

# Survivorship: Challenges, Issues and Current Status of Research

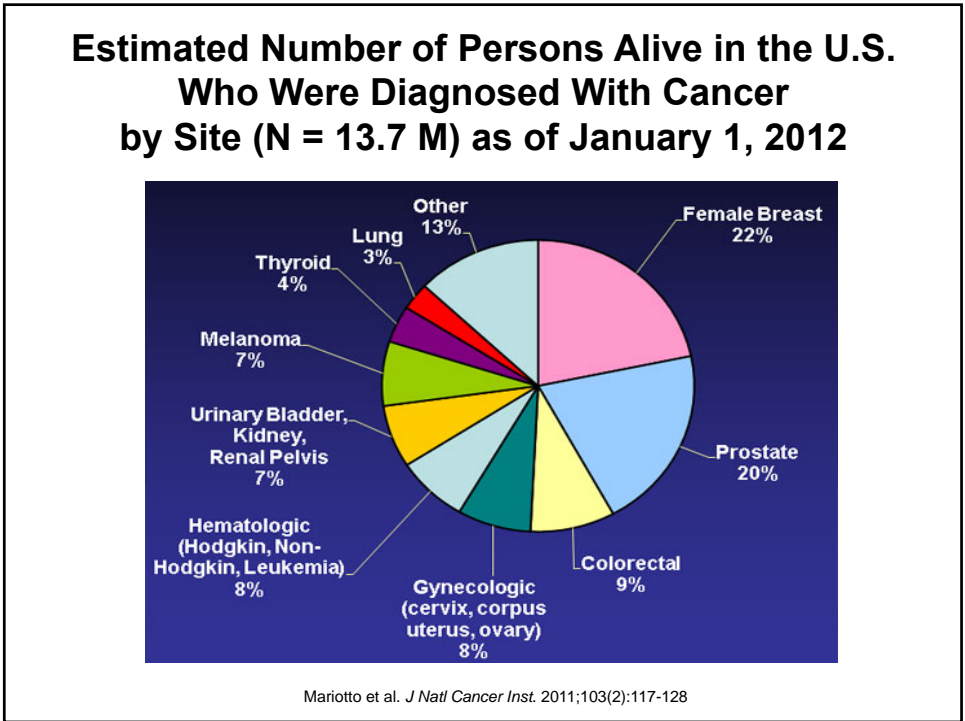
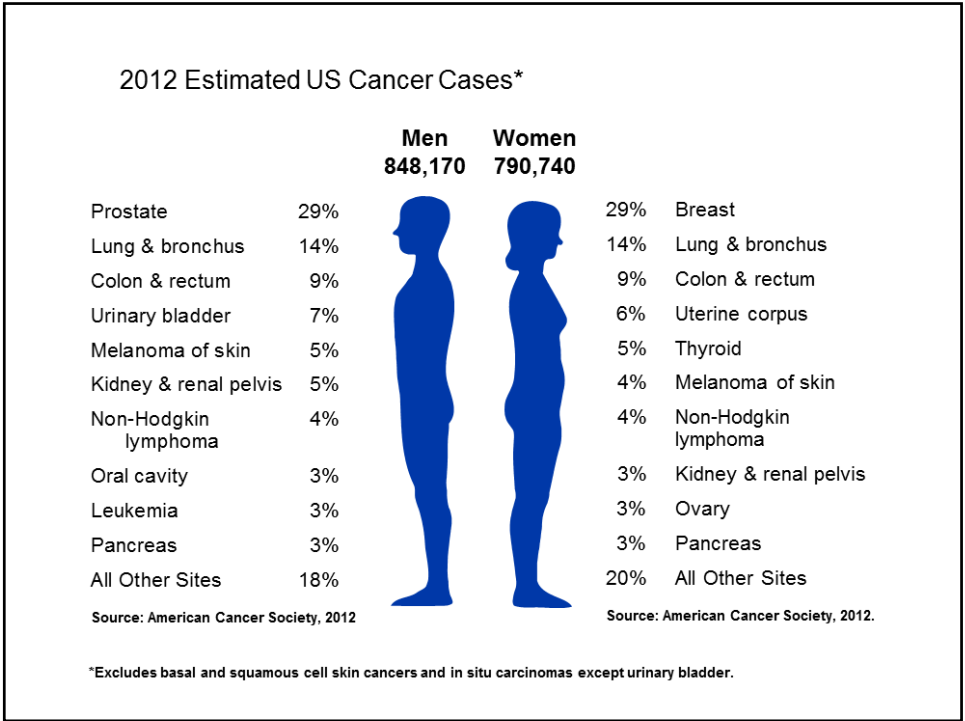
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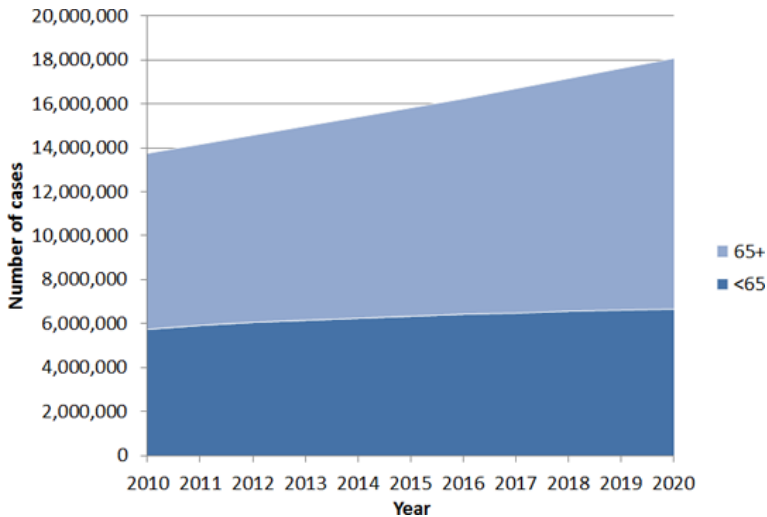
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MEDICAL CENTER MOORES CANCER CENTER

## Nutrition and Cancer

- In 1999, cancer replaced heart disease as the leading cause of death among men and women in the U.S. aged 85 years and younger.
- Between 1990/1991 and 2007, cancer death rates decreased by 22.2% in men and by 13.9% in women; however, 1 in 4 deaths in the U.S. is currently due to cancer.
- Due to advances in early detection and treatment, 65% of Americans diagnosed with cancer now live more than 5 years. Over 12 million persons in the U.S. are cancer survivors – roughly 4 out of 100 Americans.

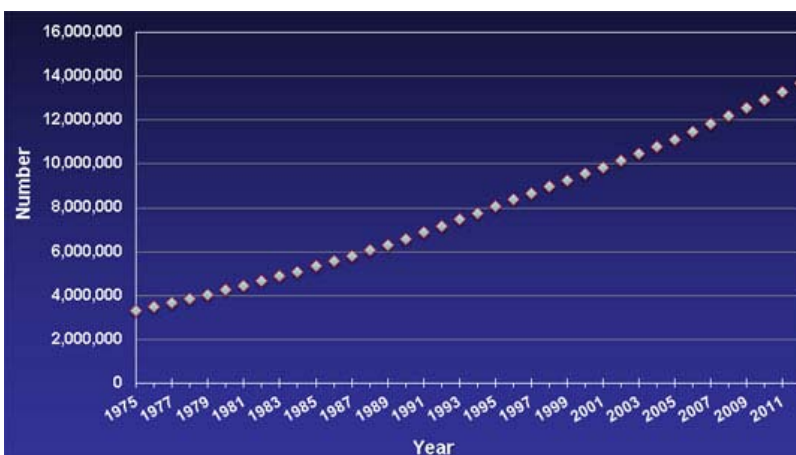


### U.S. Cancer Prevalence Projections (2010-2020)



Parry et al. *Cancer Epidemiol Biomarkers Prev* 2011;20:1996-2005.

### Estimated Number of Cancer Survivors in the U.S From 1975 to 2012



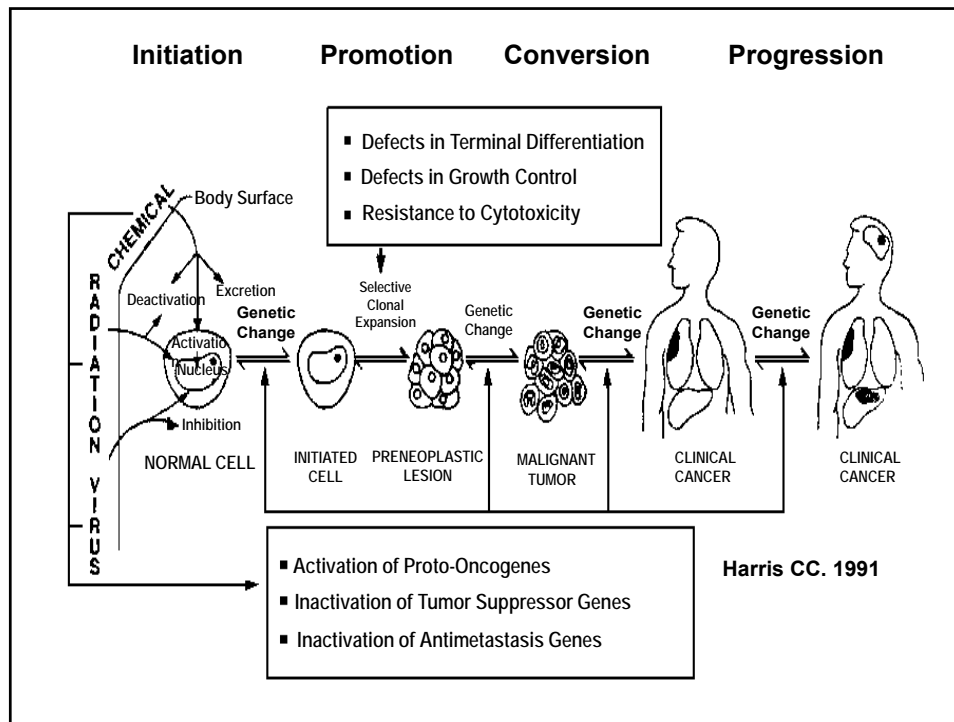
Mariotto et al. *J Natl Cancer Inst.* 2011;103(2):117-128

## **Cancer Survivors**

- Of the over 12 million people living with cancer, 7 million are ages 65 years or older
- Women make up a large proportion of cancer survivors (54%)
- Breast cancer survivors are the largest group of cancer survivors, followed by prostate cancer survivors and colorectal cancer survivors
- Among all survivors, over 4.7 million received their diagnosis 10 or more years earlier

## **Nutrition and Cancer Risk and Progression**

- Cancer etiology is multifactorial – both genetic susceptibility and a variety of environmental factors determine risk
- Accumulated evidence suggests that approximately 30-40% of cases are potentially preventable by modifying food choices and nutritional factors
- Disentangling effects of various foods, specific dietary constituents and associated lifestyle factors is challenging



## Diet, Recurrence and Survival

- Biological evidence suggests that nutritional factors are likely to influence cancer progression
- Epidemiological studies suggest that many of the nutritional factors associated with risk for primary cancer may affect survival following diagnosis
- For breast cancer, clinical trials examining whether diet modification can affect risk for recurrence and survival have been conducted, and more are ongoing

## **The Continuum of Cancer Survivorship**

Nutritional needs, issues and challenges change over the course of survivorship:

- During active treatment and recovery
- Long-term disease-free living
  - Reduce risk for cancer recurrence and progression
  - Prevention and treatment of comorbidities
- Advanced cancer and end-of-life

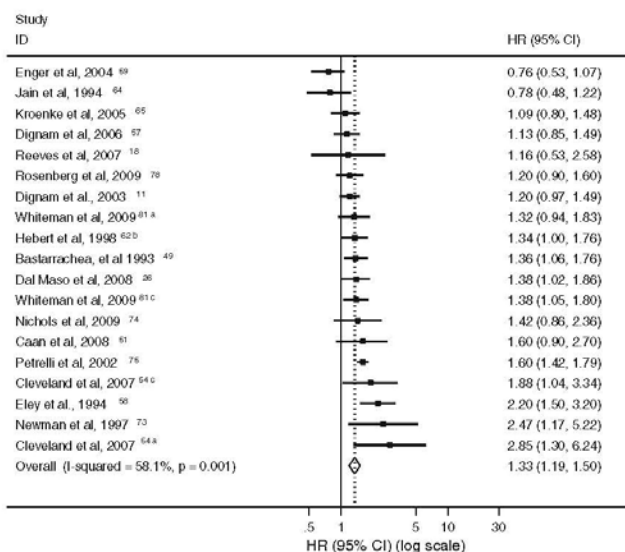
## **Emerging Evidence from Observational Studies**

- Dietary patterns, rather than specific nutrients: For example, evidence suggests that a prudent/healthy dietary pattern (vegetables, fruit, poultry, fish, low-fat dairy foods and whole grains) is associated with lower risk for cancer and greater likelihood of survival after diagnosis
- Current patterns of overweight and obesity in the U.S. could account for 14% of all deaths from cancer in men and 20% of those in women

## Obesity and Cancer Risk and Progression

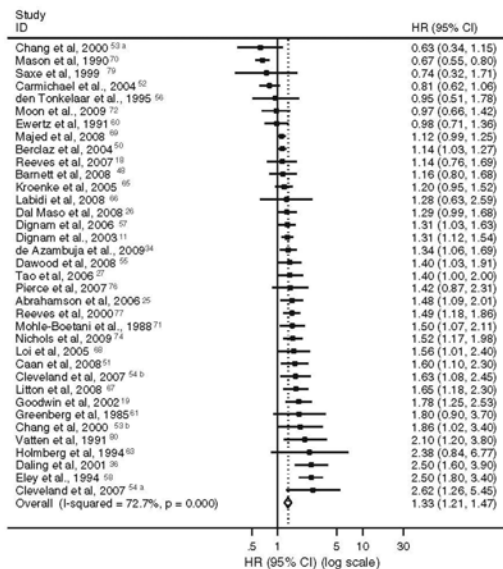
- Overweight/obesity is associated with mortality from cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, kidney, non-Hodgkin's lymphoma, multiple myeloma; stomach and prostate (men); breast, uterus, cervix and ovary (women)
- Cancer-related biomarkers respond to even a modest degree of intentional weight loss, suggesting a reduction in cancer risk even with latencies as short as a few years

### Meta-Analysis and Pooled Hazard Ratio of the Effect of Obesity on Breast Cancer-Specific Survival in Breast Cancer Patients



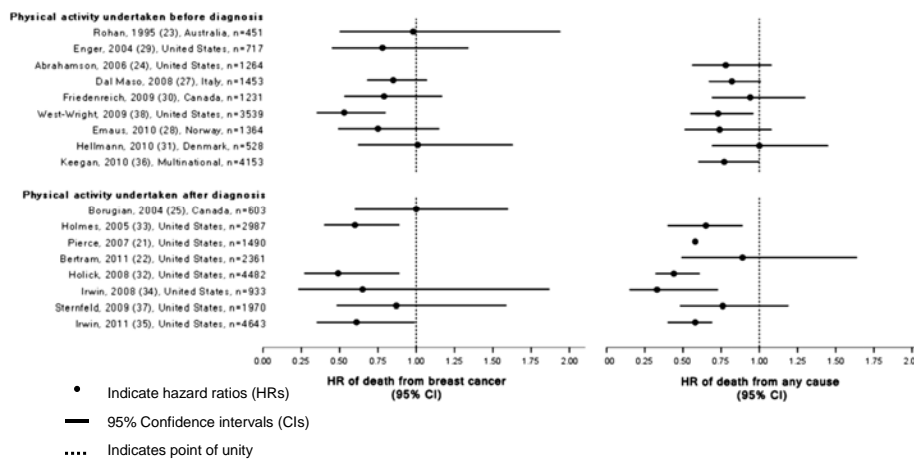
Protani et al. *Breast Cancer Res Treat* 2010;123:627-635

### Meta-Analysis and Pooled Hazard Ratio of the Effect of Obesity on Overall Survival in Breast Cancer Patients



Protani et al. *Breast Cancer Res Treat* 2010; 123: 627-635

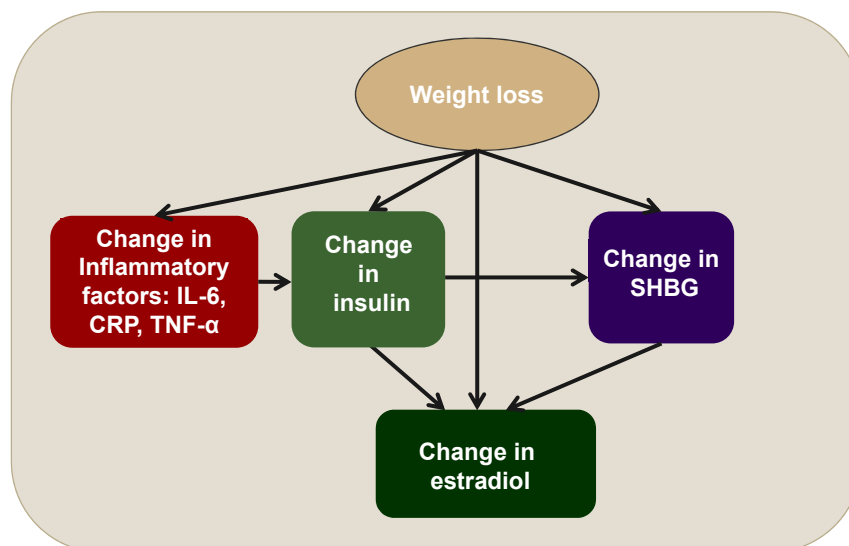
### Forest Plot of Risk Estimates from Observational Studies of Physical Activity and Mortality Outcomes in Breast Cancer Survivors



Ballard-Barbash et al. *J Natl Cancer Inst* 2012; 104: 815-840



### Proposed Relationship between Obesity, Weight Loss and Change in Hormones and Inflammation



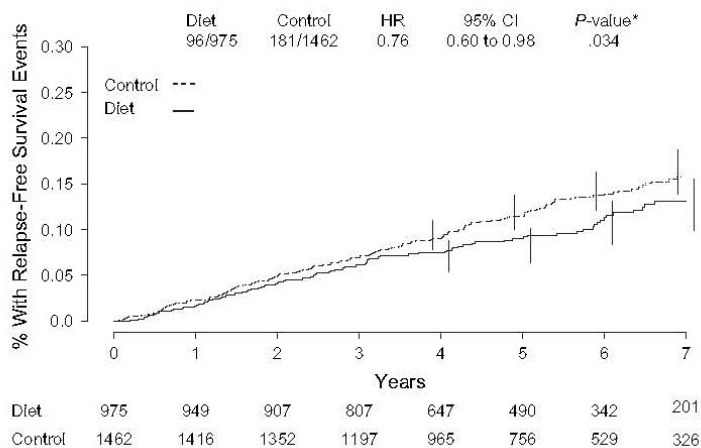
### Completed Randomized Clinical Trials

- 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 but expected 20%
- Primary analysis was of borderline significance; exploratory analysis showed a significantly reduced risk in the intervention group, especially in women with ER- cancer
- Considerations: Greater weight loss, and higher frequency of mastectomy, in the intervention group

## Kaplan-Meier Estimates of Relapse



Chlebowski et al. *J Natl Cancer Inst* 98 (2006) 1767-1776

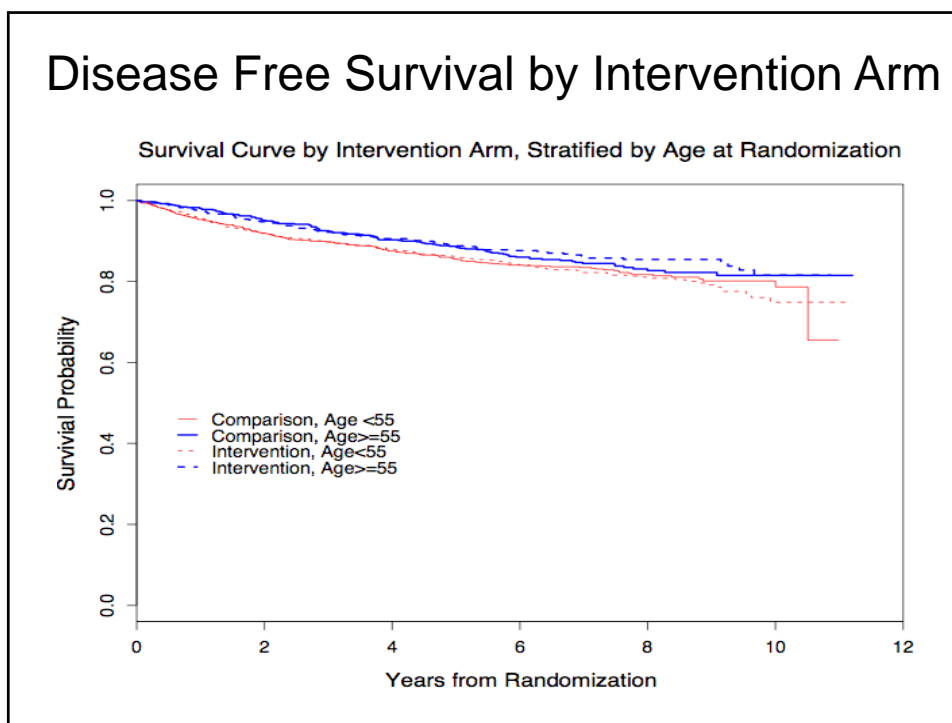
## WINS Adherence

- At 12 months, self-reported fat intake averaged 33.3 g/day (approximately 20.3% energy intake) in the intervention group vs. 51.3 g/day (approximately 29.2% energy intake) 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 breast cancer events in the intervention group
- Considerations: Average intake of vegetables and fruit at baseline was 7.3/day; higher longitudinal exposure to carotenoids was associated with greater recurrence-free survival

## Disease Free Survival by Intervention Arm

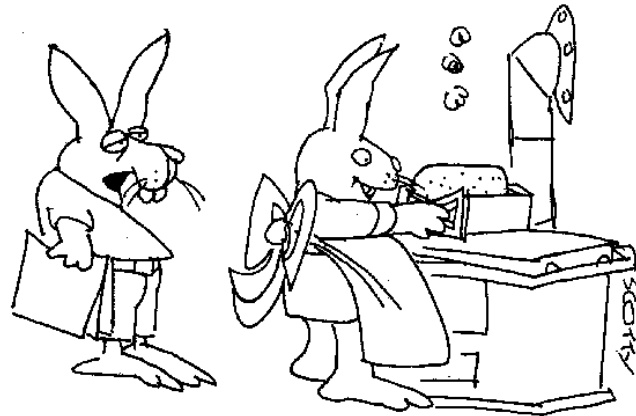
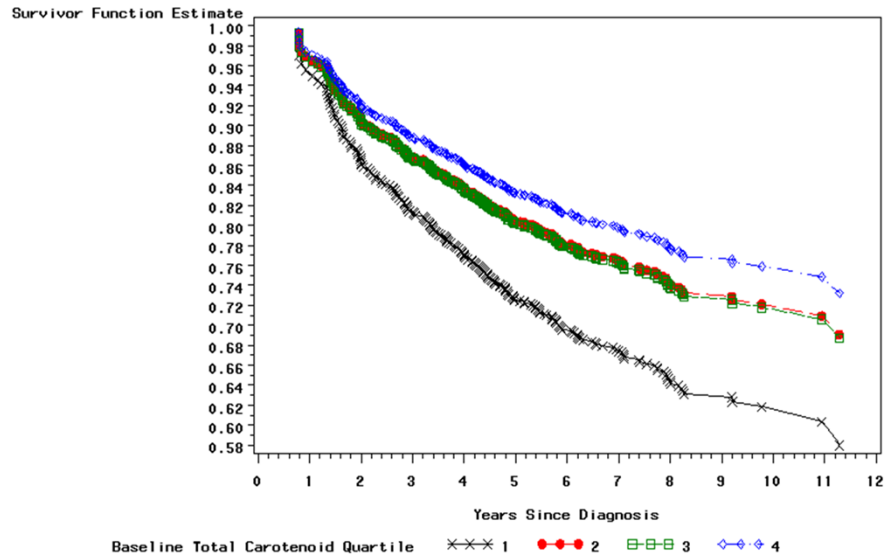


## WHEL Adherence

- 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) intakes.
- 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.

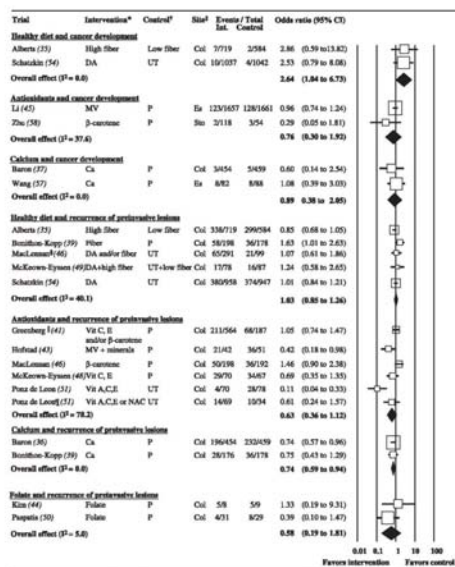
# Recurrence-Free Survival

Stage II, Grade II, participants on tamoxifen



*"Not another carrot cake!"*

## Meta-analyses Examining the Effect of Dietary Factors on Preinvasive Lesions, Development of Cancer or Recurrence



Davies et al. *J Natl Cancer Inst* 98 (2006) 961 – 973

## Weight Loss Interventions

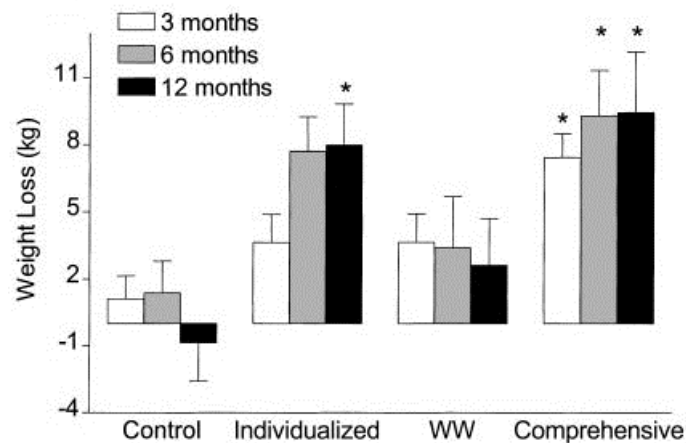
- Several small studies have examined the effect of various weight loss interventions on weight and selected biomarkers in overweight and obese breast cancer survivors
- One large weight loss intervention study is currently underway: The ENERGY trial
- Physical activity intervention studies
  - Numerous small studies have demonstrated short-term benefits
  - The CHALLENGE Study, with cancer outcomes as the focus, is currently underway

## 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: Change in Body Weight (Mean and SD)



## 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 692 overweight or obese breast cancer survivors, with demonstration of improvements in quality of life and co-morbidities

NIH/NCI: R01 CA148791 Rock

## Preliminary Studies

**Healthy Weight Management Study** (R21 CA90413 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

**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
- Weight loss was associated with favorable changes in estrogens, SHBG, insulin, leptin

Rock et al. *Clin Breast Cancer* 2013;3:188-195



## **ENERGY Trial**

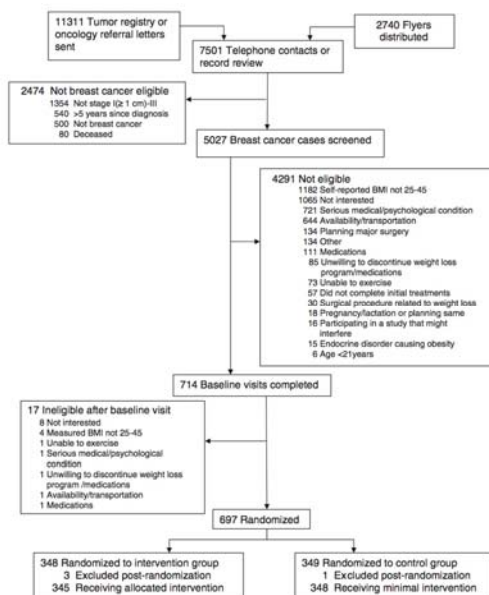
### **Specific aims**

- Conduct a 4-year vanguard randomized controlled trial with the primary endpoint of sustained weight loss in 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
- Originally designed as a vanguard component of a fully-powered trial of 2500 women to be evaluated for breast cancer recurrence endpoints
- Sites: UCSD (Rock) also Coordinating Center; UC Denver (Byers); Washington Univ. (Colditz), Univ. of Alabama (Demark-Wahnefried)

## **Intervention Group**

- Cognitive-behavioral closed group sessions
  - First 4 months: sessions every week
  - Next 2 months: sessions every other week
  - Month 6 onward: session every month
- Tailored newsletters
- Individual participant contacts (by email and/or telephone)
- Intervention components: Diet, emphasis on increased physical activity, behavioral strategies, cognitive restructuring, social support, self-nurturing and alternative behaviors, body image and self-acceptance, issues specific to cancer survivors

## Energy Trial Consort Diagram



C.L. Rock et al. / Contemporary Clinical Trials 34 (2013) 282–295

## Weight Loss and Percent Weight Change\*

	Weight (lbs) Mean (SD)	Weight Loss (%) <sup>*</sup> Mean (SD)
<b>Baseline</b>		
Intervention (n=344)	187.0 (31.5)	
Usual Care (n=348)	186.3 (30.3)	
<b>6 months</b>		
Intervention (n=296)	174.3 (31.0) <sup>***</sup>	-6.3 (5.4) <sup>***</sup>
Usual Care (n=283)	182.8 (30.0) <sup>***</sup>	-1.3 (4.8) <sup>***</sup>
<b>12 months</b>		
Intervention (n=278)	174.5 (32.3) <sup>**</sup>	-6.3 (6.7) <sup>***</sup>
Usual Care (n=252)	180.7 (29.9) <sup>**</sup>	-2.0 (6.6) <sup>***</sup>

\*Relative weight loss (%) from baseline weight

\*\*\*P&lt;0.001

\*\*P&lt;0.05

## Physical Activity

Godin, Mean (SD)	Intervention	Usual Care
<b>Moderate exercise (min/week)</b>		
Baseline	64.6 (99.4)	67.8 (97.7)
6 months	127.8 (143.0)**	82.4 (104.1)**
12 months	113.0 (133.2)**	69.4 (101.9)**
<b>Strenuous exercise (min/week)</b>		
Baseline	27.6 (63.3)	33.3 (86.6)
6 months	75.0 (115.0)*	48.7 (104.5)*
12 months	65.3 (107.8)*	42.3 (89.5)*

\*P<0.02

\*\*P<0.001

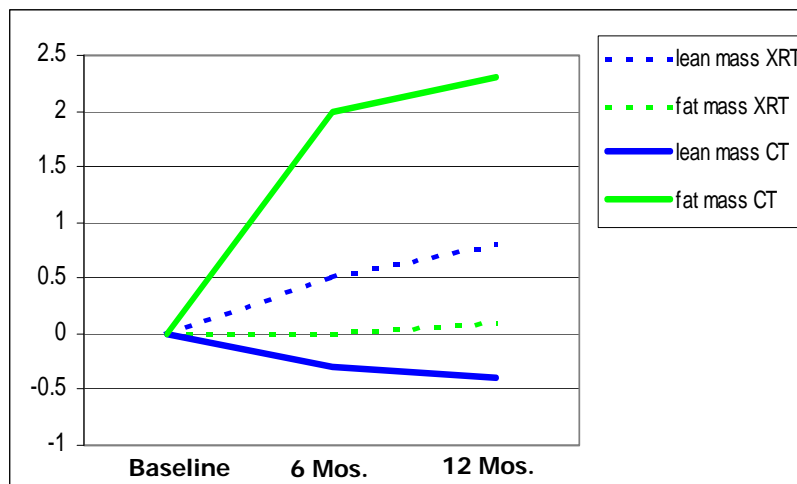
## Lessons Learned in Weight Management for Survivors

- Diet and weight loss studies aimed toward survivors need to address issues specific to cancer survivors
- This target population is motivated and able to make diet and lifestyle modifications
- Individualized counseling (in person or by telephone), group sessions, and mailed material can promote weight reduction
- More intensive interventions produce greater weight loss

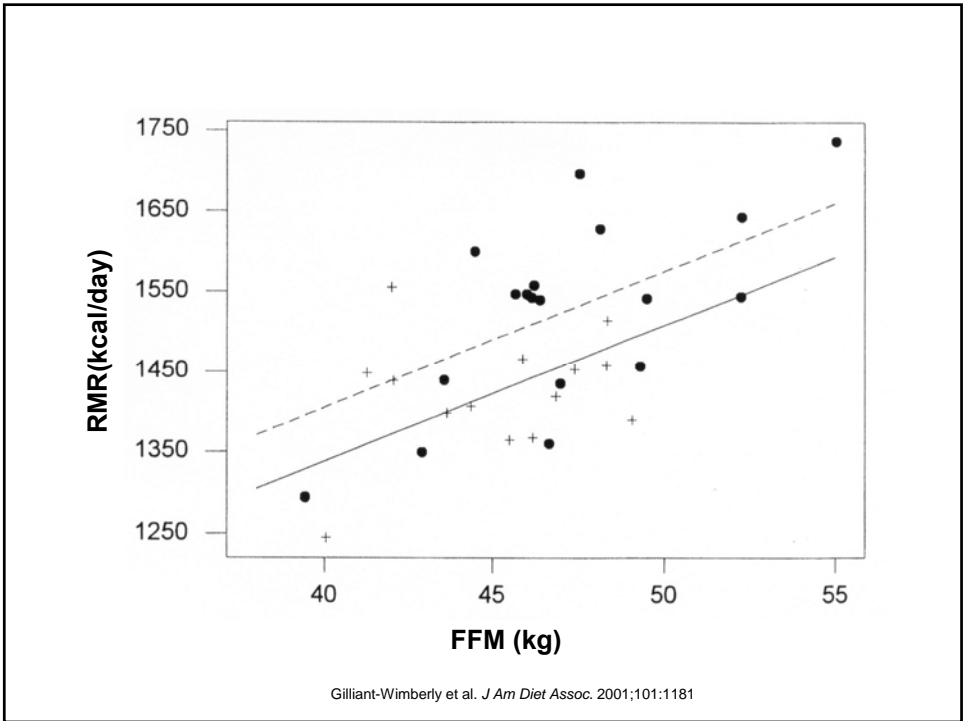
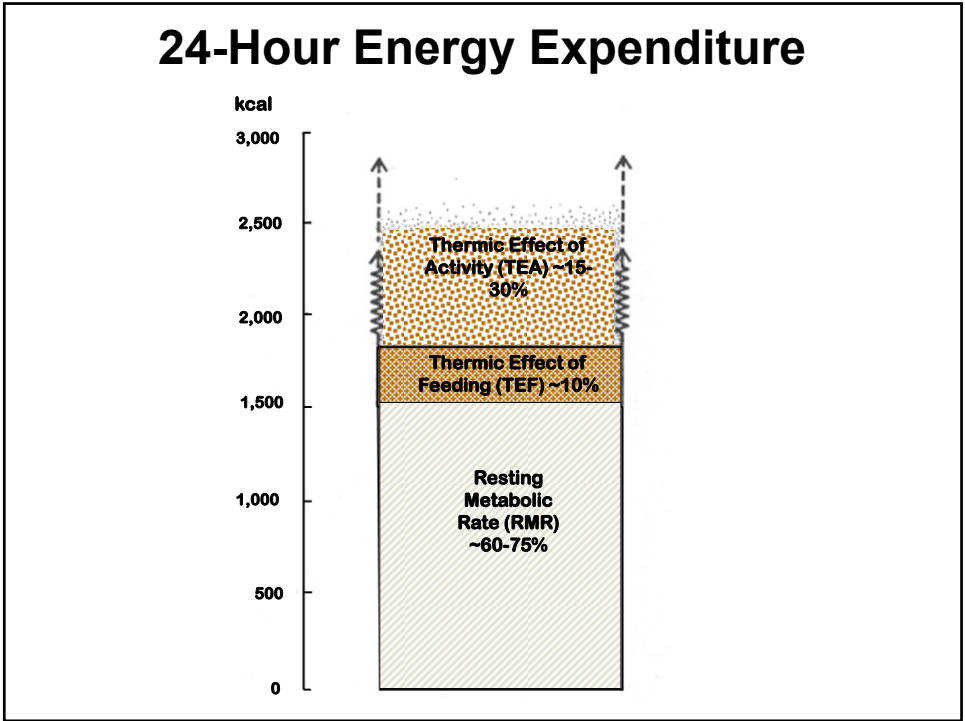
## Issues Specific to Cancer Survivors

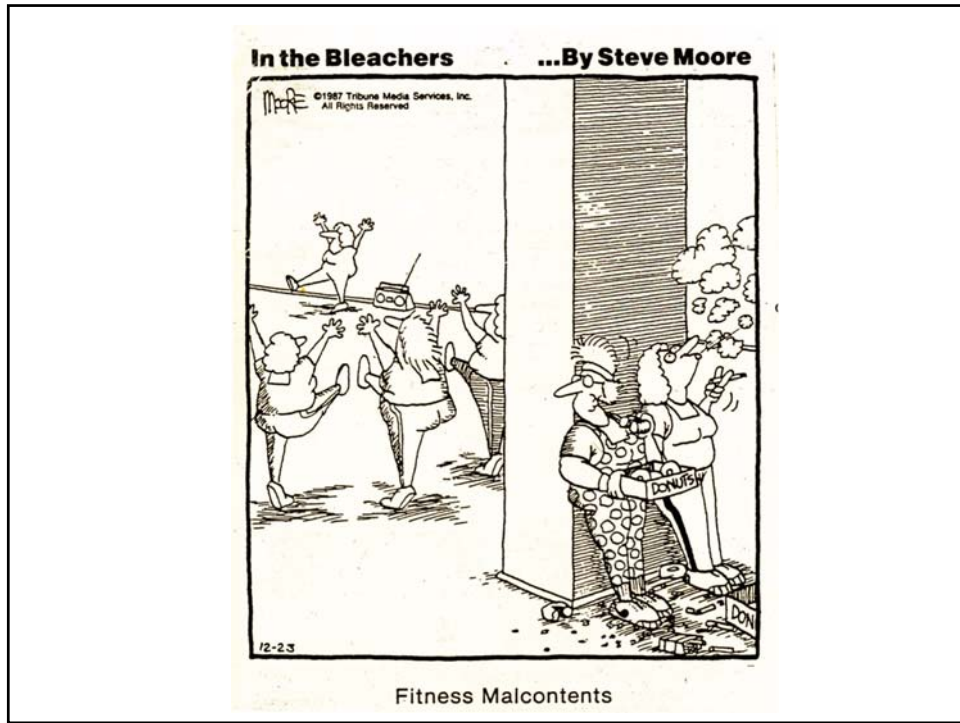
- Body image issues related to cancer and cancer treatments
- Enduring psychosocial symptoms, such as depression and fatigue, which affect efforts to make changes in behaviors
- Enduring treatment-related side effects, such as lymphedema, arthralgias and myalgias (joint and muscle pain)
- Changes in family dynamics and social support
- The importance of physical activity, due to the relationship between lean body mass and resting energy expenditure, and effects of treatments

## Changes in Body Composition in Breast Cancer Patients Post-Diagnosis



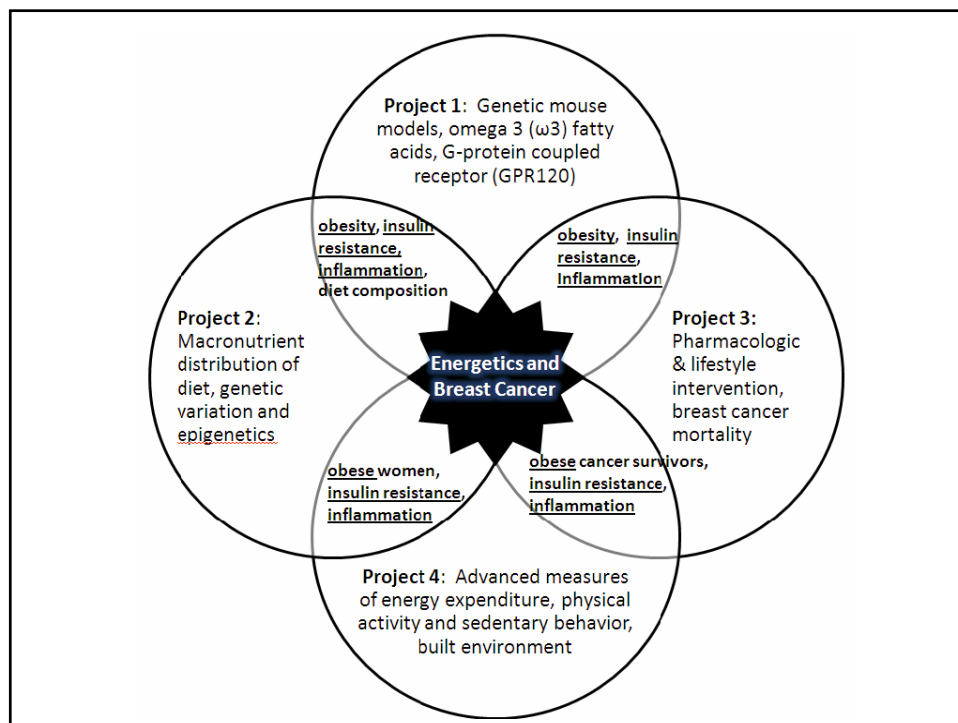
Demark-Wahnefried et al. *Am J Clin Nutr* 1997;65:1495





## Transdisciplinary Research in Energetics and Cancer (TREC)

- Cooperative agreement initiative (U54) that explores the relationship between obesity and cancer, funded by the National Cancer Institute (Patterson et al. *Cancer Causes Control* 2012;24:695-704)
- Integrates the study of diet, weight, and physical activity and their effects on energy balance and cancer
- Projects: Biologic and physiologic mechanisms of energy balance; behavioral, sociocultural, and environmental influences on diet, physical activity and weight in cancer survivors and other populations
- Across the four centers, two (at UCSD and Univ. of Penn.) are focused on energy balance and weight loss interventions in breast cancer prevention and control



## **The Colon Health and Life-Long Exercise Change (CHALLENGE) Study**

- Designed to determine the effects of a structured physical activity intervention on outcomes for survivors of high-risk stage II or III colon cancer who have completed adjuvant therapy within the past 2-6 months, endpoint is disease-free survival
- Participants (N=962) randomly assigned to a structured physical activity intervention or general health education materials
- Intervention consists of a behavioral support program and supervised sessions delivered over a 3-year period
- National Cancer Center Institute of Canada, trial being conducted in Canada and Australia

Courneya et al. *Current Oncol* 2008;15:1

## **The Alberta Moving Beyond Breast Cancer (AMBER) Study**

- Enrolling a cohort of newly-diagnosed early stage breast cancer survivors (N=1500) in Alberta, Canada, over a 5-year period to examine the role of physical activity and health-related fitness in breast cancer survivorship
- Assessments at baseline (within 90 days of surgery), 1 year, and 3 years, consisting of objective and self-reported measurements of physical activity, fitness, and patient reported outcomes

Courneya, Friedenreich, et al. *BMC Cancer* 2012;12:525.



## Childhood Cancer Survivors

- Advances in cancer treatment have contributed to improvements in survival rates (5-year survival rates now >80%) - a growing population of long-term survivors
- 5-Year survivors of acute lymphoblastic leukemia, the most common cancer diagnosed in children, have a life expectancy of only 54.7 years
- At increased risk of cardiovascular disease: 10 times more likely to develop CVD and 8 times more likely to die of heart failure during their first 30 years post-diagnosis
- Although cancer treatments likely contribute, traditional CVD risk factors (dyslipidemia, insulin resistance), diet, low physical activity levels and obesity probably exacerbate risk

## Childhood Cancer Survivors

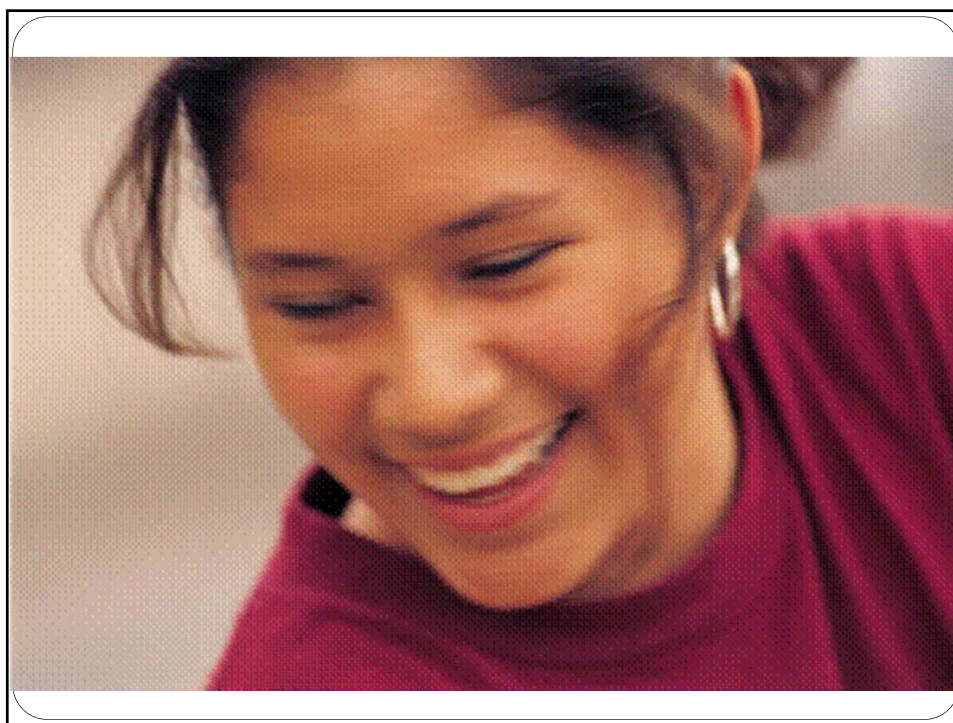
- Weight loss and physical activity intervention studies targeting this population have been completed and are underway
- Fit4Life Study: Cancer survivor-tailored weight management intervention tested in a randomized clinical trial of youth 8-18 years old with BMI  $\geq 85\%$  (N=38)
  - Intervention was a 4-month web, telephone and text message delivered intervention tailored for cancer survivors
  - Results: Participants  $\geq 14$  years had less weight gain (P=0.05) and increased moderate/vigorous physical activity (P<0.01) while all participants reported improved psychological outcomes compared to controls

Huang et al. *Pediatr Blood Cancer* 2014;61:894

### Changes in Weight and BMI-z Over Time According to Treatment Group

Treatment group	Weight (kg) (N = 35)		BMI-z (N = 35)	
	Values	P-value	Values	P-value
Fit4Life	Baseline (N = 18): 65.6 (19.5)	0.06 <sup>a</sup>	Baseline (N = 18): +1.84 (0.32)	0.13 <sup>a</sup>
	4 months: 65.5 (18.8)		4 months: +1.77 (0.36)	
Control	Baseline (N = 17): 70 (17.6)		Baseline (N = 17): +2.00 (0.41)	
	4 months: 71.4 (18.1)		4 months: +1.99 (0.41)	

Huang et al. *Pediatr Blood Cancer* 2014;61:894–900



## Comments and Considerations

### Limitations of observational studies

- Confounding: Difficult if not impossible to control for other influencing factors, clustering of behaviors
- Obesity is inextricably linked to behavioral determinants: Energy restriction versus physical activity versus adiposity
- Measurements are crude

### Limitations of randomized clinical trials

- With diet intervention trials, the intervention effort itself is being tested, in addition to cancer outcomes; degree of change may not be sufficient to have a biological effect
- Time frame of the intervention: Length of trial may be too short, relative to the long latency of most cancers
- Effect modification by baseline status

