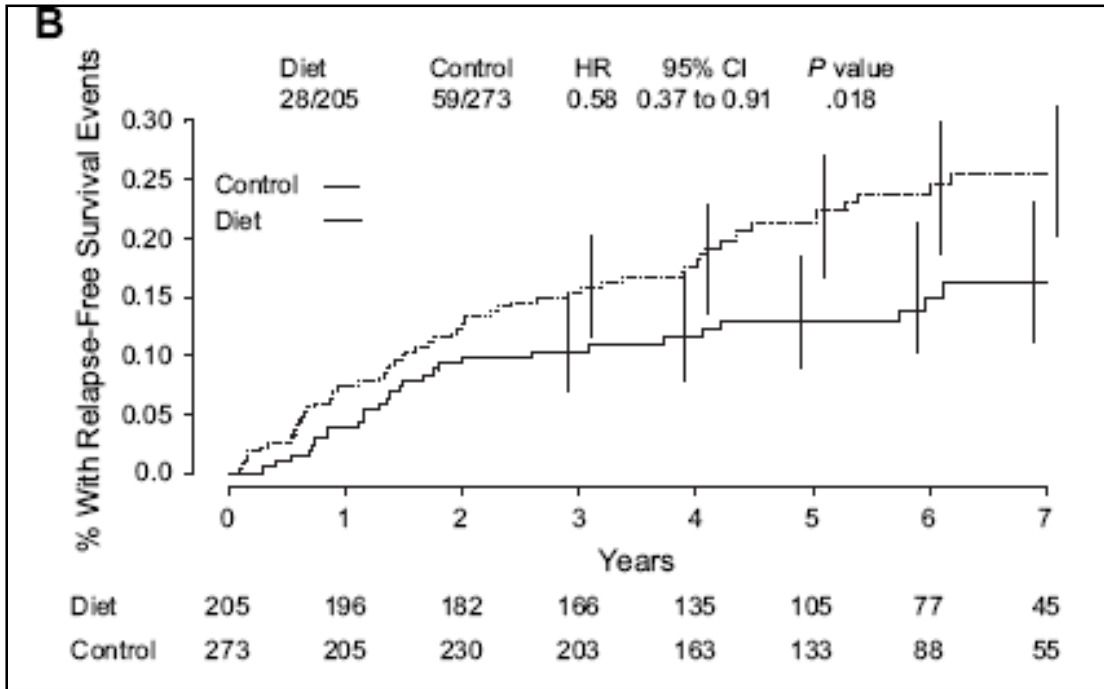
Chlebowski, Blackburn, Elashoff, et al. JNCI 2006; 98:1767-1776

Results by hormonal subtype



ER Positive

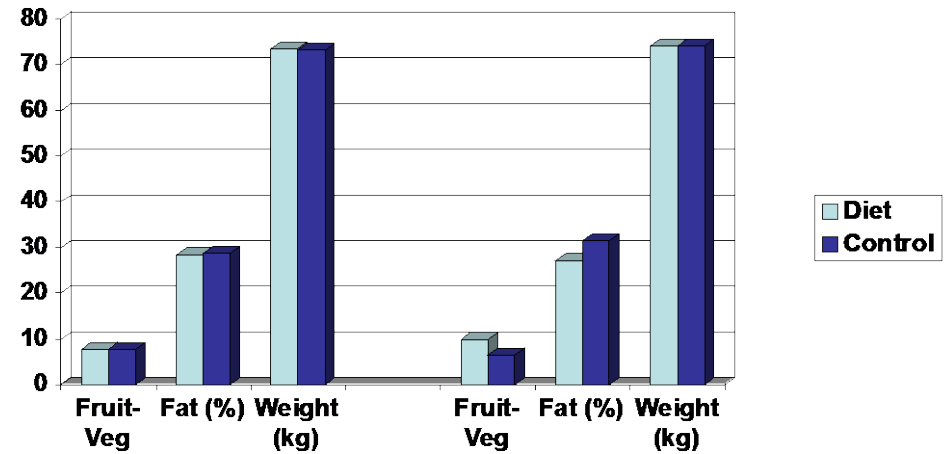
ER Negative



Chlebowski, JNCI 2006: 98: 1767-1776

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

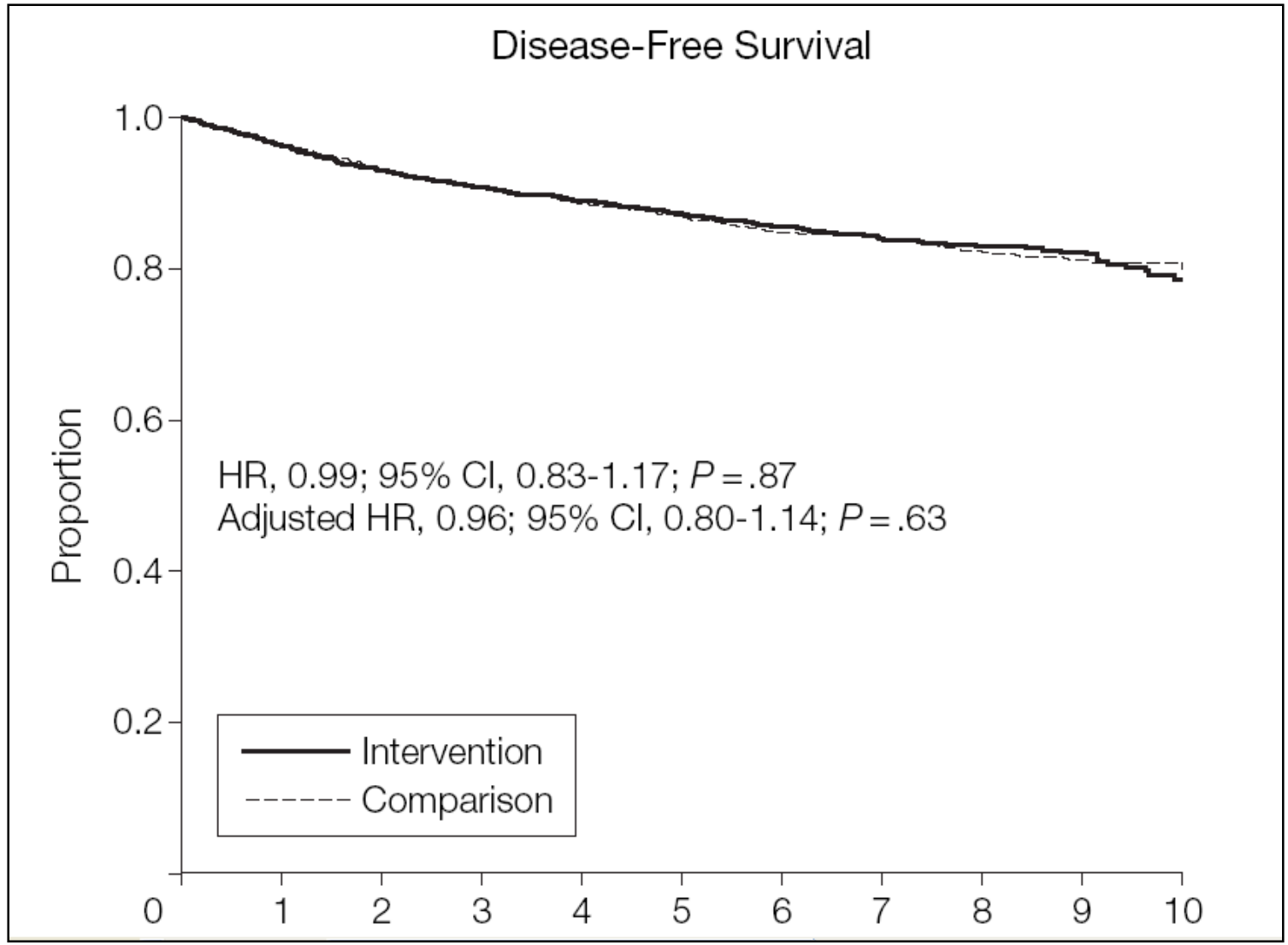
- Included 3088 women with early-stage breast cancer
- Randomized to phone-based diet intervention or control
- WHEL Diet:
  - High fruits and vegetables
  - Low fat
  - High fiber



Baseline **4 Years**

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

Impact of Dietary Intervention on DFS



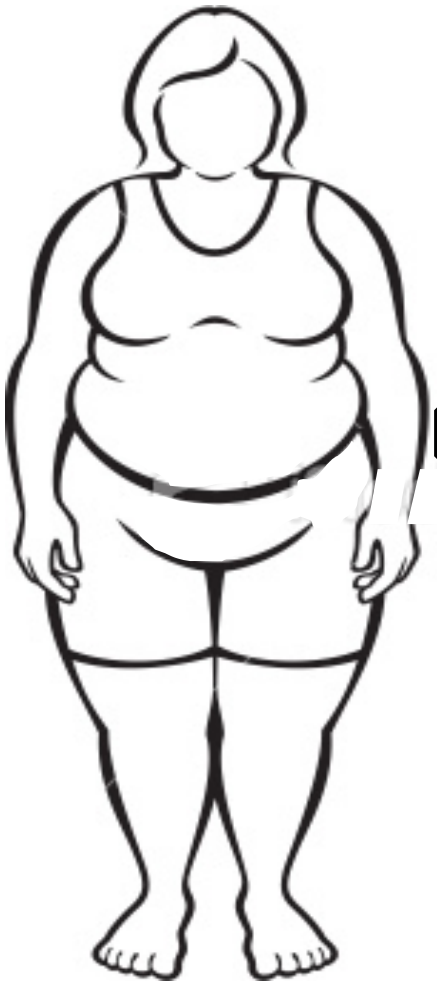
Pierce et al., JAMA 2007; 298: 289-98.

What do WINS and WHEL tell us about modifying lifestyle behaviors and breast cancer?

- Lifestyle modification is feasible in large groups of cancer survivors
- WINS provides the only clear evidence that lifestyle modification could impact cancer
- Results of WINS and WHEL seem to provide evidence that weight loss, achieved through dietary fat reduction, could impact cancer outcomes
- Caveats:
  - Neither study was designed as a weight loss/energy restriction trial
  - We do not know if the women who did better in WINS were the ones who lost weight

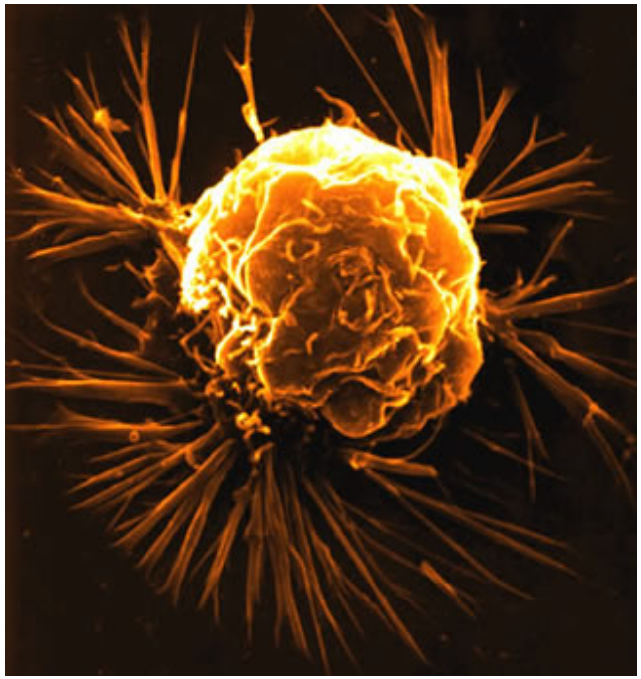
Does it make sense biologically that lifestyle factors affect cancer risk and prognosis?

Increased recognition that obesity and inactivity affect the body both systemically and at the level of breast tumors



Host Physiologic Alterations

Glucose
Insulin
Diabetes
Inflammation
Adipokines
Sex Steroids
Lipids

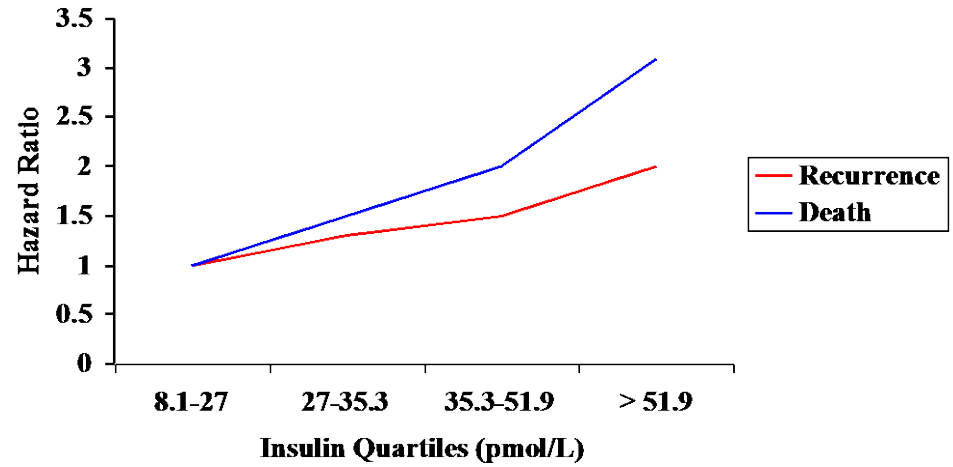


Tumour Micro-environment

Inflammation
Cytokines/growth factors
Angiogenic factors
Other alterations

Insulin and Breast Cancer Prognosis

- Fasting blood collected from 512 women with Stage I-III breast cancer
  - Collected 4-12 weeks after surgery, before adjuvant therapy
  - Pre and postmenopausal women
  - No diabetes
- At time of report, 50 months median follow up
  - 76 distant recurrences
  - 45 deaths



HR recurrence 2.0 (95% CI, 1.2 to 3.3)

HR mortality 3.1 (95% CI, 1.7 to 5.7)

Goodwin et al. JCO 2001;20:42-51

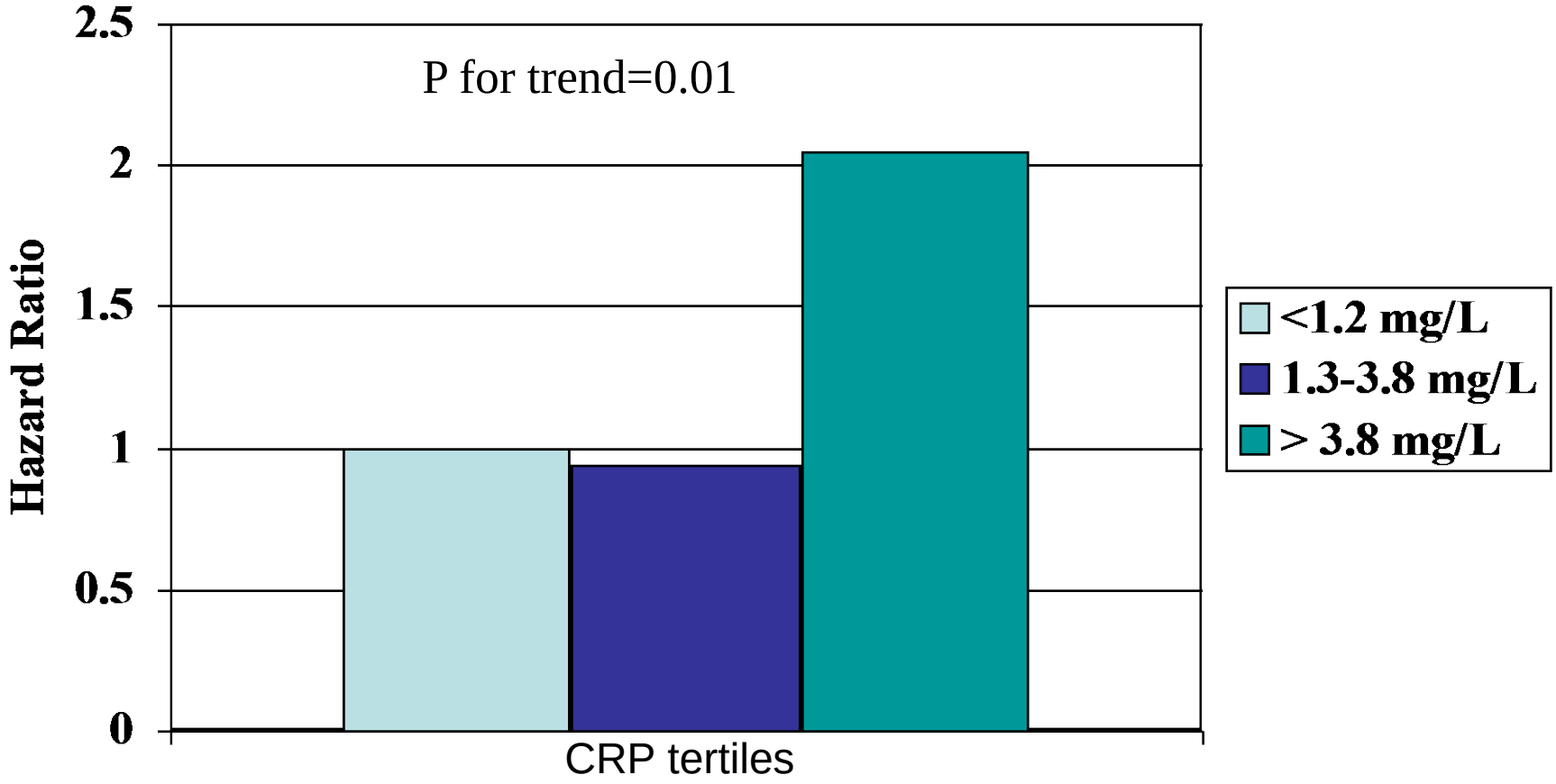
A number of other studies have also evaluated prognostic effects of insulin in breast cancer

		n	Factor Measured	Recurrence	Death
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)

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

Inflammatory Biomarkers also linked to breast cancer prognosis:

CRP and Risk of Total Death in the HEAL study



Pierce, et al. JCO, 2009

Can changes in lifestyle factors impact biomarkers linked to cancer prognosis?

Exercise and Insulin Study in Breast Cancer Survivors

101 Breast Cancer Patients

Eligibility:

- **Stage I-III**
- **Inactive**
- **BMI ≥ 25kg/m^2**
- **Completed treatment**

→ RANDOMIZE

→ **Exercise intervention**

→ **Usual care control** → **Delayed exercise program**

LIVESTRONG LANCE ARMSTRONG FOUNDATION

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

ASCO

Aims

- Primary: To evaluate the impact of a 16-week exercise intervention upon fasting insulin in sedentary, overweight/obese breast cancer survivors

- Secondary:
  - To evaluate the impact of the exercise intervention upon:
    - Leptin, adiponectin, HOMA
    - Weight and body composition
    - Strength
  - To evaluate adherence to the exercise prescription
    - Attendance at supervised sessions
    - Minutes of home-based aerobic exercise

Exercise Intervention

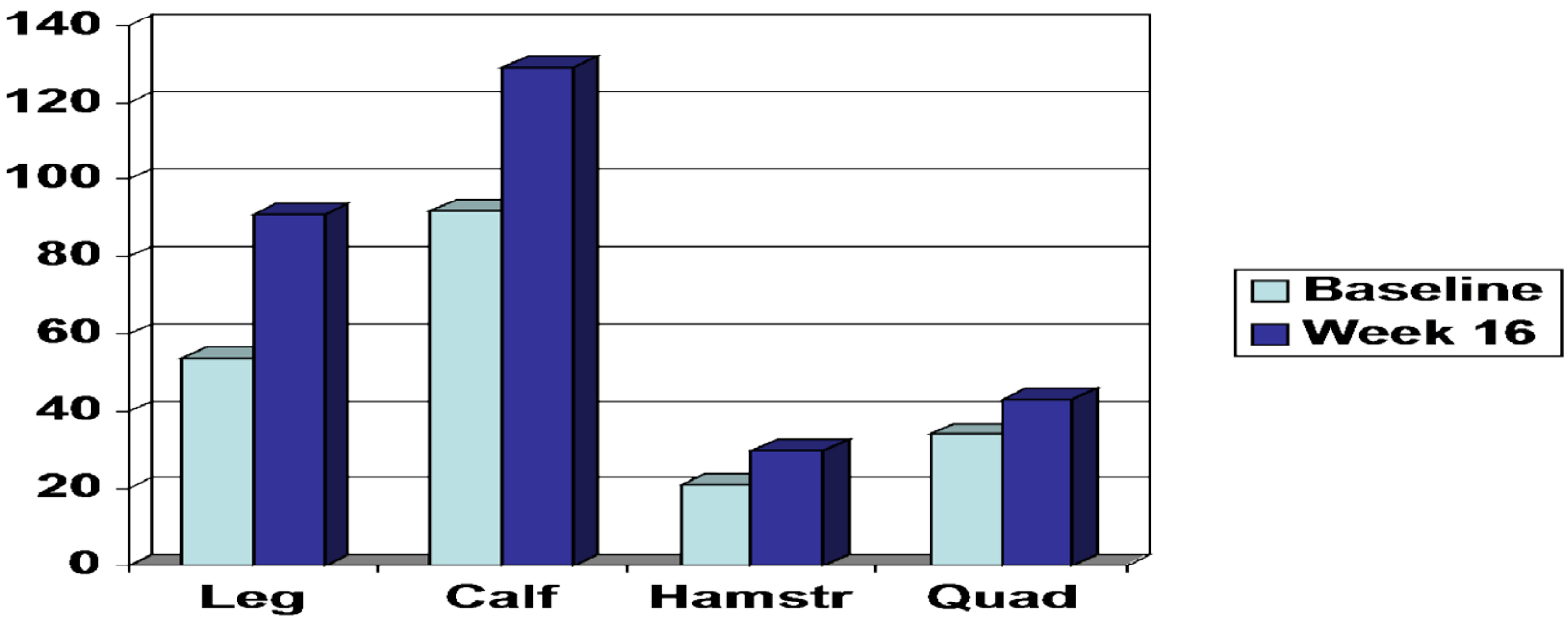
- 16-week aerobic and strength training intervention
- Goals
  - 100 minutes of strength training
  - 90 minutes of aerobic exercise
- Aerobic exercise
  - Home-based walking program
  - Participants provided with pedometer and heart rate monitor
- Strength training
  - 2 supervised 50 minute sessions/week
  - Focused on lower-body and core exercises

Patient Characteristics

	Exercise (n=51)	Control (n=50)
Age	52 ± 9	53 ± 9
BMI	30.3	30.3
Minutes PA/week	11 ± 22	13 ± 22
Stage:		
I	43%	43%
II	43%	44%
III	12%	8%
Chemotherapy	76%	67%
Hormonal therapy	73%	61%
Surgery		
Mastectomy	37%	41%
Lumpectomy	63%	55%

Exercise Outcomes

Strength: **Participants attended 73% of sessions**

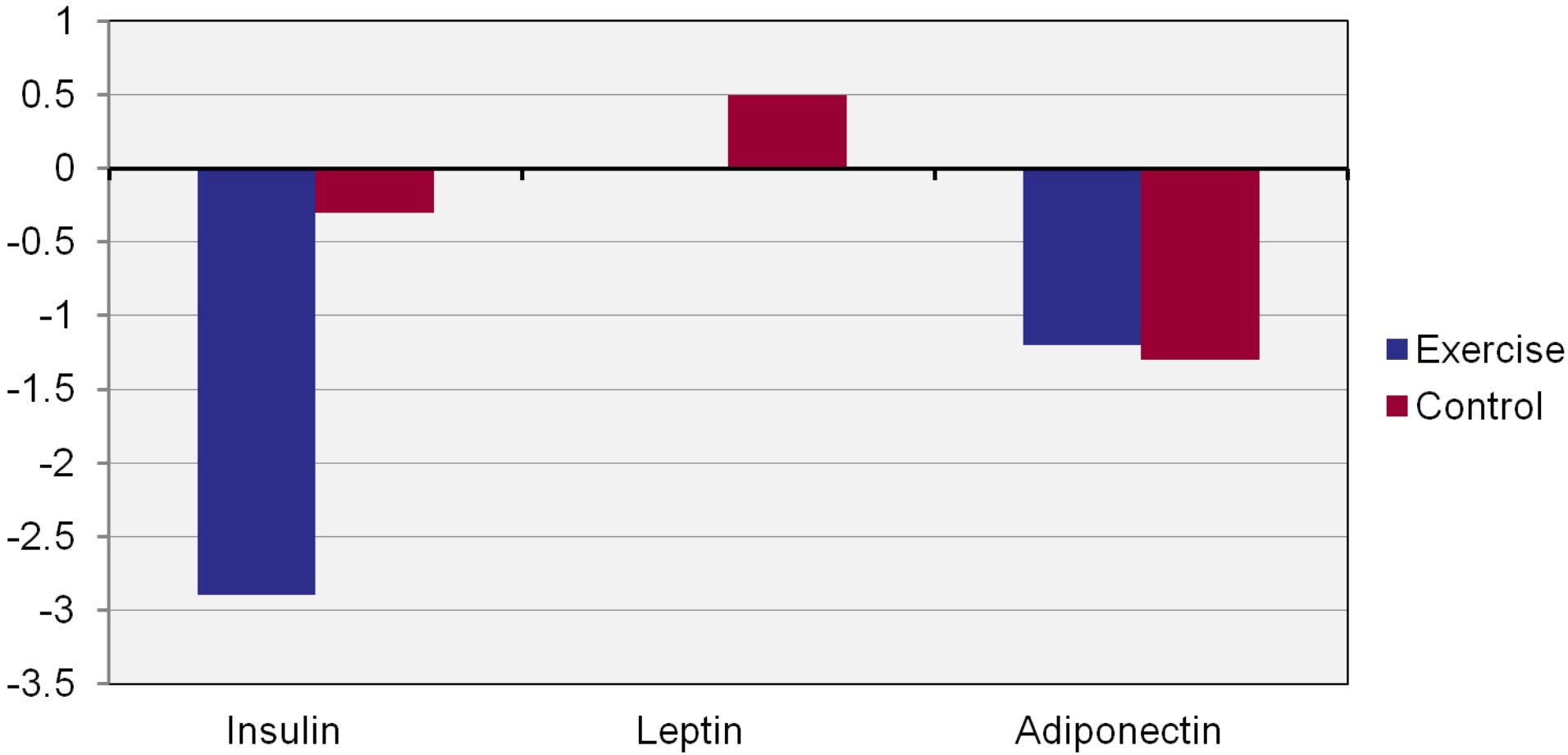


Aerobic Activity: **Increase of 100 minutes/week (11 vs 110)**

Anthropometric Measurements

	Intervention	Control	P value
BMI			
Baseline	30.3 kg/m2	31.4 kg/m2	0.42
Change	0.0 kg/m2	0.2 kg/m2	
Waist Circumference			
Baseline	90.7 cm	91.9 cm	0.06
Change	-1.5 cm	0.3 cm	
Hip Circumference			
Baseline	112.3 cm	113.8 cm	0.02
Change	-2.3 cm	-0.5 cm	

% Change in metabolic markers between baseline and week-16



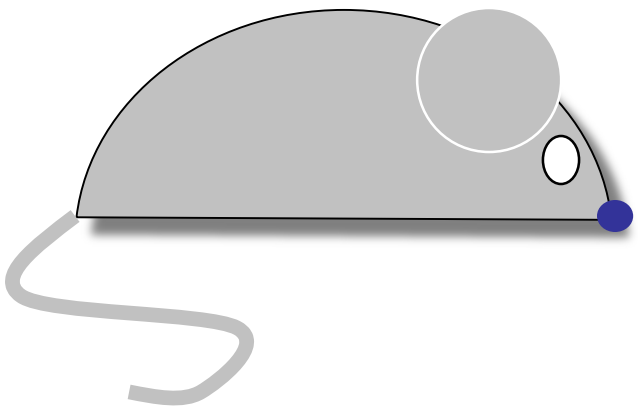
*P=0.07

Do lifestyle changes affect breast tumors?

- Studies show lifestyle interventions can impact serum hormones linked to cancer outcomes
- Assumption is that changing serum hormones indirectly causes changes in tumor cells
- Microenvironment surrounding a breast tumor influenced by local factors
- Is there more direct evidence that a lifestyle intervention can impact breast tumor tissue?

In animal models, lifestyle interventions can reduce breast tumor formation

135 Sprague-Dawley rats injected with 1-methyl-1-nitrosurea and randomized after 7 days:

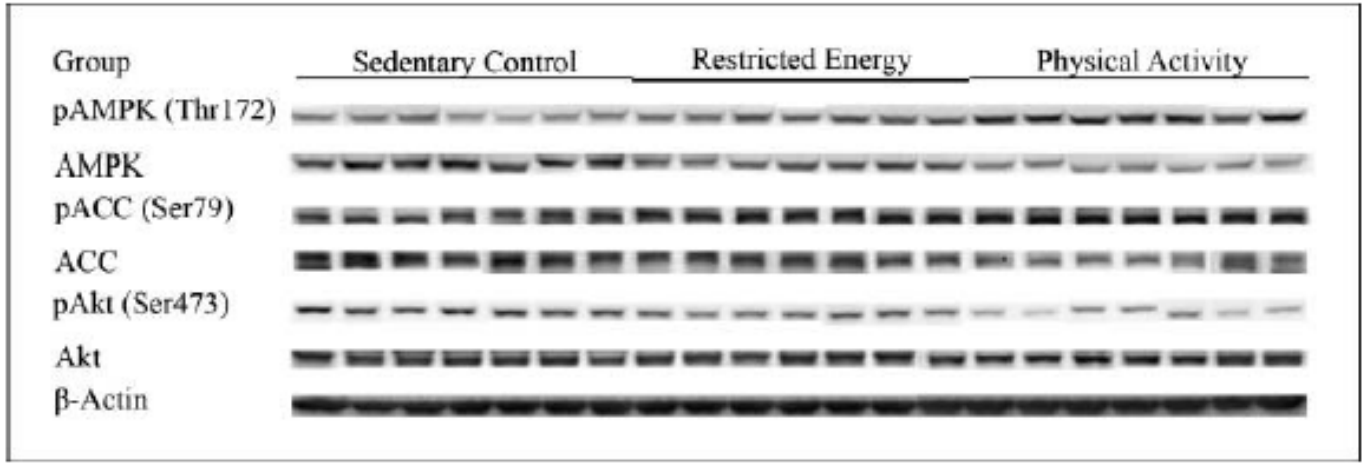


	Tumor	
	Incidence	Multiplicity
Sedentary Controls	98%	3.6
Energy restriction*	89%	3.1
Physical Activity*	84%	2.6

*92% net energy balance as compared to control group

Weiqui et al. Cancer Prev Research, 2009.

Exploratory analyses suggest that physical activity may affect AMP-kinase/MTOR pathways



Western blot images of proteins involved in energy-sensing pathways in mammary carcinomas from SC, RE and PA rats

How could we evaluate the impact of exercise on breast cancer?

PreHAB | Pre-Operative Health and Body Study

50 breast cancer patients

Eligibility:
- Newly diagnosed
- Stage I-III
- Plan to undergo definitive surgery
- < 90 minutes of exercise/wk

→ Baseline Research Biopsy

→ Exercise Intervention / Mind Body Intervention

→ **Definitive Surgery**

Currently open to enrollment at Dana-Farber and Yale University

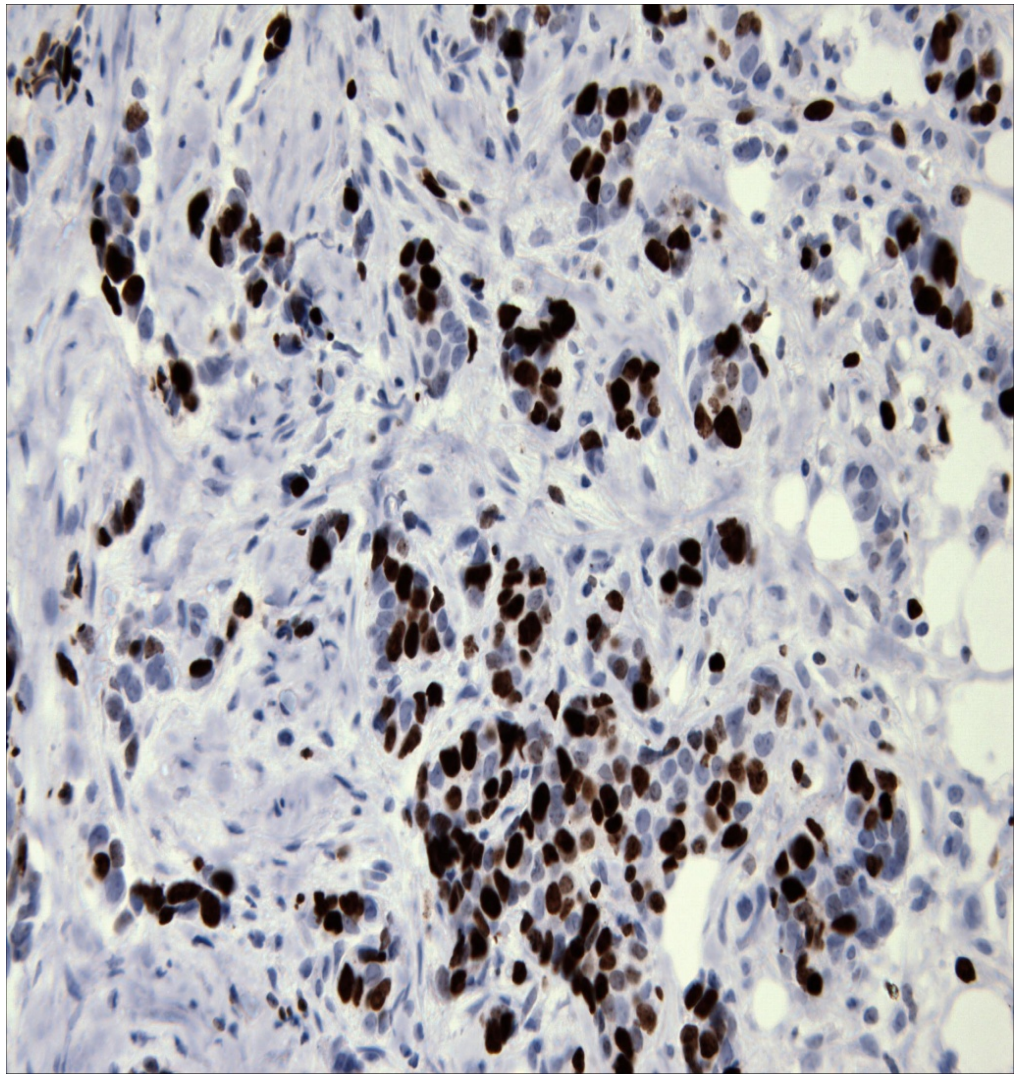
Objectives

- Primary aim: Evaluate the impact of exercise on Ki-67
  - tissue-based marker of proliferation
  - linked to prognosis
  - best established endpoint for window of opportunity studies
  - prior work shows impact of endocrine therapy, metformin

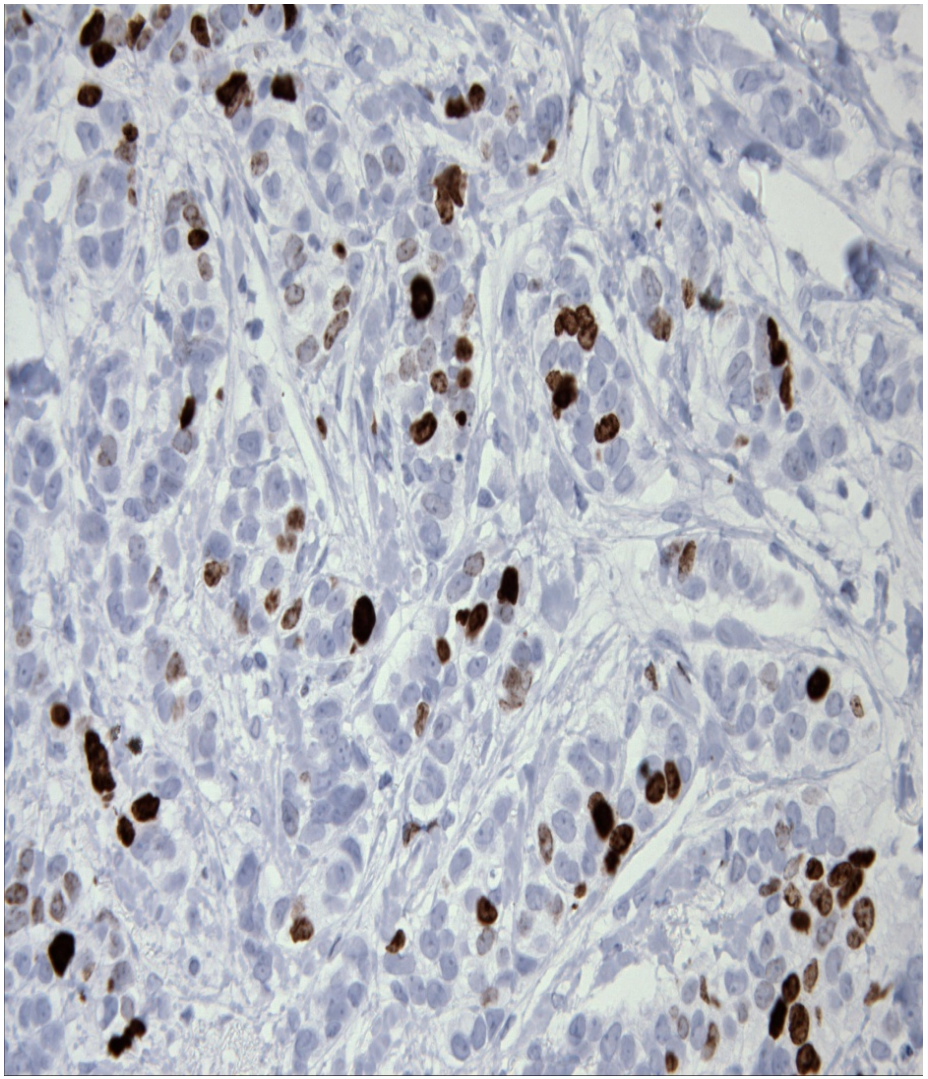
- Secondary tissue aims:
  - Insulin receptor expression
  - IGF-1 receptor expression
  - Apoptotic marker (CC3 vs TUNL)
  - ER, PR, HER-2

Ki-67 expression pre and post- tissue samples

Baseline biopsy (44%)



Post-intervention/control (16%)



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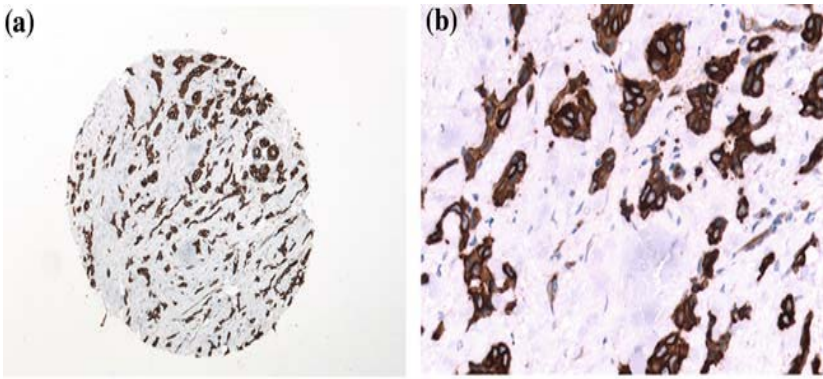
Insulin Receptor

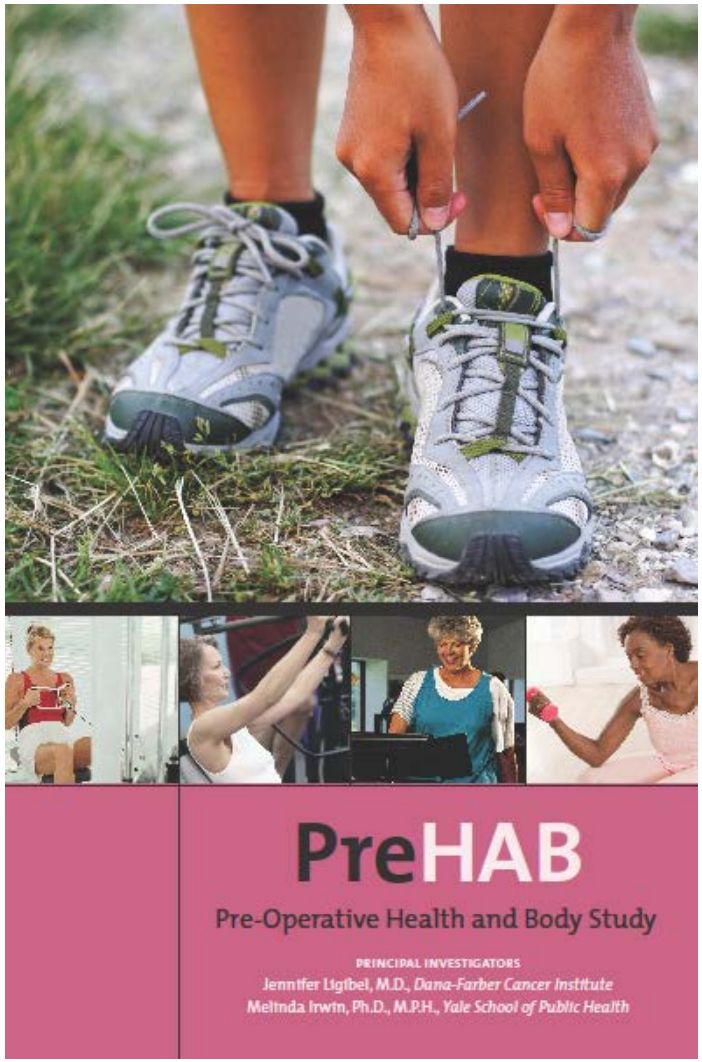
- Expressed in 50+% of breast tumors
- Exists as 2 isoforms:
  - IR A: higher expression in breast and other tumors
  - IR B: role in metabolism
- IR A binds insulin and IGF-II and forms heterodimers with IFG-1R
- Some evidence that expression linked to prognosis but independent of serum insulin levels



Mulligan et al. BCRT 2011.

Exercise Intervention

- Supervised, moderate-intensity exercise intervention
- Intervention duration: enrollment until surgery
- 2 supervised exercise sessions per week at DFCI/Yale + home-based exercise
- Target goals:
  - 180 minutes of aerobic activity per week
  - 40 minutes of strength training

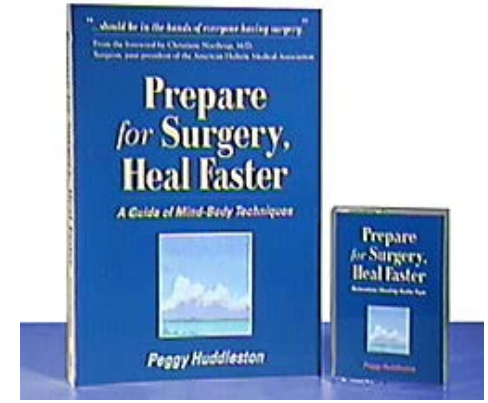


Mind Body Intervention: "Prepare for Surgery, Heal Faster"

- Mindful meditation surgical preparation program developed by Peggy Huddleston

- Program consists of a book and meditation CDs

- Involves a 5 step program for surgical preparation:
  - Relax to feel peaceful
  - Visualize your healing
  - Organize a support group
  - Use healing statements
  - Meet your anesthesiologist



Participant Summary : Participants 1-42

- Age ~52 yrs
- 24 post menopausal : 18 premenopausal
- Average BMI 34.2 kg/m2
- Average baseline exercise 55 minutes moderate activity/wk
- Average final minutes for exercise participants 221 minutes (15 METs)

Tumor Characteristics : Participants 1-42

- Tumor Subtype:

- HR+, HER-2 -	24
- TNBC	8
- HR+, HER-2+	8
- HR-, HER-2+	2

- Average tumor size 2.5cm

- Average week between registration & surgery 3.68 weeks

Lifestyle and breast cancer: What do we know?

- Hundreds of observational studies show links between lifestyle factors—weight, diet and physical activity—and breast cancer
- Little data from randomized trials demonstrating that changing lifestyle behaviors will improve breast cancer prognosis
- Mechanistic work suggests biologic feasibility of connection between lifestyle factors and breast cancer
- Lifestyle interventions impact systemic (and hopefully) tissue biomarkers linked to cancer

Lifestyle and Cancer: What don't we know?

- Does lifestyle modification after diagnosis reduce the risk of dying from breast cancer?

- Which lifestyle factor is most essential?
  - Dietary quality?
  - Weight?
  - Physical activity?

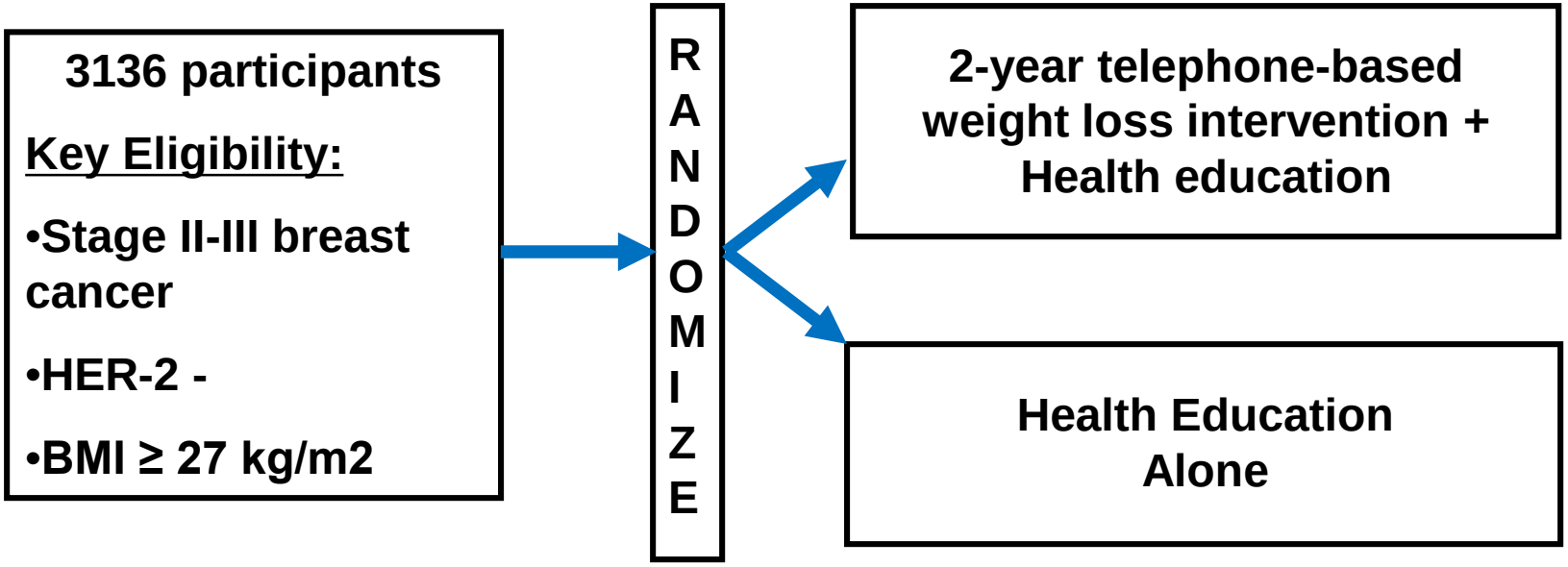
- Which patients are most likely to benefit?
  - Patients who are overweight or inactive?
  - Patients with medical problems like diabetes or high blood pressure?
  - Patients with a particular tumor type?

Randomized Phase III Trial Evaluating the Role of Weight Loss In Adjuvant Treatment of Overweight and Obese Women with Early Breast Cancer (Alliance 011401)

The Breast cancer WEight Loss (BWEL) Study

PI Jennifer Ligibel
Co-PI Pamela Goodwin

Study Overview



Conducted through NCTN/NCORP

Anticipated opening: Spring 2016

Objectives

- **<u>Primary</u>:** **Assess the impact of a weight loss intervention upon Invasive Disease Free Survival (STEEP)**

- **Secondary:**
  - Assess the relationship between weight loss and IDFS and OS
  - Assess the impact of the weight loss intervention upon:
    - Overall mortality
    - Distant disease free survival
    - Weight change
    - Hospitalizations for cardiovascular disease or diabetes
  - To evaluate the impact of the weight loss intervention upon IDFS in subsets of participants defined by:
    - Hormone receptor status of the tumor
    - Menopausal status

- **Correlative**

Select Eligibility Criteria

- Breast cancer diagnosed within past 12 months
- Her-2 negative
- Stage II-III
  - Triple negative tumors: T2-T3, N0-3; any T, N1-3
  - ER+: any T, N1-3
- Completed with all chemotherapy and surgery (current radiation and hormonal, bisphosphonate, and biologic therapies okay)
- Life expectancy from other causes at least 5 years
- BMI ≥ 27 kg/m2
- Pre- or postmenopausal

Weight Loss Intervention Overview

- **Centralized, 2 year telephone-based intervention based on DPP, Look Ahead and LISA study**
  - Remote technology integrated to increase adherence and help maintain weight loss
- **Individualized goals:**
  - **10% weight loss**
  - **500-1000 kcal/day deficit**
  - **700-900 kcal/week activity (150-200 minutes walking) in first 6 months, goal of 45-60 minutes of activity/day in maintenance phase**

Health Educational Intervention

- **Twice yearly mailings of materials regarding cancer survivorship and general health**
- **Twice yearly webinars regarding updates in breast cancer (following the San Antonio Breast Cancer Symposium and ASCO)**
- **Twice yearly study newsletter**
- **2 year subscription to Health magazine**
    - *Health* for English-speaking participants
    - *NIH El Salud* for Spanish speaking participants

Statistical Considerations

- **1:1 Randomization**

- **Stratification Factors:**
  - Menopausal status (pre or peri-menopausal s. post)
  - Hormone receptor status of the tumor (ER and/or PR + vs both -)
  - Race/ethnicity (African American vs. Hispanic vs. Other)

- **<u>Sample Size Calculation</u>:**

HR	Control 5yr DFS	Abs. Diff	80% power		85% power		90% power	
			IDFS events	Total N *	IDFS events	Total N *	IDFS events	Total N *
0.75	0.75	5.6%	379	1510	434	1741	508	2022
	0.77	5.2%		1652		1890		2212
	0.8	4.6%		1883		2127		2521
0.8	0.75	4.4%	631	2448	721	2822	844	3302
	0.77	4.1%		2678		3063		3585
	0.8	3.7%		3051		3516		4145
0.85	0.75	3.3%	1189	4506	1360	5193	1591	6033
	0.77	3.1%		4927		5636		6596
	0.8	2.7%		5611		6466		7511

- **Final sample size: 3136 participants**
  - Equates to 4.1% absolute improvement in iDFS in intervention arm
  - Assumptions:
    - » 4 years of accrual and 4 years additional follow up
    - » Two-sided alpha 0.05
    - » 5% loss to follow up and 10% complete discontinuation of intervention

What does this all mean for our patients today?

Optimizing health behaviors for cancer survivors

- **Recommend weight loss and increased physical activity**

- **Be aware of local resources**
  - Many cancer centers offer nutrition advice and exercise classes for cancer survivors
  - An increasing number of community-based programs also focus on cancer survivors
  - The American College of Sports Medicine offers a cancer certification program for fitness professionals

- **Support randomized trials of lifestyle interventions in cancer survivors**

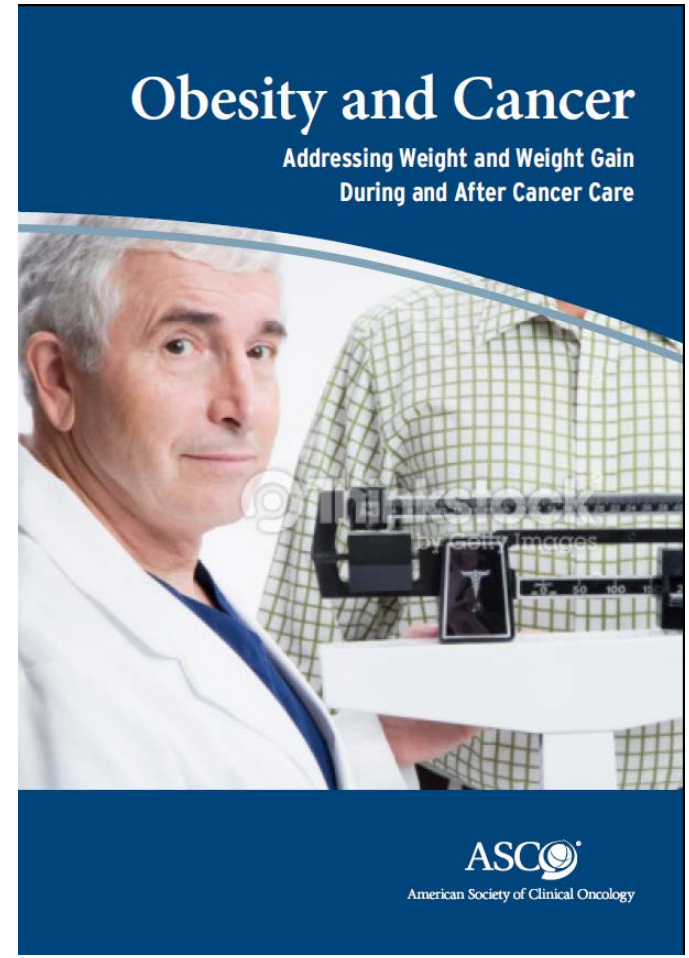
ASCO Obesity Initiative

- ASCO selected Obesity and Cancer as a core initiative for 2014

- Priorities:
  - Promote education and awareness of the links between obesity and cancer
  - Develop tools and resources to help providers communicate with their patients about healthy lifestyle behaviors and encourage behavior change
  - Support research to study the impact of weight loss/lifestyle change on cancer risk and outcomes
  - Advocate for policies to support healthy lifestyles for the general population and cancer survivors

ASCO Obesity Toolkit

- Released May 2014
- Developed to provide information regarding link between obesity and cancer and to help patients make lifestyle changes
- Provider and patient materials available
- Provided in paper and electronic versions
- Information available at cancer.net



JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Position Statement on Obesity and Cancer

Jennifer A. Ligibel, Catherine M. Alfano, Kerry S. Courneya, Wendy Demark-Wahnefried, Robert A. Burger, Rowan T. Chlebowski, Carol J. Fabian, Ayca Gucalp, Dawn L. Hershman, Melissa M. Hudson, Lee W. Jones, Madhuri Kakarala, Kirsten K. Ness, Janette K. Merrill, Dana S. Wollins, and Clifford A. Hudis

- Position Statement describes ASCO's priorities and initiatives in this area
- ASCO Summit on Obesity Clinical Trials in Cancer Survivors held in November 2014
- Manuscript describing Summit recommendations to move field of obesity research forward is under development
- Plan for research meeting across disciplines scheduled for fall 2015

ASCO Research Summit on Advancing Obesity Clinical Trials in Cancer Survivors

Central Question:

How do we move from conducting observational studies and small feasibility trials to generating the data needed to incorporate energy balance interventions into clinical practice and ultimately improve cancer outcomes?

Conclusions

- Observational evidence shows links between lifestyle behaviors and cancer outcomes
- Growing prevalence of obesity threatens our ability to reduce morbidity and mortality form cancer
- Few randomized trials test impact of lifestyle interventions upon prognosis
  - WINS: 24% reduction in cancer recurrence with a low fat diet and/or weight loss
  - WHEL: no benefit of increased fruits/vegetable/fiber and fat reduction
- Better understanding of biology can help guide selection of interventions and patients
- On-going studies will test the hypothesis that weight loss reduces breast cancer recurrence and mortality

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