


THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

WORKING EVERYDAY TO PROVIDE THE HIGHEST QUALITY OF LIFE FOR PEOPLE WITH CANCER

Dissecting the Obesity-Cancer Link: Is it Caloric Restriction? Is it Physical Activity? Is it Obesity?

WENDY DEMARK-WAHNEFRIED, PHD, RD

PROFESSOR AND WEBB CHAIR OF NUTRITION SCIENCES

ASSOCIATE DIRECTOR OF CANCER PREVENTION & CONTROL

UNIVERSITY OF ALABAMA AT BIRMINGHAM

Objectives

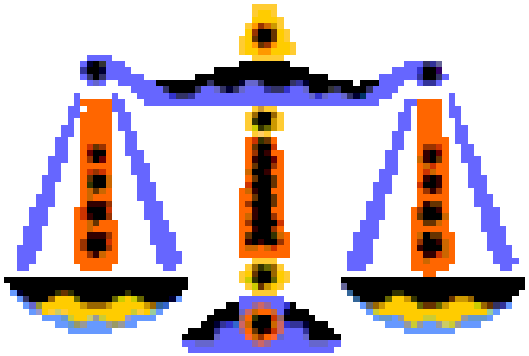
- Brief overview of energy balance
- Brief overview/examples of studies (animal and human) that support energy restriction, increased physical activity or overall negative energy balance in hindering cancer progression
- Need to disentangle these factors with well-designed studies
- Issues that need to be addressed in designing trials to answer these questions

Energy Balance

<u>Energy Intake</u>

(Calories In)

Modified by ingestion and/or absorption



<u>Total Energy Expenditure (TEE)</u>

(Calories Out)

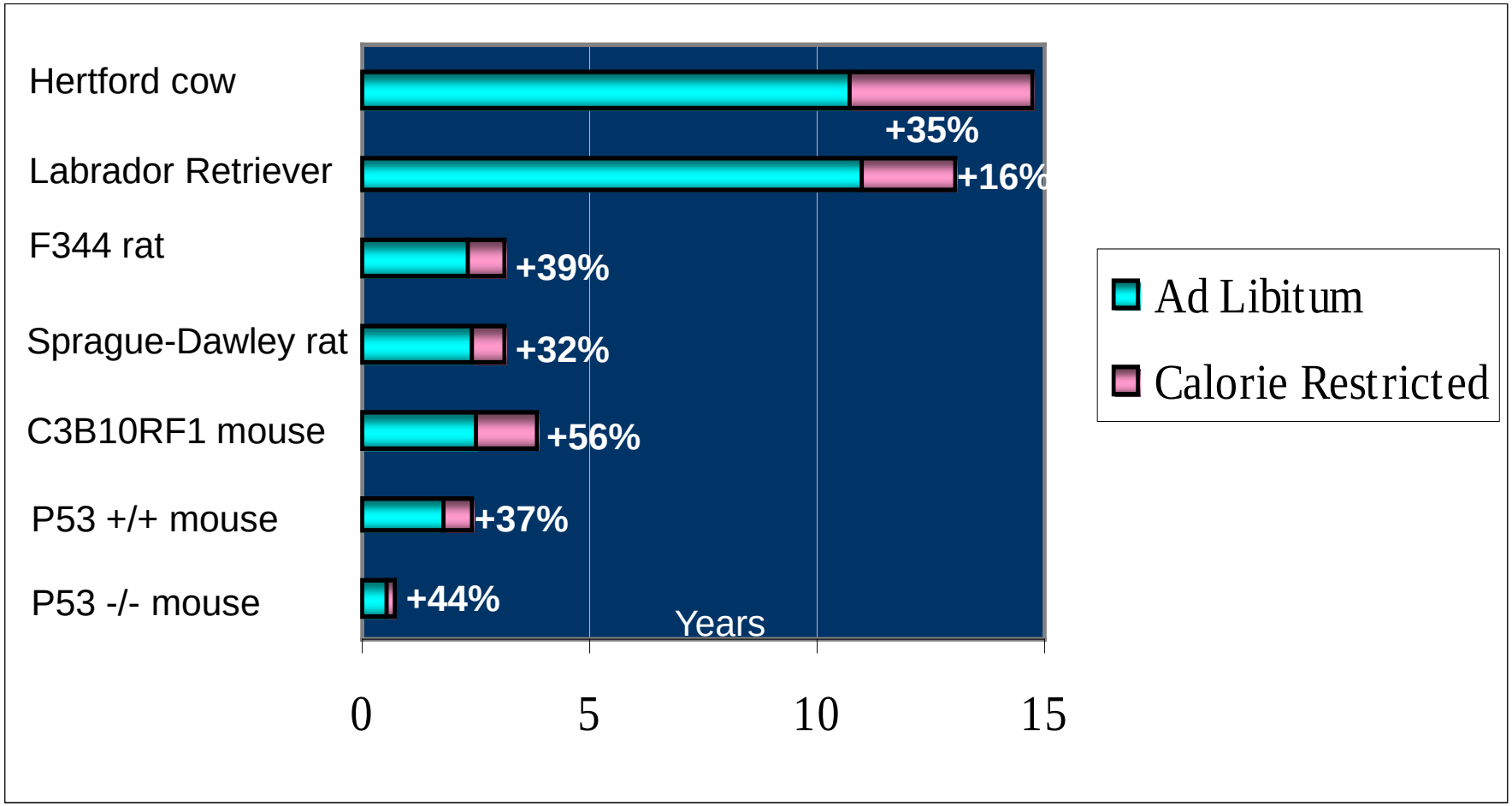
<u>Resting Metabolic Rate (RMR)</u>
(energy needed to maintain body function at rest - 60-75% TEE)

<u>Thermic Effect of Food</u>

(energy for digestion/metabolism 5-10% TEE)

<u>Physical Activity</u> 15-30%

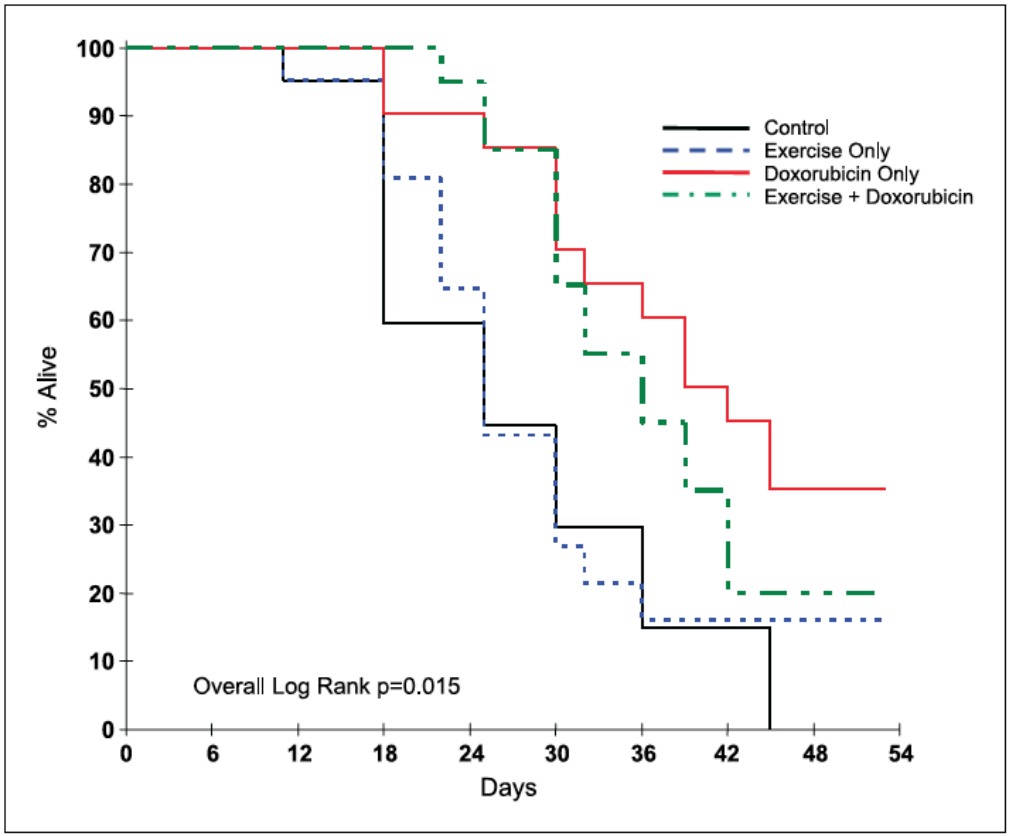
Caloric Restriction Results in Reduced Cancer Mortality & Increased Lifespan Across Species



Hursting et al. Ann. Rev. Med 54:131,2003

Effects of Exercise on Cancer Progression

Fig. 1. Survival curves of athymic female mice implanted with MDA-MB-231 breast carcinoma xenografts. All animals were s.c. implanted with MDA-MB-231 breast carcinoma cells (5×10^6) in the right flank. Following tumor establishment (14 days, tumor volume ~ 300 mm^3), mice were stratified by body weight and tumor volume and randomly assigned to receive doxorubicin (4 mg/kg every 7 days), exercise training (18 m/min, 0% grade, 45 minutes, 5 d/wk for 8 weeks), doxorubicin + exercise or no intervention control. Tumor volume and body weight were measured twice weekly. Tumor growth delay was significantly prolonged in the doxorubicin-only and exercise + doxorubicin groups compared with the exercise-only and control groups (overall log rank, $P = 0.015$). There was no significant difference between doxorubicin-only and exercise + doxorubicin groups or exercise-only and control groups. At 45 days, Kaplan-Meier estimates indicated a 35% (95% CI, 17-54%) survival rate for the doxorubicin-only mice compared with 20% (95% CI, 7-33%) in the doxorubicin + exercise group, 16% (95% CI, 2-31%) in the exercise-only group and 0% in the control group.



Jones LW, Eves ND, Courneya KS, Chiu BK, Baracos VE, Hanson J, Johnson L, Mackey JR. *Clin Cancer Res* 11:6695-8, 2005

Results differ from Kline and Rusch (1944) – no differences with implanted sarcoma, Welsch et al. (1995) smaller tumors in implanted MDA-MB-231, and Zheng et al. (2008) – smaller tumors in pancreas xenograft model.

Gene Expression Patterns in Mammary Glands of normal 9-week C57BL/6 mice followed for 6 weeks (Ad Libitum vs. 30% Caloric Restriction &/or access to running wheel)

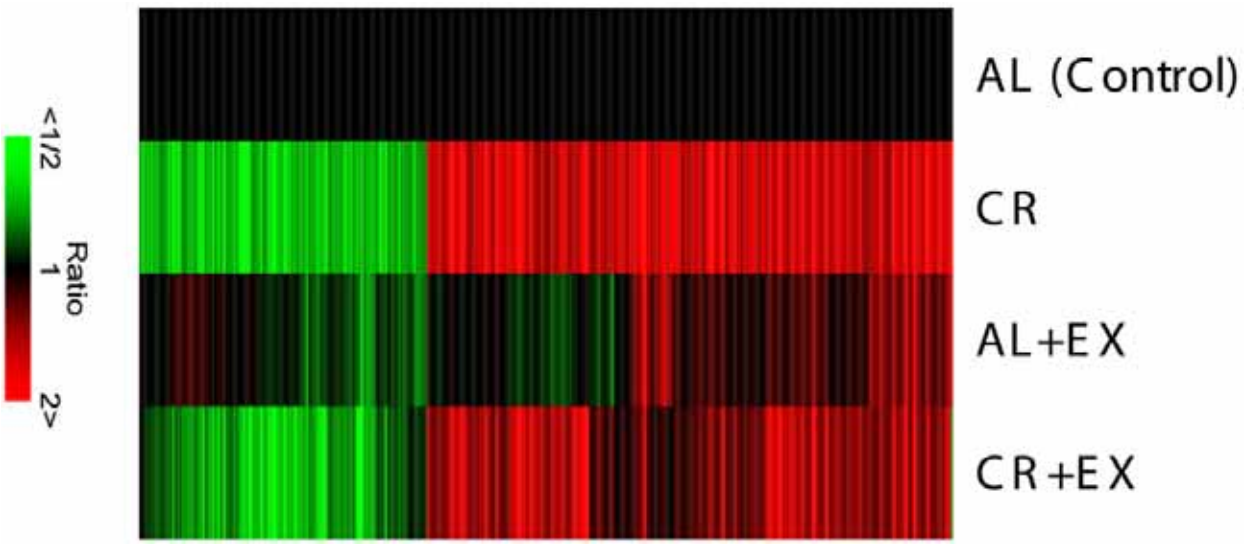


Figure 3
Heat map of genes for which CR significantly altered expression vs. AL
Cluster analysis of genes significantly changed by the CR intervention as compared to AL ($p \leq 0.005$, fold change ≥1.5) was performed as described in Materials and Methods. Findings are depicted as a heat map, with red indicating up-regulated and green indicating down-regulated genes. Columns represent different treatment groups and rows represent different genes. Changes for all treatment groups are shown for the genes for which CR as compared to AL significantly changed expression, including those treatments that did not achieve statistical significance vs. AL

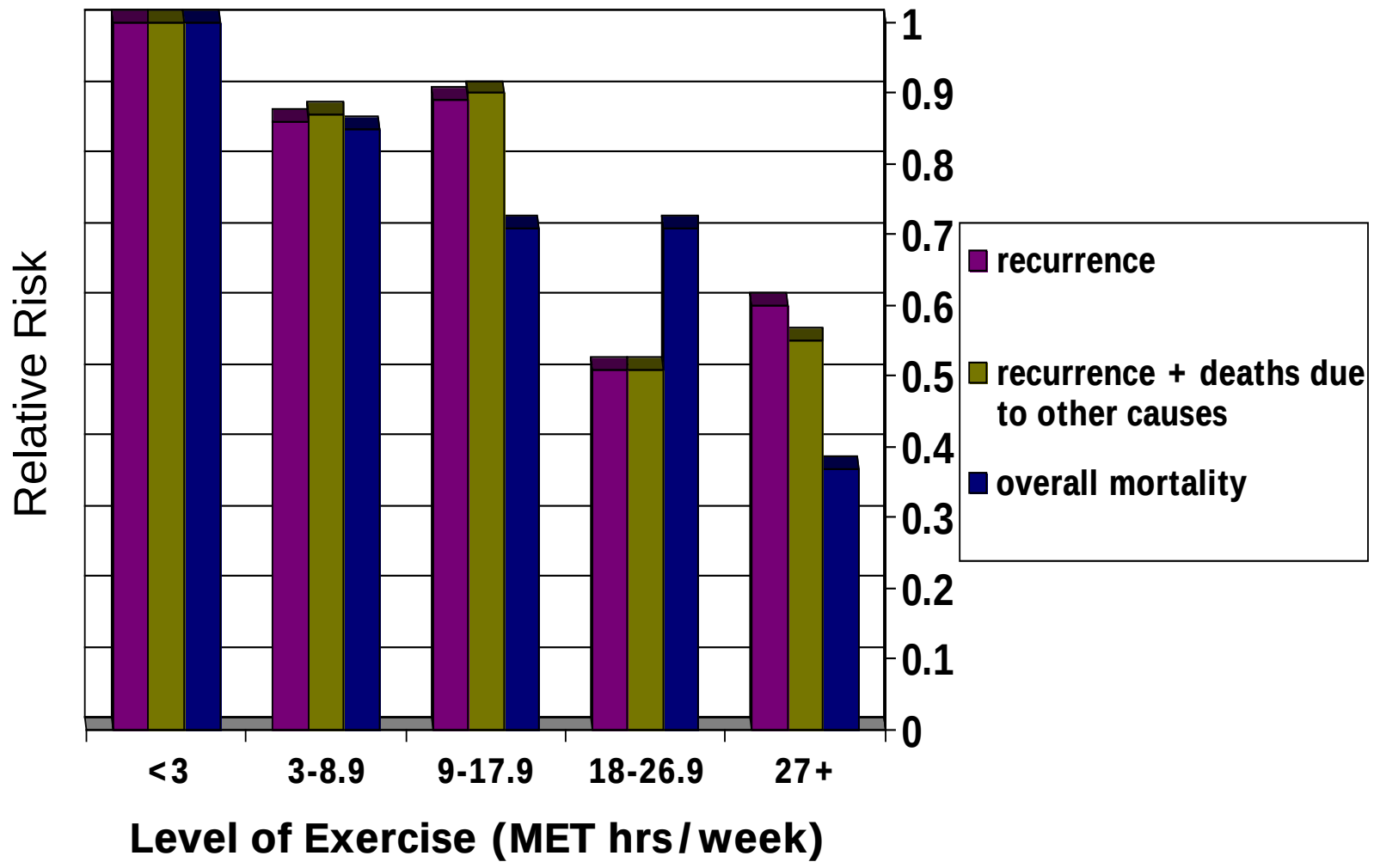
425 genes significantly affected by CR

45 genes significantly affected by exercise

Overlap for 3 genes

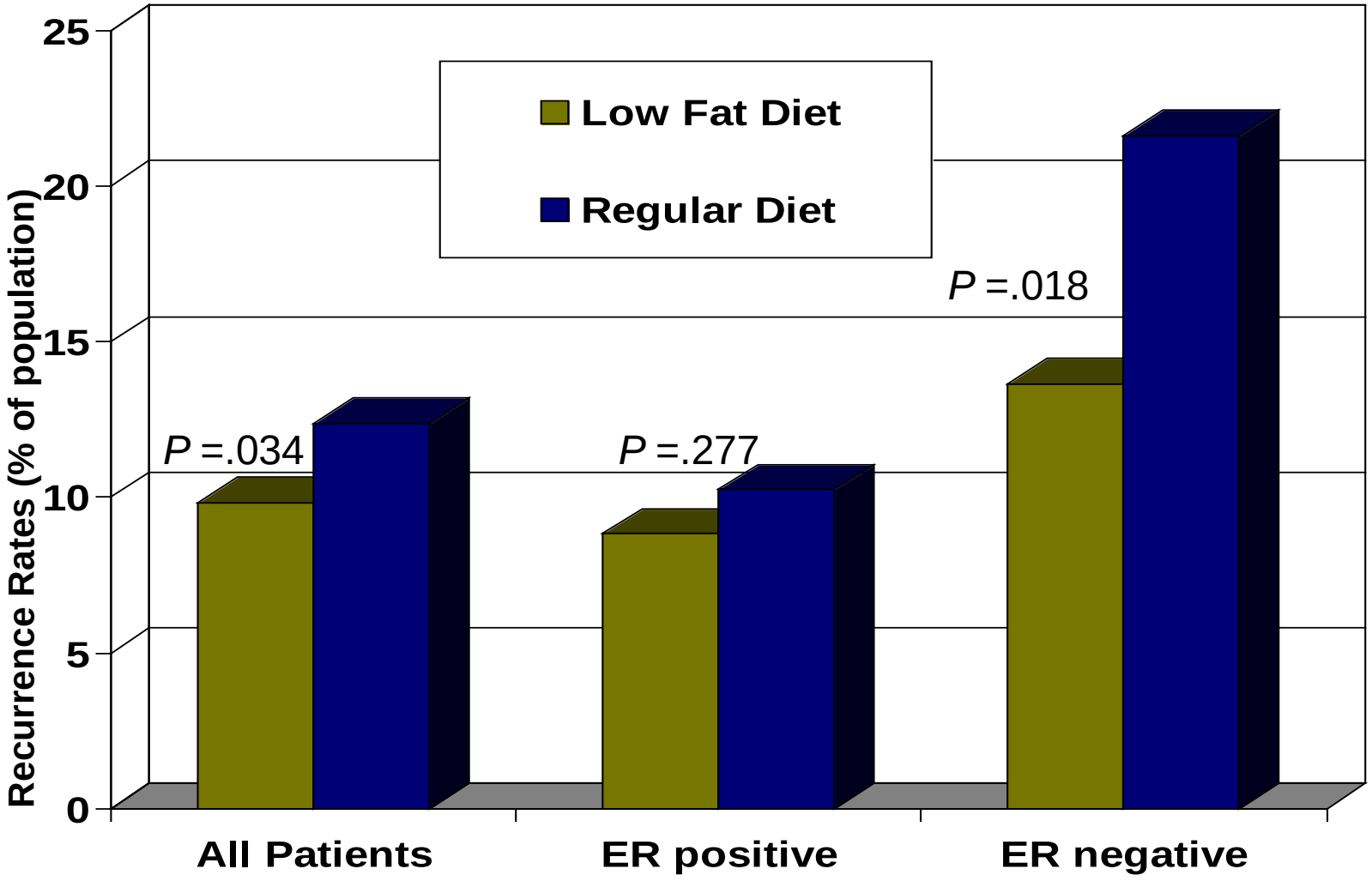
Padovani M, Lavions JA, Chandramouli GV, Perkins, JC, Hursting SD, Bennett LM, and Berrigan D ***Cancer Prev Res*** 2(12):1076-87, 2009.

Exercise & Association with Recurrence & Survival - CALGB 89803 (Stage III CRC) N=832



Meyerhardt et al. JCO 24:3535, 2006

Results of the Women's Intervention Nutrition Study (WINS/n=2,437) Show Reduced Rates of Recurrence in Patients Assigned to a Low Fat Diet (Weight Loss 6 Pounds)

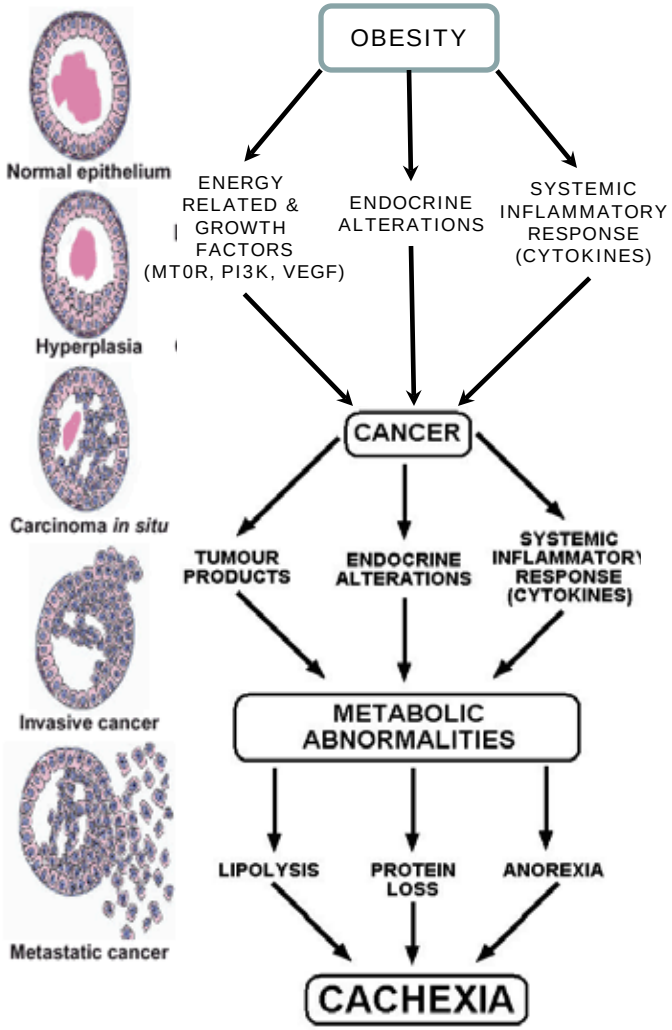


Chlebowski et al. JNCI 98:1767, 2006

Need to Disentangle Effects of Caloric Restriction and Increased Physical Activity (and Obesity)

- Head to Head Comparison (2 x 2 trial) - albeit a challenge to impose same magnitude of energy deficit with exercise as with diet. In animals also could independently assess effect of adiposity by surgically removing fat.
- Issues to be considered in interpreting extant studies or in designing future studies
  - process of cancer is complex
  - energy balance is complex
  - body composition
  - inherent error in ascertaining levels of caloric intake & physical activity
  - calories come from many sources - one can exercise in many ways
  - adherence and long-term change
  - accrual, drop-in, drop-out
  - co-morbidities/late effects

Cancer is a Complex Process:
Energy Balance Affects It…It Affects Energy Balance



- At early stages the host environment may influence the metabolism of the tumor; at later stages the tumor drives the catabolic state (cachexia).
- There is a need to investigate the effects of energy restriction, increased physical activity and adiposity at various stages (hyperplasia, in situ, localized cancer, post-treatment, advanced disease)
- Presurgical Models (pre-operative or during active surveillance) offer unique opportunities to study the impact of negative energy balance directly on the tumor tissue

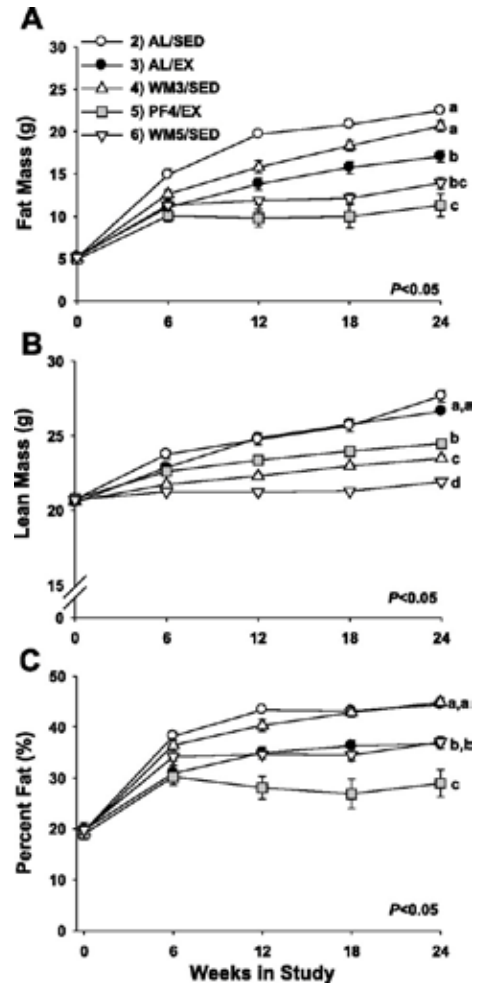
Energy Balance is Complex

- Difficult to make a change in one factor without impacting another.
- Physiologic responses
- Potential for Behavioral Clustering –

  - 978 breast and prostate cancer survivors shows kappa statistics 0.25 (0.19, 0.31) between low fat diet and regular exercise (Demark-Wahnefried et al Cancer 88:674-84, 2000)

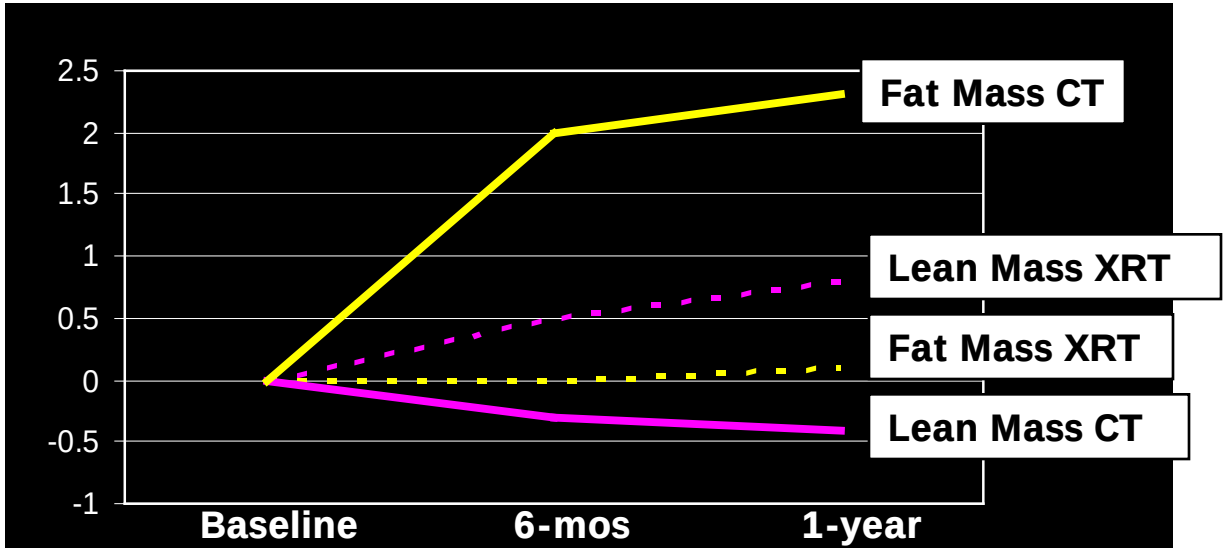
  - Moderate-to-Vigorous PA increased 44.6 $\pm$ 80.8 to 212.3 $\pm$ 4 min week in 20 bariatric surgery patients (Bond et al. Obesity 13: 2395-7, 2010)

Controlling for Body Composition



Huffman D,Moellering DR, Grizzle WE, Stockard CR, Johnson MS, Nagy TR, *Am J Physiol Regul Integr Comp Physiol* 294: R1618–27, 2008.

- Body Composition Affected by Exercise and Energy Intake
- Cancer Treatment Affects Body Composition



Demark-Wahnefried W, Peterson BL, Winer EP, Marks L, Aziz N, Marcom PK, Blackwell K, Rimer BK *J Clin Oncol.* 19:2381, 2001

Monitoring Dietary Intake and Physical Activity

- Improvements have been made in tools to assess energy intake (dietary recalls most appropriate for studies assessing energy balance).

  e.g., ASA24 (http://riskfactor.cancer.gov/tools/instruments/asa24)
  EMA technology

- Over-reporting in small eaters and under-reporting in large eaters (flat slope phenomena) but also affected by SES and dietary restraint. General trend toward underreporting -2% to -25%

  Hill & Davies Brit J Nutr 2001

- Similar problems with physical activity instruments (similar developments ACT24 and EMA). Moderate correlations between accelerometry (.39-.68) lower correlations with fitness. Among cancer survivors correlations .24-.54

  Mader et al. MSSE 48: 1255, 2006

  Sloane et al. MSSE 42:1334, 2009/Jovanovic et al. AJ Health Behav, 35: 71, 2011

- Doubly labelled water has a relative accuracy of 1% and within-subject repeatability of 5 to 8%. Expensive.

  Schoeller DA, Public Health Nutr. 5(6A):883, 2002

Is a Calorie…a Calorie…a Calorie? Is Exercise…Exercise…Exercise?

- Calories can come from Fat (9 kcal/g), Protein (4 kcal/g), Carbohydrate (4 kcal/g) and Alcohol (7 kcal/g) and from a multitude of foods. Diet composition may impact cancer progression.

Adjusted Hazards Ratios for Stage III CRC patients (n=1009) 5.3 year follow-up (Meyerhardt et al. JAMA 298:754, 2007)		
	Cancer Recurrence/Death	Overall Mortality
Western Diet	2.85 (1.75-4.63) P <.001	2.32 (1.36-3.96) P <.001
Prudent Diet	1.13 (.77-1.67) P = 0.84	1.32 (.86-2.04) P=0.54

- Exercise can be aerobic, resistance-training, and range in intensity

Accrual

- To date few diet and exercise interventions in cancer populations characterize enrollees vs. larger pool of cancer cases.
- Most conducted in breast cancer survivors and Caucasian samples
- Baumgartner et al. HEAL Study (Am J Epidemiol 160:1087-97, 2004)

		BMI			
Tumor Size ≥ 1 cm		<22.5	22.5-29.4	≥ 29.5	p_{trend}
	Hispanic (n=131)	1.0	0.41 (0.08, 2.06)	0.16 (0.03, 0.84)	0.06
	Non-Hispanic Whites (n=416)	1.0	1.50 (0.94,2.40)	1.82 (1.0, 3.34)	0.04

Attrition

- To date few diet and exercise interventions in cancer populations characterize completers vs. drop-outs.

- Many studies use last observation carried forward for dietary and exercise outcomes

Adherence and Long-term Change

- Very few studies, especially those in cancer populations assess long-term change. Most studies 12-weeks.
- Challenge to promote long-term adherence and balance subject burden with adequate control

Long-term Adherence is Possible

RENEW, 641 Older Prostate, Breast and CRC Survivors

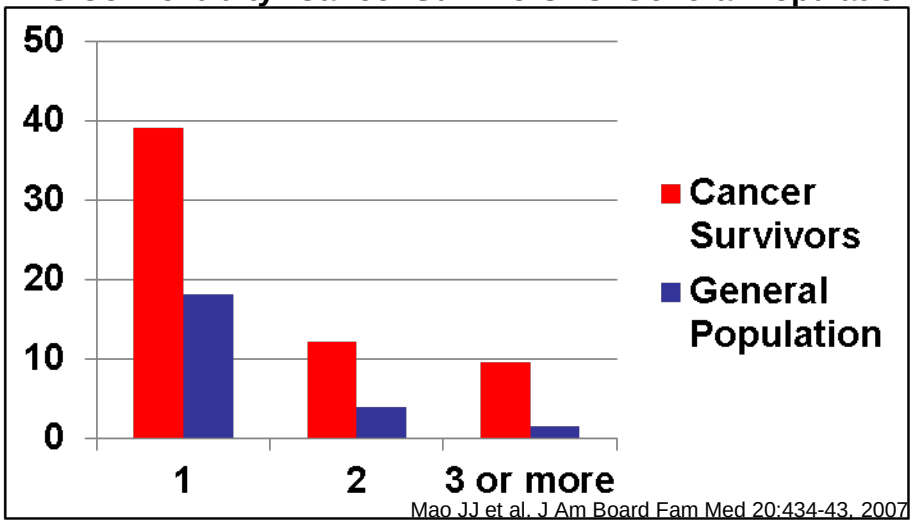
Co-morbidities - Late effects

Consensus exists regarding the benefits of exercise and achievement of a healthy weight for…

- Cardiovascular disease
- Metabolic Syndrome
- Diabetes
- Physical Functioning

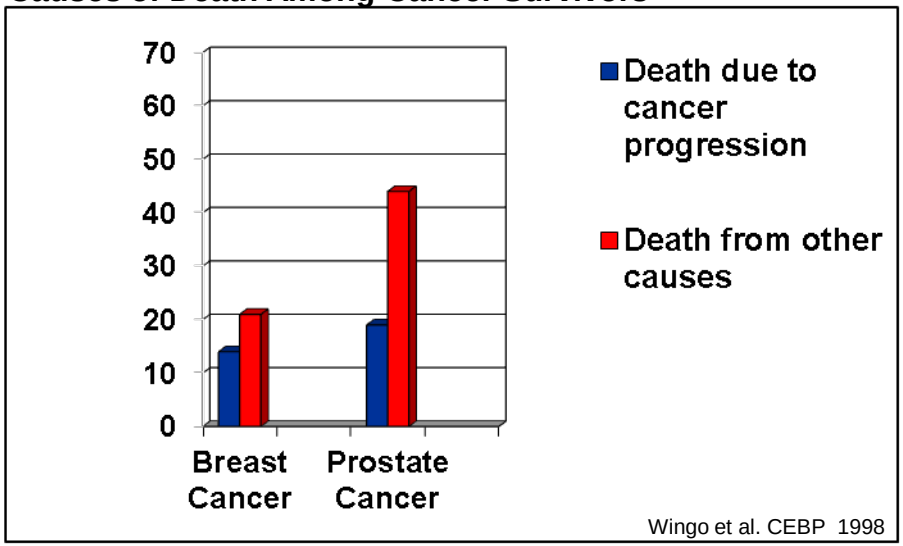
These are important outcomes and also impact survival (would a trial based on cancer-survival or even cancer-free survival run to completion before stopping rules are engaged?)

NHIS Co-Morbidity: Cancer Survivors vs. General Population



Mao JJ et al. J Am Board Fam Med 20:434-43, 2007

Causes of Death Among Cancer Survivors



Wingo et al. CEBP 1998

Summary

- Both energy balance and cancer are complex – studying them together is a challenge
- There is a need disentangle the effects of energy restriction, physical activity and adiposity on neoplasia
- There are a multitude of issues to consider to appropriately interpret current studies and design new ones