

# Evidence from Diet and Weight Loss Studies for Cancer Survivors: What Works?

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# Diet, Recurrence and Survival

- Biological and observational evidence suggests that diet and obesity may influence cancer progression and survival after the diagnosis and treatment of cancer
- For breast cancer, clinical trials examining whether diet modification or weight loss can affect risk for recurrence and survival have been conducted and are ongoing

# Recently Completed Randomized Clinical Trials (RCTs)

## Primary cancer prevention

- Women's Health Initiative (WHI)
- Selenium and Vitamin E Cancer Prevention Trial (SELECT)
- Physicians' Health Study II (PHS II)

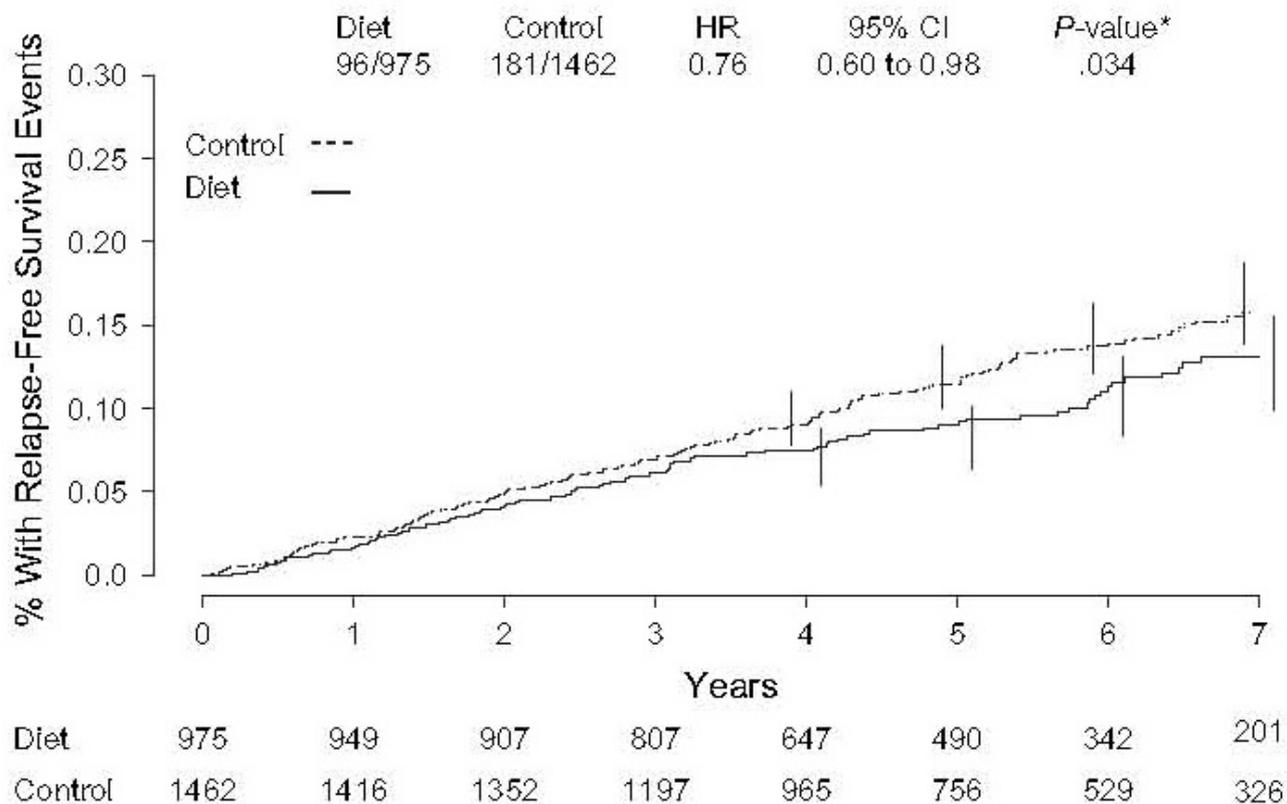
## Secondary cancer outcomes (recurrence, survival)

- Women's Intervention Nutrition Study (WINS)
- Women's Healthy Eating and Living (WHEL) Study

# WINS

- 2437 postmenopausal women who had been diagnosed and treated for early stage breast cancer, 5-yr follow-up
- Diet intervention: Reduced fat intake, with the goal of 15% energy from fat
- Primary analysis was of borderline significance; exploratory analysis showed a significantly reduced risk of a new breast cancer event in the intervention group, especially in women with ER- cancer
- Considerations: Greater weight loss (a 6-lb difference, or approximately 4% of initial weight, at year 5), and higher frequency of mastectomy, in the intervention group

# Kaplan-Meier Estimates of Relapse



# WINS Adherence

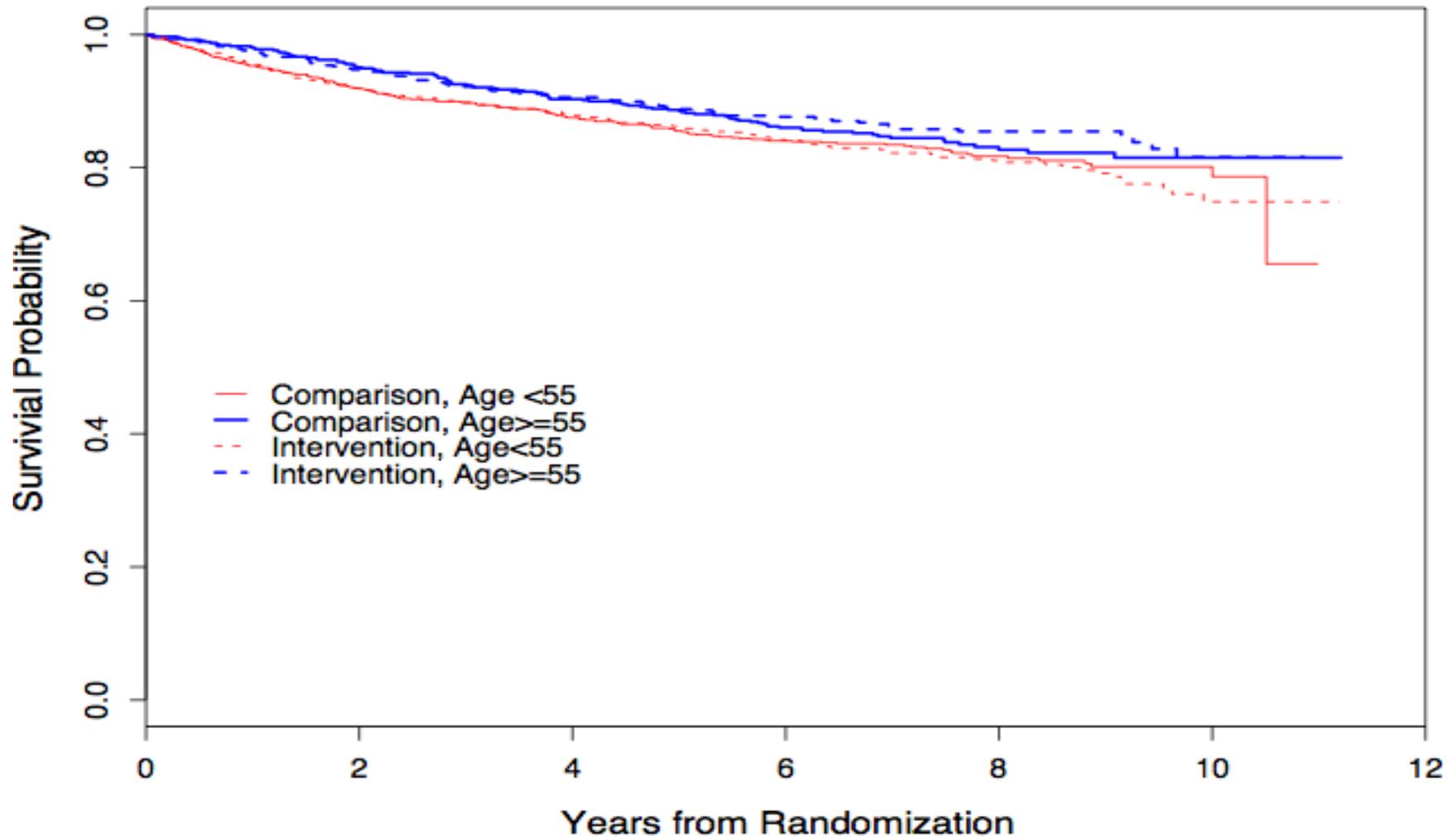
- At 12 months, self-reported fat intake averaged 33.3 g/day (approximately 20.3% of kcal) in the intervention group vs. 51.3 g/day (approximately 29.2% of kcal) in controls
- Incomplete follow-up data on dietary adherence: 67% of the intervention group and 74% of controls at year 3

# WHEL Study

- 3088 pre- and postmenopausal women who had been diagnosed and treated for early stage breast cancer, 7.3-yr follow-up
- Diet intervention: 5 Vegetable servings plus 16 oz vegetable juice or equivalent, 3 fruit servings, 30 g fiber, 15-20% energy from fat, each day
- No significant differences in breast cancer recurrence or survival; secondary analysis found women without hot flashes (indicative of higher circulating estrogens) had 31% fewer events in the intervention group
- Considerations: Average intake of vegetables and fruit servings at baseline was 7.3/day; higher longitudinal exposure to carotenoids was associated with greater recurrence-free survival

# Disease Free Survival by Intervention Arm

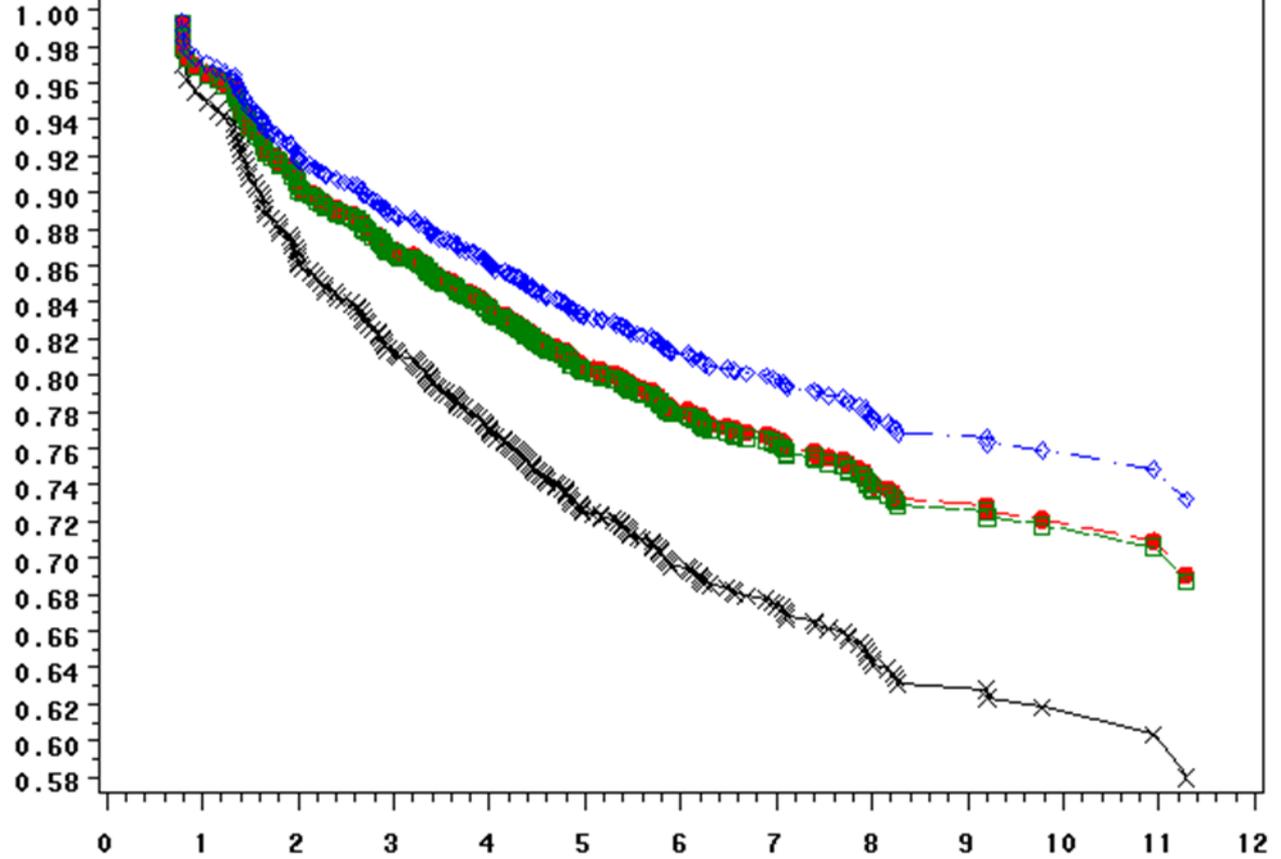
Survival Curve by Intervention Arm, Stratified by Age at Randomization



# Recurrence Free Survival

Stage II, Grade II, participants on tamoxifen

Survivor Function Estimate



Baseline Total Carotenoid Quartile

××× 1

●●● 2

□□□ 3

◇◇◇ 4

# WHEL Adherence

- Small but significant increase in plasma triglycerides, and decreased HDL cholesterol and apoprotein-A1, at one year in the intervention group ( $P < 0.05$ ), reflecting increased dietary carbohydrate (and concurrent reduction in fat) intake.
- Plasma carotenoids, a biomarker of vegetable and fruit intake, were 73% higher at one year and 43% higher at four years in the intervention vs. control groups.
- Significant difference in change in serum bioavailable estradiol concentration from baseline to one year in the intervention (vs. comparison) group; change in fiber (but not fat) was significantly related to change in serum bioavailable estradiol ( $P < 0.01$ ) and total estradiol ( $P < 0.05$ ) concentrations.

# Survivor Training for Enhancing Total Health (STRENGTH)

- To explore the feasibility of conducting and testing home-based exercise and diet interventions using the infrastructure of the cooperative group
- To ascertain effects of three interventions (workbook and materials, 14 telephone counseling sessions) on percent body fat and other secondary endpoints

**Attention Control:** calcium-rich diet (CA)(1,200-1,500 mg/day)

**Exercise:** CA + strength training/aerobic exercise (EX)

**Exercise + Healthy Diet:** CA + EX +  $\leq 20\%$  energy from fat plus  $\geq 5$  fruit and vegetable servings/day

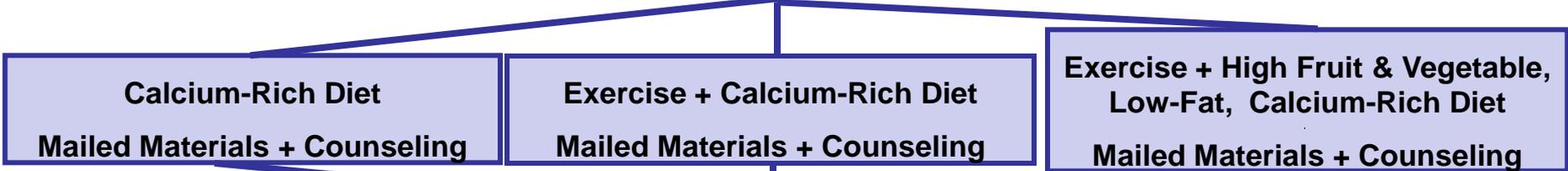
R21 CA92468 (Demark-Wahnefried)

Demark-Wahnefried et al. Clin Breast Cancer 2008;8:70)

# 90 Early Stage, Newly Diagnosed Premenopausal Breast Cancer Patients *(from Duke and selected CCOP sites)*



Baseline Measures Sites: DXA scans, Weight, Height, Waist Circumference and Blood Collection  
Duke: Mailed Surveys re: Quality of Life, Depression and Anxiety, Diet, and Physical Activity (activity monitor). Serum Analyses of IGF-1, Insulin, SHBG, Lipid Profile



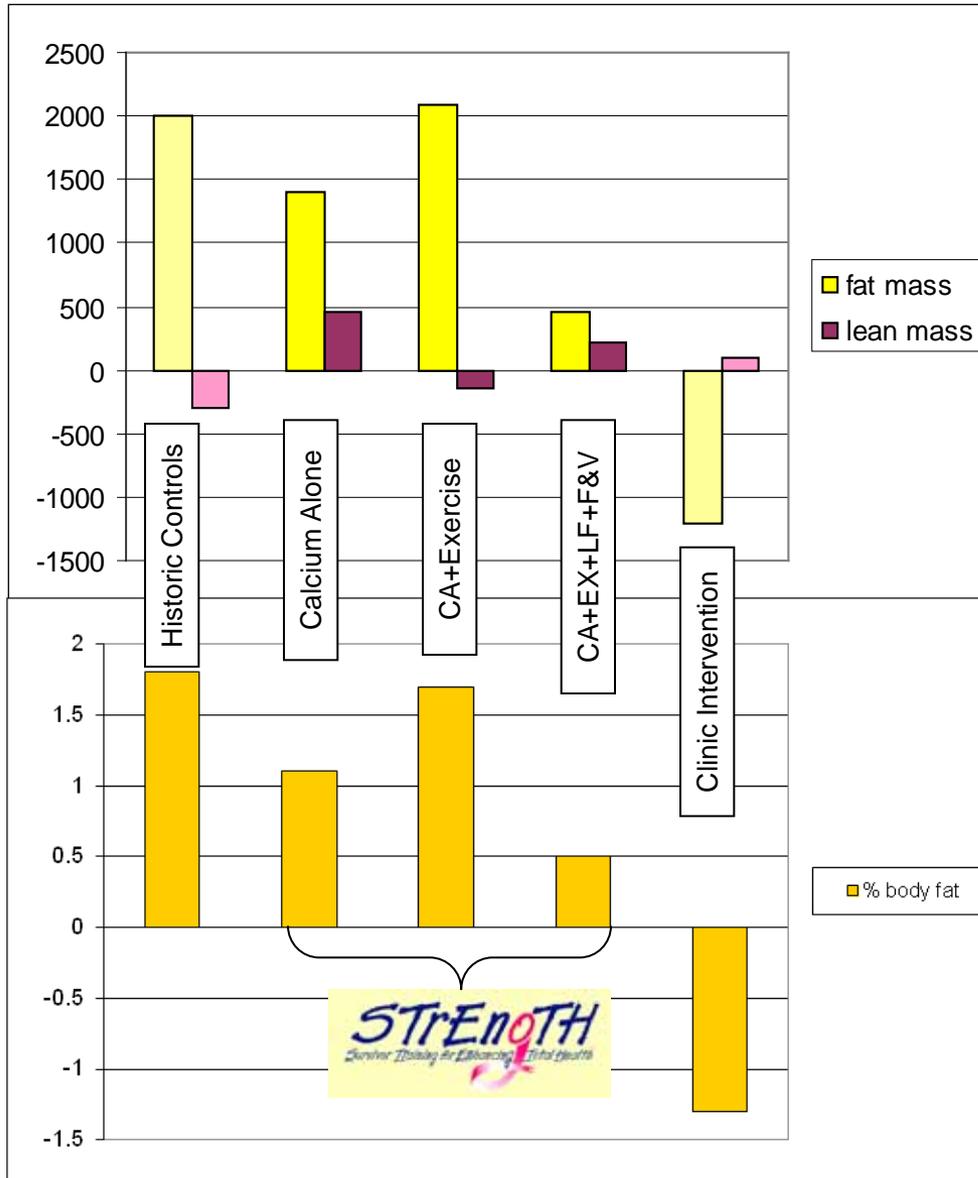
3-Month Measures: Duke Mailed Questionnaires and Activity Monitor

6-Month Measures: Repeat of Measures Obtained at Baseline

# Dietary Measures

<b>Measure</b>	<b>CA</b>	<b>CA+EX</b>	<b>CA+EX+DIET</b>	<b>P-Value</b>
<b>D Dietary CA (mg/day)</b>	173 (404)	159 (1017)	105 (221)	.1527
<b>D Suppl. Calcium (mg/day)</b>	330 (375)	321 (437)	276 (324)	.9322
<b>D %kcal Total Fat</b>	1.5 (5.3)	0.5 (4.7)	-5.2 (6.0)	.0004
<b>D %kcal Sat Fat</b>	0.8 (2.2)	1.0 (2.8)	-1.6 (1.9)	<.0001
<b>D F&amp;V serv/day</b>	0 (3.0)	-0.7 (4.2)	1.9 (2.9)	.0269
<b>D kcal</b>	-67 (561)	-185 (772)	-187 (670)	.2908

# Changes in Body Composition: STRENGTH Study in Contrast to Historic Controls and Clinic-Based Diet and Exercise Intervention



# FRESH START Trial

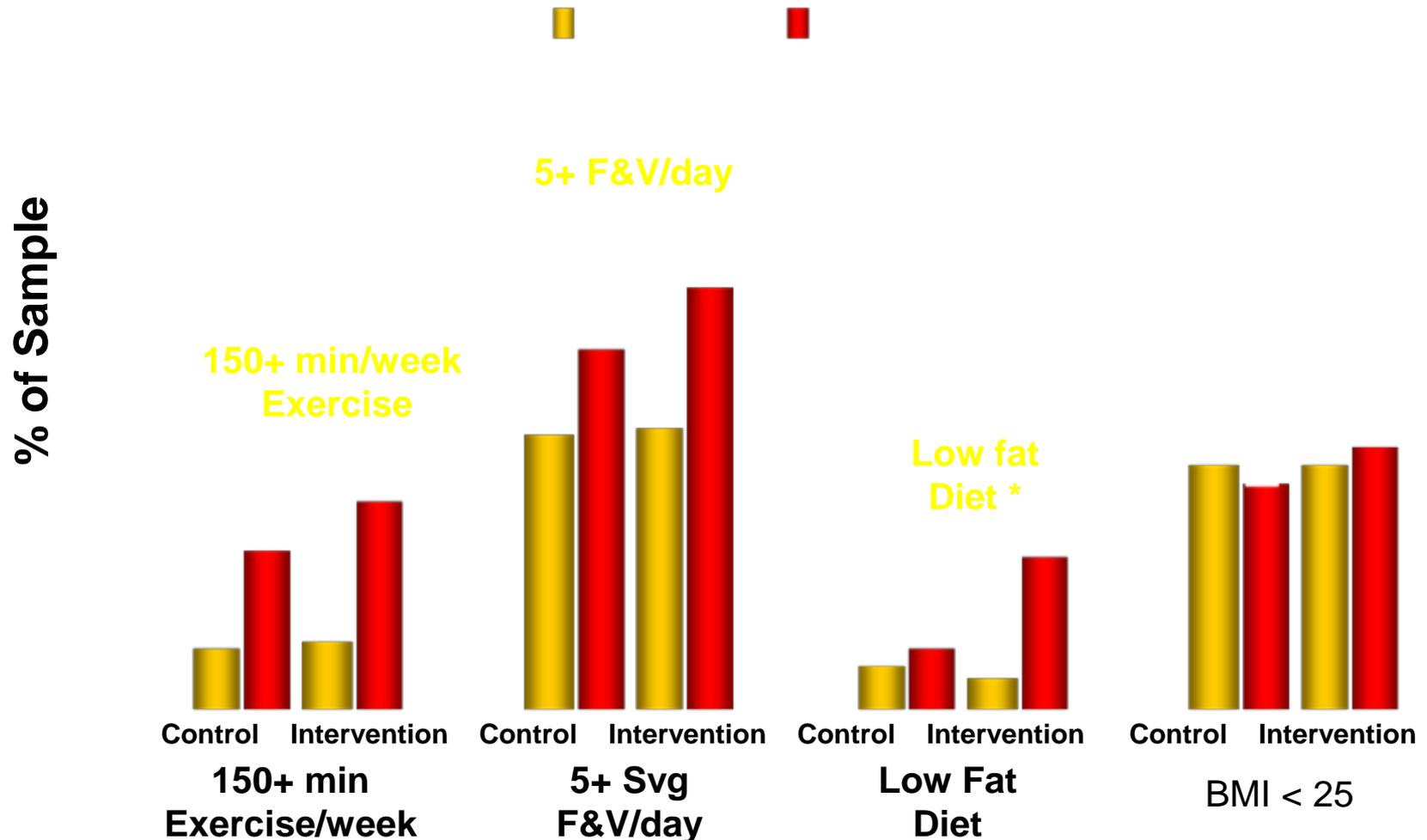
- RCT to test sequentially tailored print material diet (increased fruit and vegetables and decreased saturated fat intakes) and exercise intervention on improving health behaviors of breast and prostate cancer survivors (N=543) newly diagnosed with early stage disease
- Randomized to tailored vs. standardized material arms, 10-month intervention period and one-year follow-up

R01 CA81191 (Demark-Wahnefried)

Demark-Wahnefried et al. Med Sci Sports & Exerc 2003;35: 415, J Clin Oncol 2007;25:2709

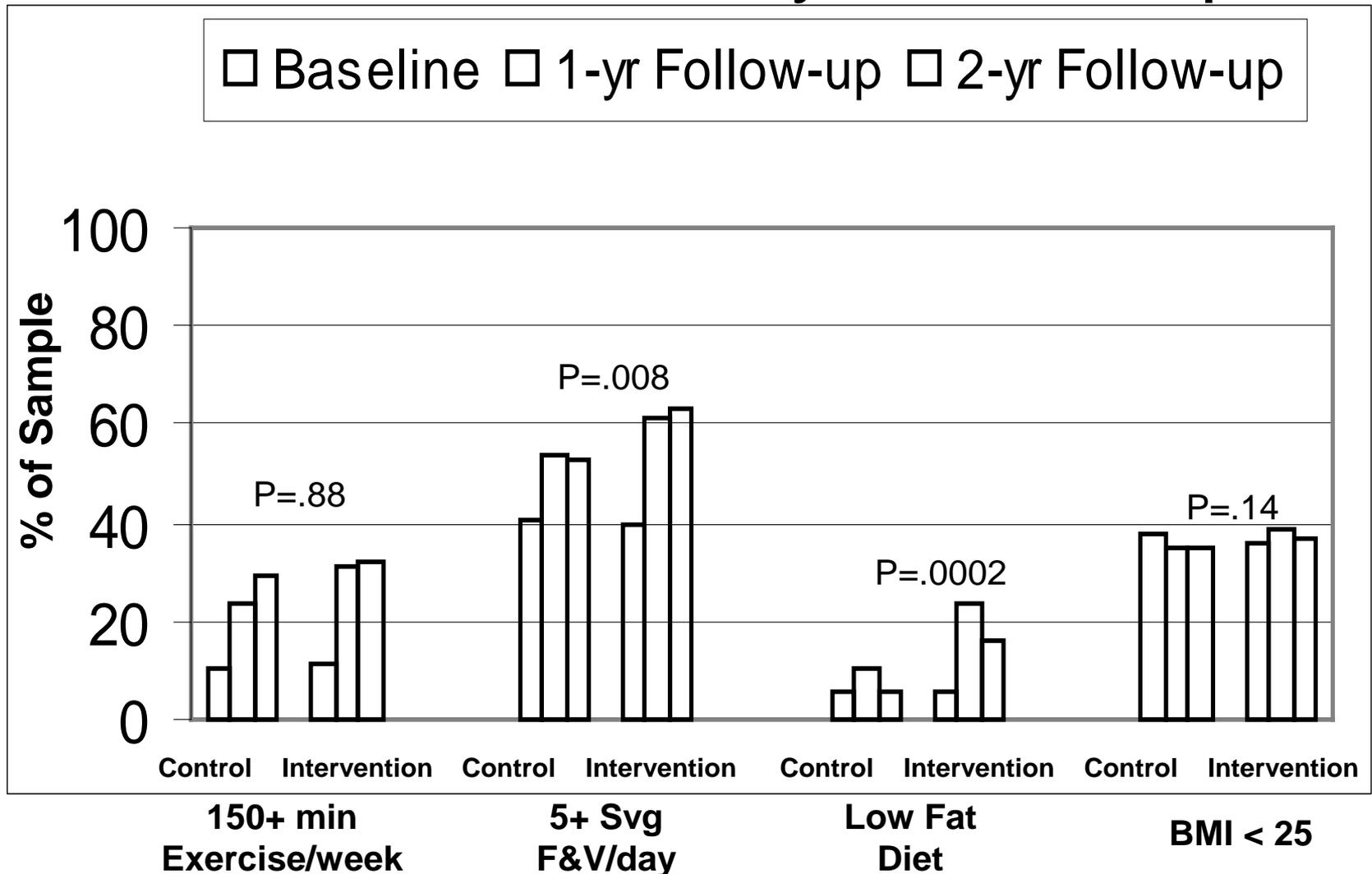
# Achieving Goal: Intervention vs. Control Baseline vs. 1-yr. follow-up

(all p's <.0001)



\* <30% total, <10% sat. fat

# Achieving Goal: Intervention vs. Control Baseline vs. 1 & 2-yr. Follow-up



\* <30% total, <10% sat. fat

# Reach Out to ENhance Wellness in Older Survivors (RENEW)

- Test the impact of a diet-exercise mailed material/telephone counseling program on weight loss and physical functioning in prostate, colorectal and breast cancer survivors (N=641)
- Study participants:  $\geq 65$  years of age and overweight, within 5 years of diagnosis, 45% male

R01 CA106919 (Demark-Wahnefried)

Morey et al. JAMA 2009;301:1883

# Results

	D Intervention Mean (SE)	D Wait List Control Mean (SE)	P- value
SF36 Physical Function	-2.55 (1.07)	-5.39 (1.01)	.034
Basic Lower Extremity – LLF	+0.41 (0.71)	-2.11 (0.67)	.005
Adv. Lower Extremity – LLF	+0.44 (0.60)	-2.55 (0.61)	.015
Strength Exercise (min/d)	+22.2 (2.8)	+0.5 (3.0)	<.0001
Strength Exercise (session/w)	+1.4 (2.6)	+0.2 (2.5)	<.0001
Endurance Exercise (min/d)	+43.1 (5.7)	+26.1 (6.3)	<.0001
Endur. Exercise (session/w)	+1.6 (3.9)	+0.5 (4.1)	.005
F&V Intake (servings/d)	+1.48 (0.16)	+0.15 (0.12)	<.0001
Saturated Fat Intake (g/d)	-3.64 (0.61)	-1.19 (0.55)	.002
Healthy Eating Index	+7.1 (0.9)	+1.4 (0.8)	<.0001
Weight (kg)	-2.45 (0.22) (3% of initial weight)	-1.03 (0.2)	<.0001
BMI	-0.82 (0.07)	-0.035 (0.08)	.0002
Quality-of-Life (Total SF36)	+0.91 (0.86)	-2.17 (0.90)	.025

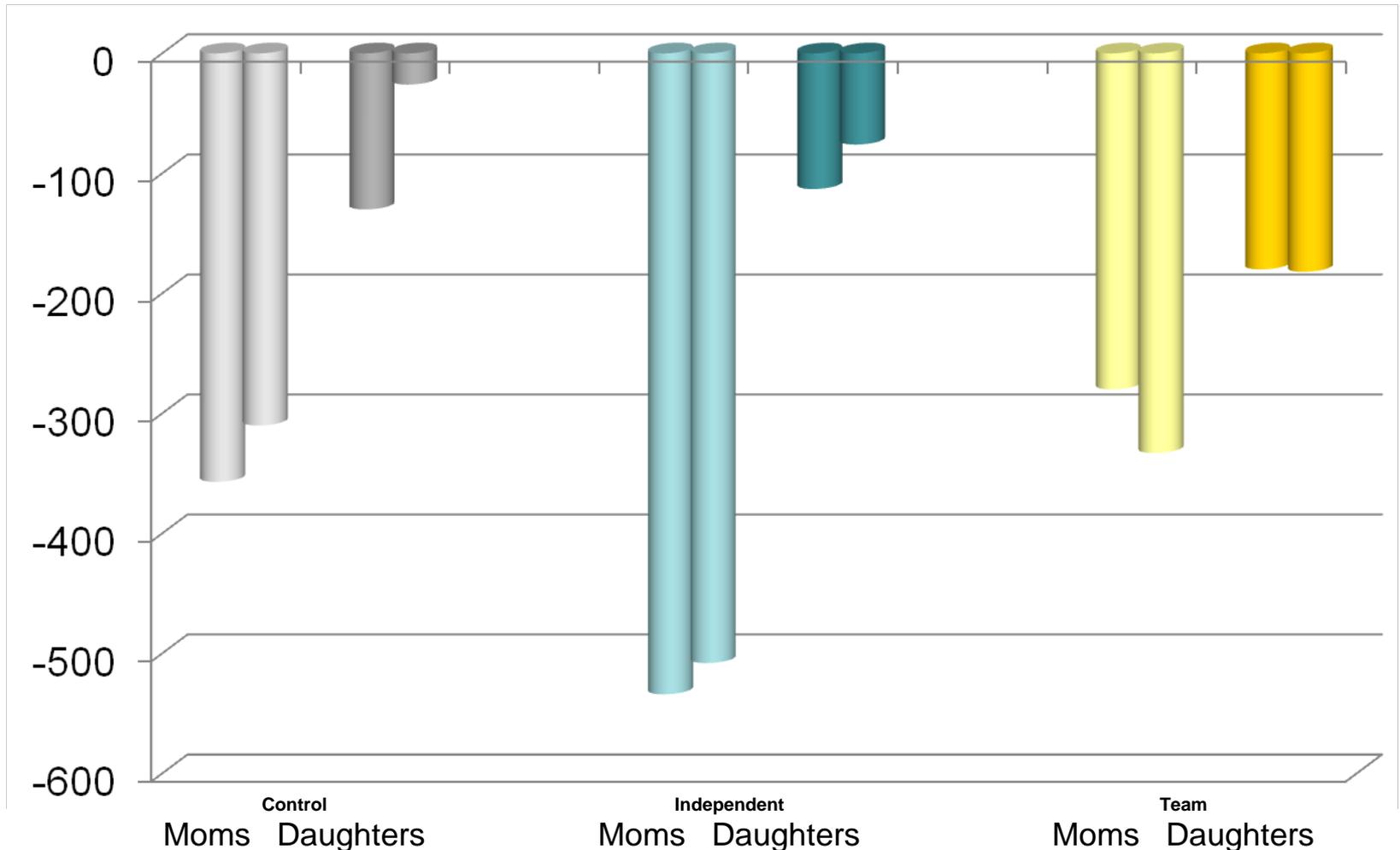
# DAMES: Daughters And MothErS Against Breast Cancer

- Pilot-feasibility trial to promote weight loss in overweight breast cancer patients and their overweight adult daughters (68 mother-daughter dyads)
- Home-based diet-exercise intervention aimed at weight loss: standardized materials, tailored materials (independent approach), tailored materials (team-based approach)

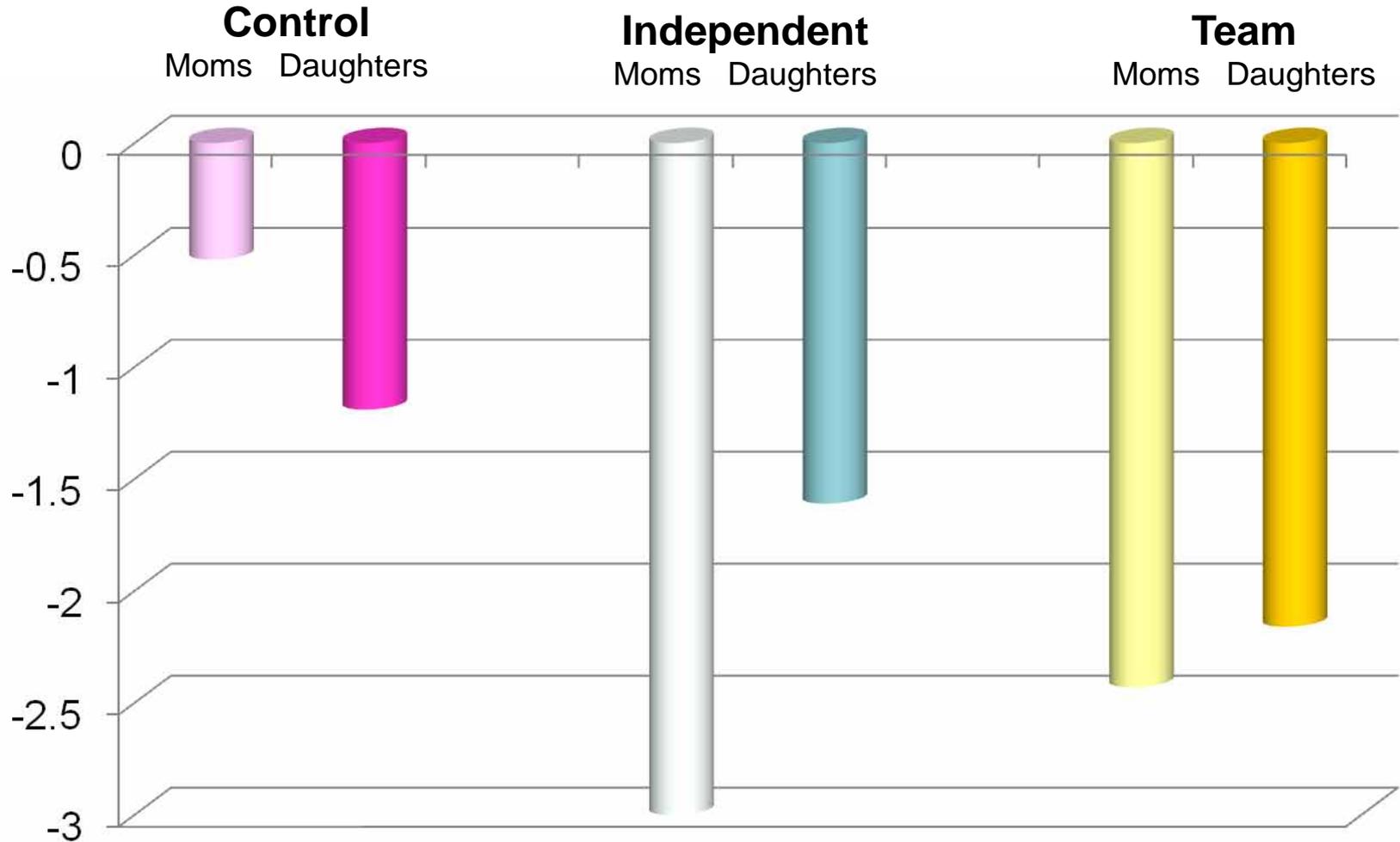
R21 CA122413 (Demark-Wahnefried)

# Unadjusted Energy Intake Change Scores

(1<sup>st</sup> bar: 0-6 months 2<sup>nd</sup> bar: 6-12 months)



# Unadjusted BMI Change Scores (Baseline to 1 Year)

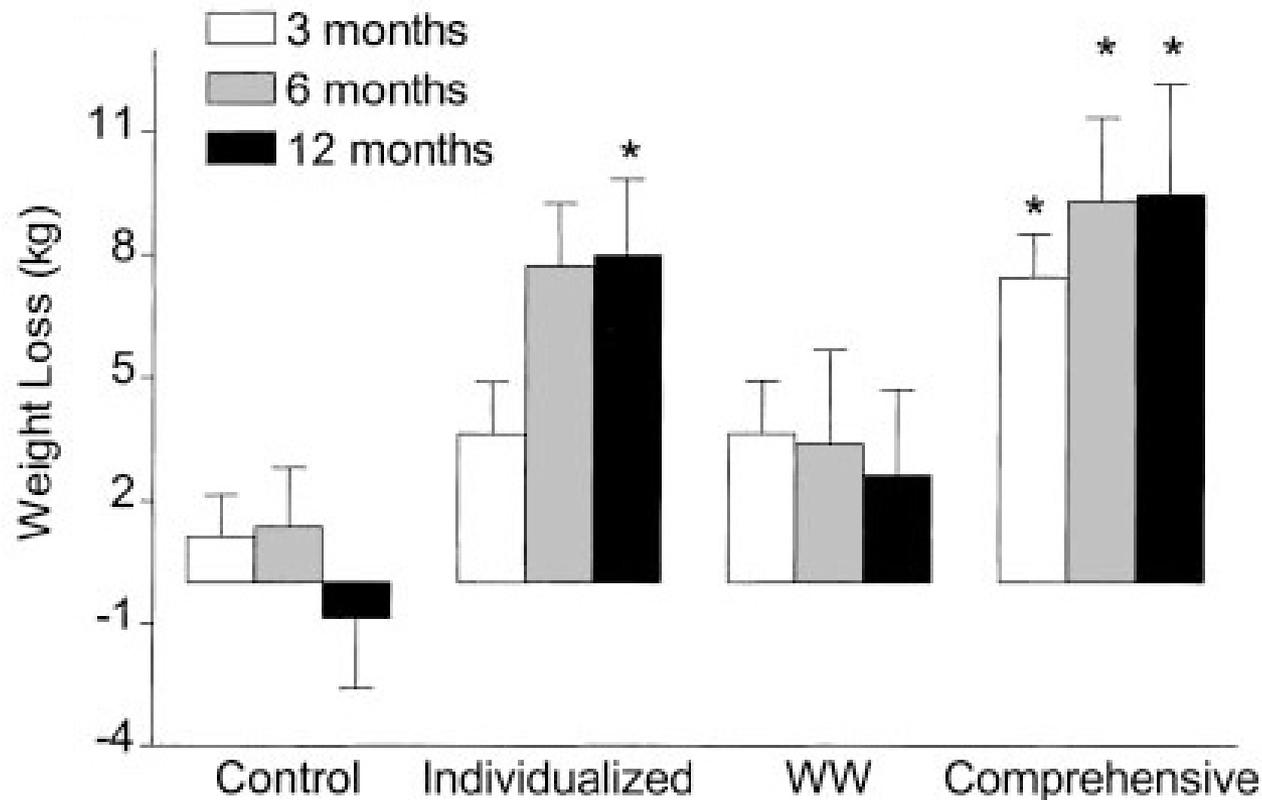


# Combining Weight Loss Counseling With Weight Watchers

- Obese breast cancer survivors (N=48) assigned to individualized weight loss counseling, referral to the Weight Watchers program, a combination of both, or control
- Weight change after 12 months of intervention was  $0.85 \pm 6.0$  kg (<1% of initial weight) in controls,  $-2.6 \pm 5.5$  kg (2.7% of initial weight) in the Weight Watchers only group,  $-8.0 \pm 5.5$  kg (8.4% of initial weight) in the individualized counseling only group, and  $-9.4 \pm 8.6$  kg (9.8% of initial weight) in the combined group

Djuric et al. Obesity Res 2002;10:657-665

# Weight Loss with Time in Each Study Arm: Mean and SD of Change in Body Weight



# Reducing Breast Cancer Recurrence with Weight Loss: A Vanguard Trial

- Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) Trial
- A randomized controlled study with the primary endpoint of clinically significant weight loss in 800 overweight or obese breast cancer survivors, with demonstration of improvements in quality of life and co-morbidities
- Sets the stage for a larger cancer outcome study that has sufficient statistical power to assess the effects of weight loss on cancer outcomes in overweight or obese breast cancer survivors

R01 CA148791 (Rock)

# Preliminary Studies

**Healthy Weight Management Study** (R21 CA90413 Rock, R03 CA101489 Rock), N=85, group-based cognitive-behavioral weight loss program plus telephone contacts

- Intervention group averaged 83.9 kg at baseline, 78.2 kg at 16 wks (7% of initial weight), and 77.3 kg (8% of initial weight) at 12 mos; reported 7.4 hrs/wk mod + vig activity at 12 months
- Associated with favorable changes in % body fat, waist circumference, SHBG estradiol, bioavailable estradiol, and total and LDL cholesterol

**Breast Cancer Survivors Health and Physical Exercise (SHAPE) Study** (ACS RSGPB-04-258 Rock), N=259, group-based behavioral weight loss program

- Intervention participants lost -4.6 kg (5.5% of initial body weight) at 6 months and -3.8 kg (4.5% of initial body weight) at 18 months
- Associated with favorable changes in depression (CSED), self-esteem (RSE), insulin, and leptin

# ENERGY Trial

## Specific aims

- Conduct a 4-year vanguard randomized controlled trial with the primary endpoint of sustained weight loss in 800 breast cancer survivors, following all subjects for 2-years post-randomization
- Evaluate weight loss at 24 months according to time since diagnosis, type of tumor and type of therapy
- Assess the impact of the intervention on QOL, particularly physical functioning and fatigue
- Prospectively collect blood and DNA samples to examine effects on hormones and other factors to explain the mechanism and probable differential response across subgroups

Strategically designed as a vanguard component of a fully-powered trial of 2500 women to be evaluated for breast cancer recurrence endpoints

- Allows the opportunity to further tailor and streamline the process and intervention for expansion into the larger trial, while at the same time accomplishing important scientific aims

# Intervention Group

## Cognitive-behavioral group sessions

- First 4 months: sessions every week
- Next 2 months: sessions every other week
- Month 6 onward: session every month

Individual participant contacts (by email and/or telephone)

## Tailored newsletters

- After the 6<sup>th</sup> month of sessions, participants receive monthly tailored newsletters

# ENERGY Trial Status

## Content of the intervention

- Diet, plus emphasis on increased physical activity
- Behavioral strategies, cognitive restructuring, skills to facilitate and maintain good choices
- Social support, self-nurturing and alternative behaviors, body image and self-acceptance
- Issues specific to cancer survivors

As of October 21, 2011, 522 enrolled and 495 randomized participants

- Overall, 6-month weight change from baseline in the first 103 participants in combined study arms is -3.6 (4.4) kg (4.3% of initial weight), range -17.1 to 7.4 kg (loss of 16.5 to gain of 9.5% of initial weight)

# ENERGY Research Team

- ENERGY Trial investigators (in alphabetical order):  
Tim Byers, MD, MPH, Graham Colditz, MD, DrPH (Data Management and Analysis), Wendy Demark-Wahnefried, PhD, RD, Patricia Ganz, MD, James Hill, PhD, Bilgé Pakiz, EdD, Barbara Parker, MD, Cheryl Rock, PhD, RD (PI of Parent Grant and Coordinating Center), Rebecca Sedjo, PhD, Kathleen Wolin, ScD, Holly Wyatt, MD
- NCI: Catherine Alfano, PhD (program officer) and Julia Rowland, PhD, Office of Cancer Survivorship; also Robert Croyle, PhD, Division of Cancer Control and Population Sciences

# Transdisciplinary Research in Energetics and Cancer (TREC)

- A cooperative agreement initiative (U54) that explores the relationship between obesity and cancer, funded by the National Cancer Institute
- Integrates the study of diet, weight, and physical activity and their effects on energy balance and cancer
- Projects range from the biologic and physiologic mechanisms of energy balance to the behavioral, sociocultural, and environmental influences on nutrition, physical activity and weight in cancer survivors and other populations at high risk
- Across the four centers, two projects (at UCSD and Univ. of Pennsylvania) are examining the effects of weight loss/diet interventions in overweight/obese breast cancer survivors

# Diet and Weight Loss: What Works?

- Results from diet and weight loss studies:
  - Demonstrate that this target population is motivated and able to make dietary and lifestyle modifications
  - Individualized counseling (in person or by telephone), group sessions, and tailored mailed material have all been shown to promote behavior change
- Specific issues for cancer survivors:
  - Enduring psychosocial symptoms, such as depression and fatigue, affect efforts to make changes in behaviors
  - Body image issues related to cancer and cancer treatments
  - Changes in family dynamics and social support
  - For weight loss, physical activity is important, due to the relationship between lean body mass and resting energy expenditure, and effects of treatments

