Evidence Gaps that Current Trials Will Address, Gaps that Remain, and How These Gaps Can be Filled

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National Cancer Policy Forum

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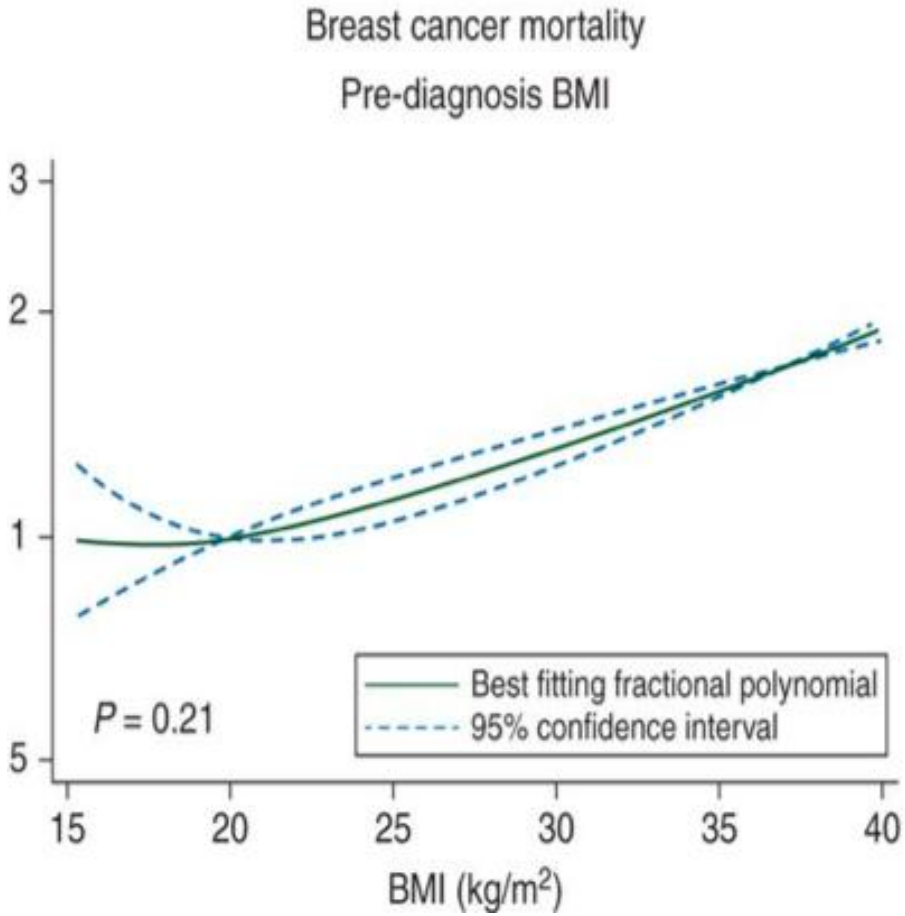
A brief recap of what we know about weight, physical activity and health outcomes for cancer survivors

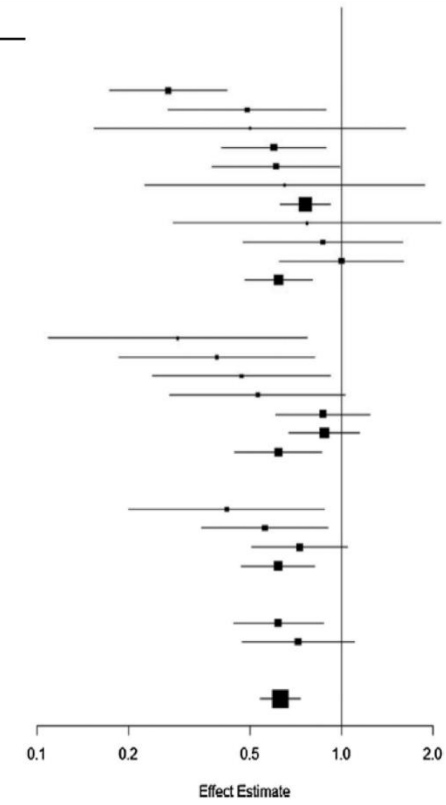
Obesity and inactivity are associated with poor prognosis in many cancers



PA and cancer-specific mortality

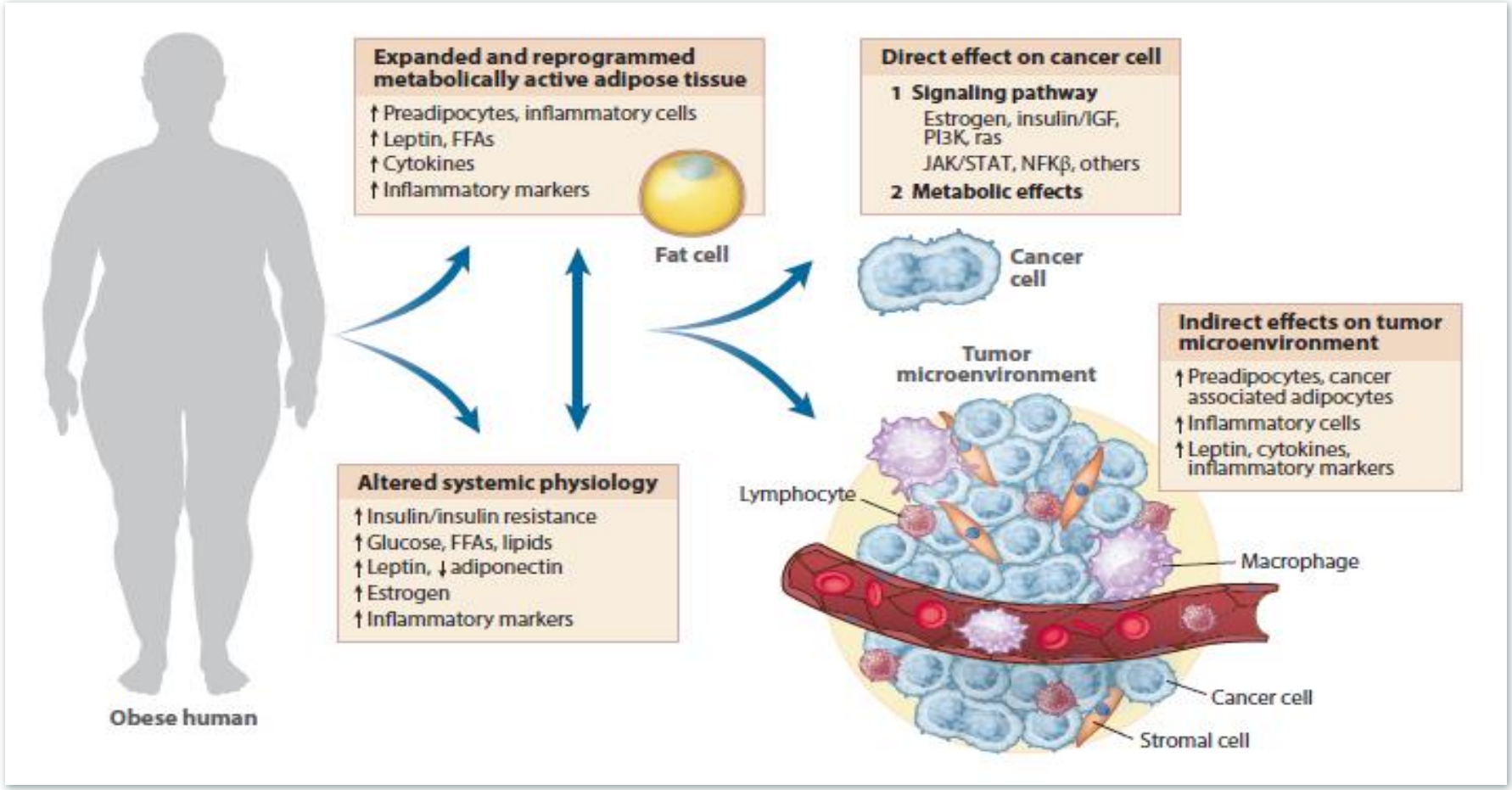
Table 1. Individual and pooled risk estimates from prospective cohort studies that related postdiagnosis physical activity to cancer-specific mortality, by cancer site

Author, year	No. of events/cases	Effect estimate	95% CI
Breast			
Bradshaw, 2014 (10)	195/1,033	0.27	0.17–0.42
Holick, 2008 (26)	109/4,482	0.49	0.27–0.89
Borch, 2015 (9)	155/1,327	0.50	0.15–1.62
Holmes, 2005 (27)	280/2,987	0.60	0.40–0.89
Irwin, 2011 (11)	86/2,910	0.61	0.38–0.99
Irwin, 2008 (28)	115/933	0.65	0.23–1.87
Williams, 2014 (8)	46/986	0.76	0.63–0.92
de Glas, 2014 (12)	39/435	0.77	0.28–2.12
Sternfield, 2009 (29)	102/1,970	0.87	0.48–1.59
Borugian, 2004 (7)	112/603	1.00	0.63–1.60
Pooled Estimate (I^2 = 61.3%)	1,239/17,666	0.62	0.48–0.80
Colorectal			
Kuiper, 2012 (13)	51/606	0.29	0.11–0.77
Meyerhardt, 2006 (30)	80/573	0.39	0.19–0.82
Meyerhardt, 2009 (31)	88/661	0.47	0.24–0.92
Arem, 2015 (14)	128/3,797	0.53	0.27–1.03
Campbell, 2013 (15)	379/2,236	0.87	0.61–1.24
Baade, 2011 (16)	345/1,825	0.88	0.67–1.15
Pooled Estimate (I^2 = 56.6%)	1,071/9,698	0.62	0.45–0.86
Prostate			
Kenfield, 2011 (17)	112/2,705	0.42	0.20–0.88
Friedenreich, 2016 (18)	170/830	0.56	0.35–0.90
Bonn, 2015 (19)	194/4,623	0.73	0.51–1.05
Pooled Estimate (I^2 = 0.8%)	476/8,158	0.62	0.47–0.82
Any			
Lee, 2014 (20)	337/1,021	0.62	0.44–0.87
Inoue-Choi, 2013 (21)	184/2,017	0.72	0.47–1.10
Overall			
Pooled Estimate (I^2 = 47.9%)	3,307/38,560	0.63	0.54–0.73



Chan DSM et al. Ann Oncol 2014; Friedenreich et al. Clin Can Res 2016;22:4766-75

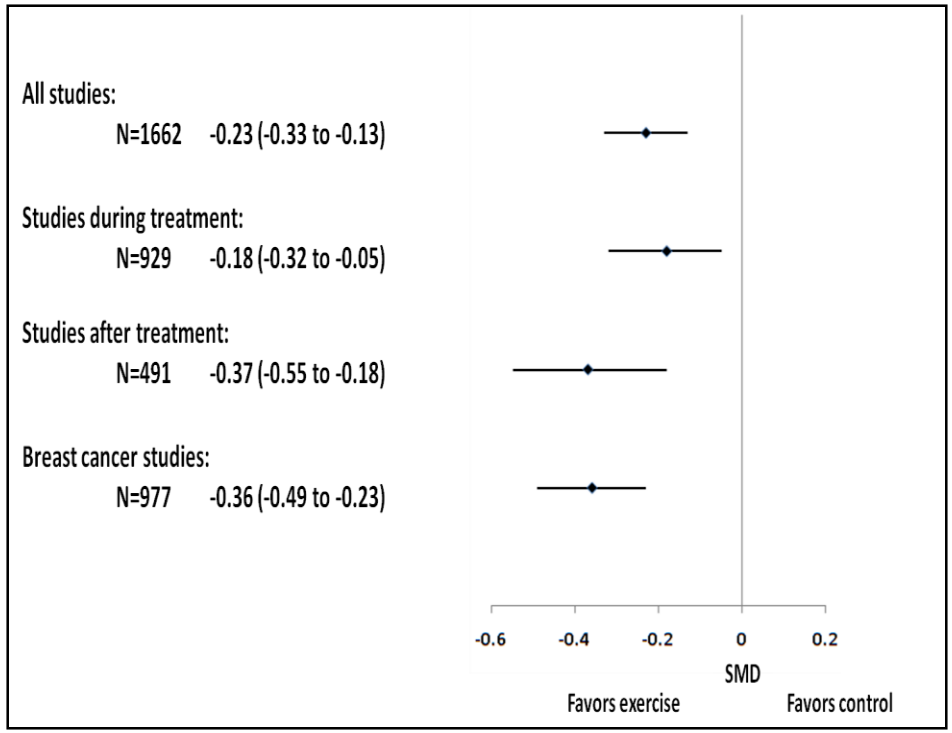
Mechanistic data support biologic plausibility of link between obesity/physical activity and cancer



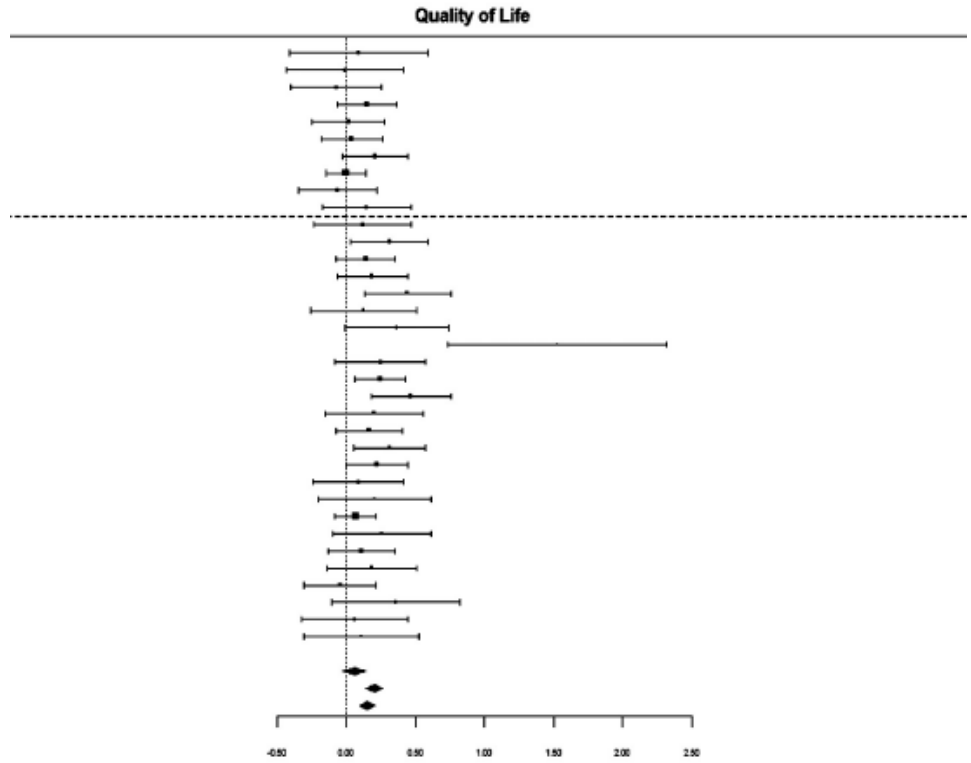
Goodwin PJ and Stambolic V Ann Rev Med 2015

Interventional studies show benefits of weight loss/increased PA in cancer survivors

Impact of exercise interventions on fatigue



Impact of exercise interventions on quality of life



Cochrane Review 2008; Buffart L et al. Cancer Treatment Reviews 2017

Obesity and inactivity are common in cancer survivors

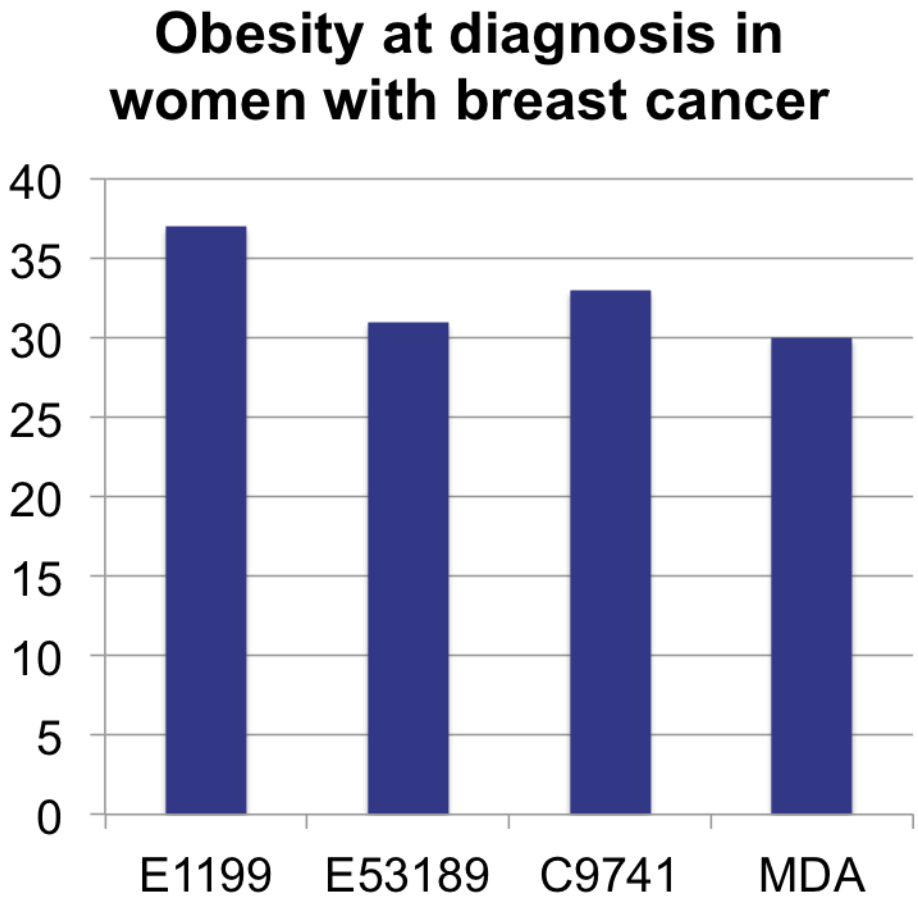


Table 2. Percentage of Cancer Survivors Meeting the Recommendations for Physical Activity, Fruit and Vegetable Consumption, and Smoking by Cancer Group

Cancer Group	Physical Activity (%)	5-A-Day (%)	Smoking (%)
Breast	37.1	18.2	88.1
Prostate	43.2	15.6	91.6
Colorectal	35.0	15.9	91.3
Bladder	36.0	16.3	82.6
Uterine	29.6	19.1	91.1
Skin melanoma	47.3	14.8	89.0

Abbreviation: 5-A-Day consumed five servings of fruits and vegetables each day.

Ligibel et al. JNCI 2015; Sparano et al. Cancer. 2012; Blanchard et al. JCO 2008.

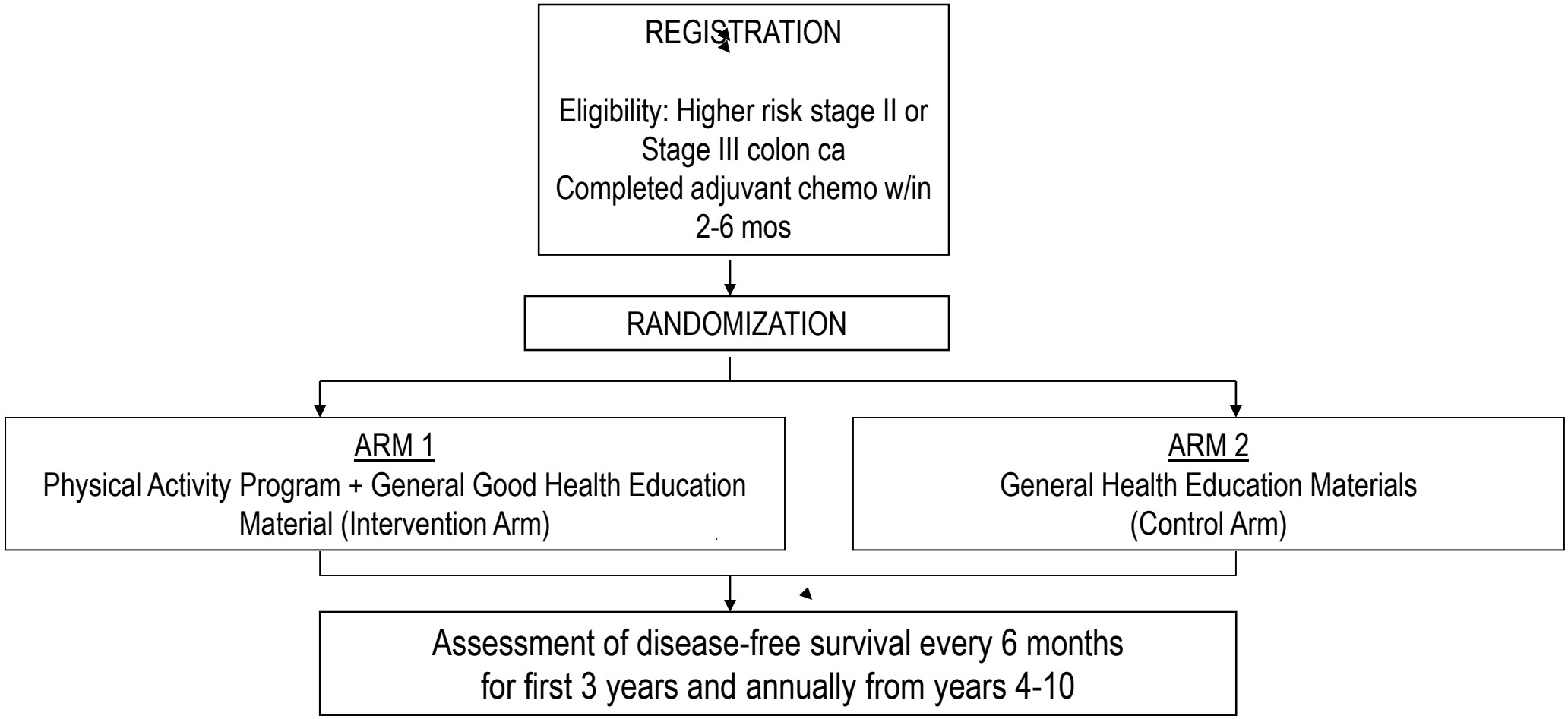
Unanswered questions

- Does weight loss/increased PA after cancer diagnosis reduce risk of recurrence and mortality?
- If so, what dose and duration are needed to impact cancer outcomes?
- What is most important? Weight? Physical activity? Diet?
- Do all patients benefit equally from lifestyle interventions? Is this cancer-specific or based on host characteristics?
- How can lifestyle interventions be disseminated across diverse populations of cancer survivors?

How do on-going trials fill these evidence gaps?

Lifestyle intervention trials with recurrence/mortality outcomes

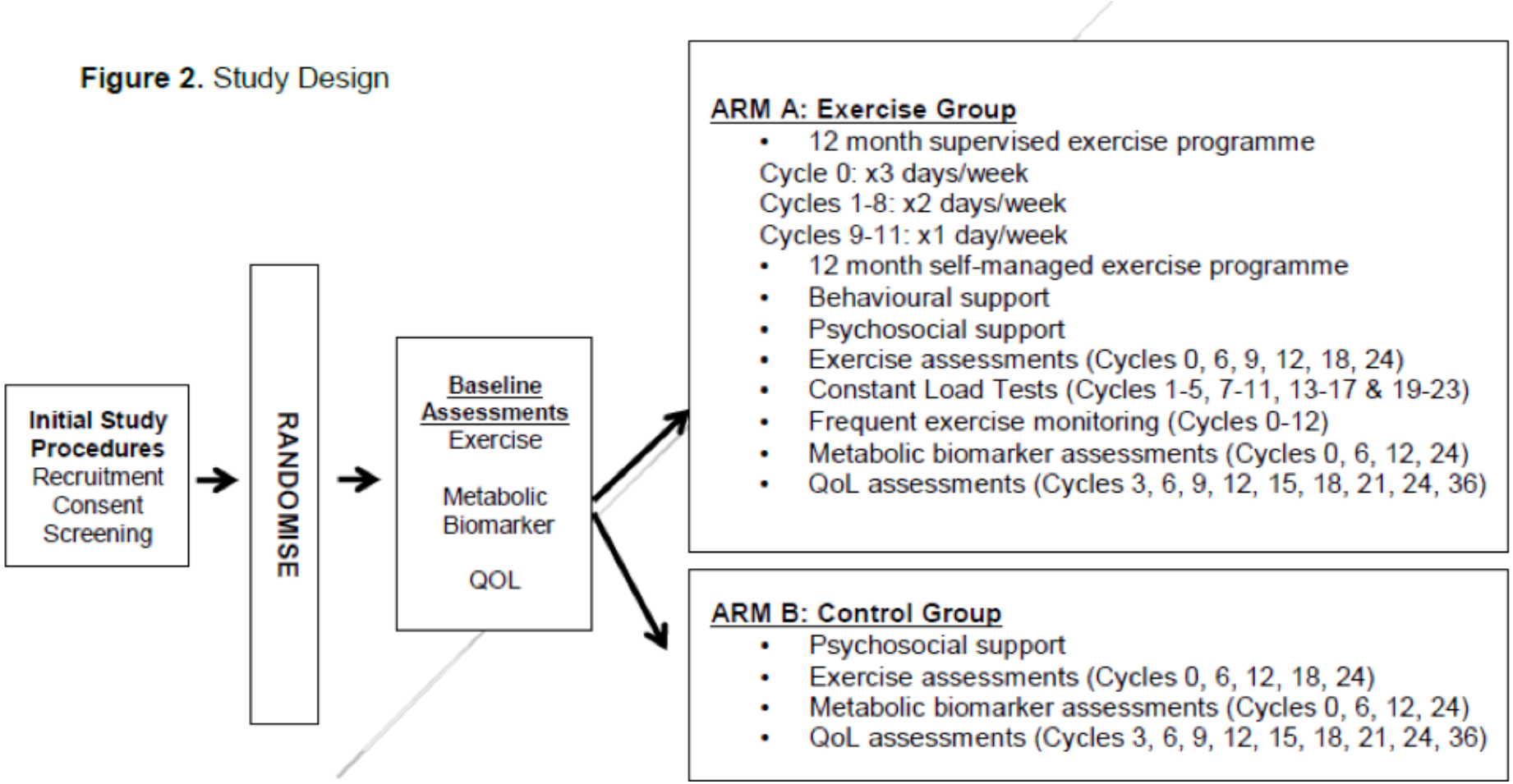
CHALLENGE: Colon Health and Life-Long Exercise Trial



Courneya Curr Oncol.2008 Dec;15(6):271-8.

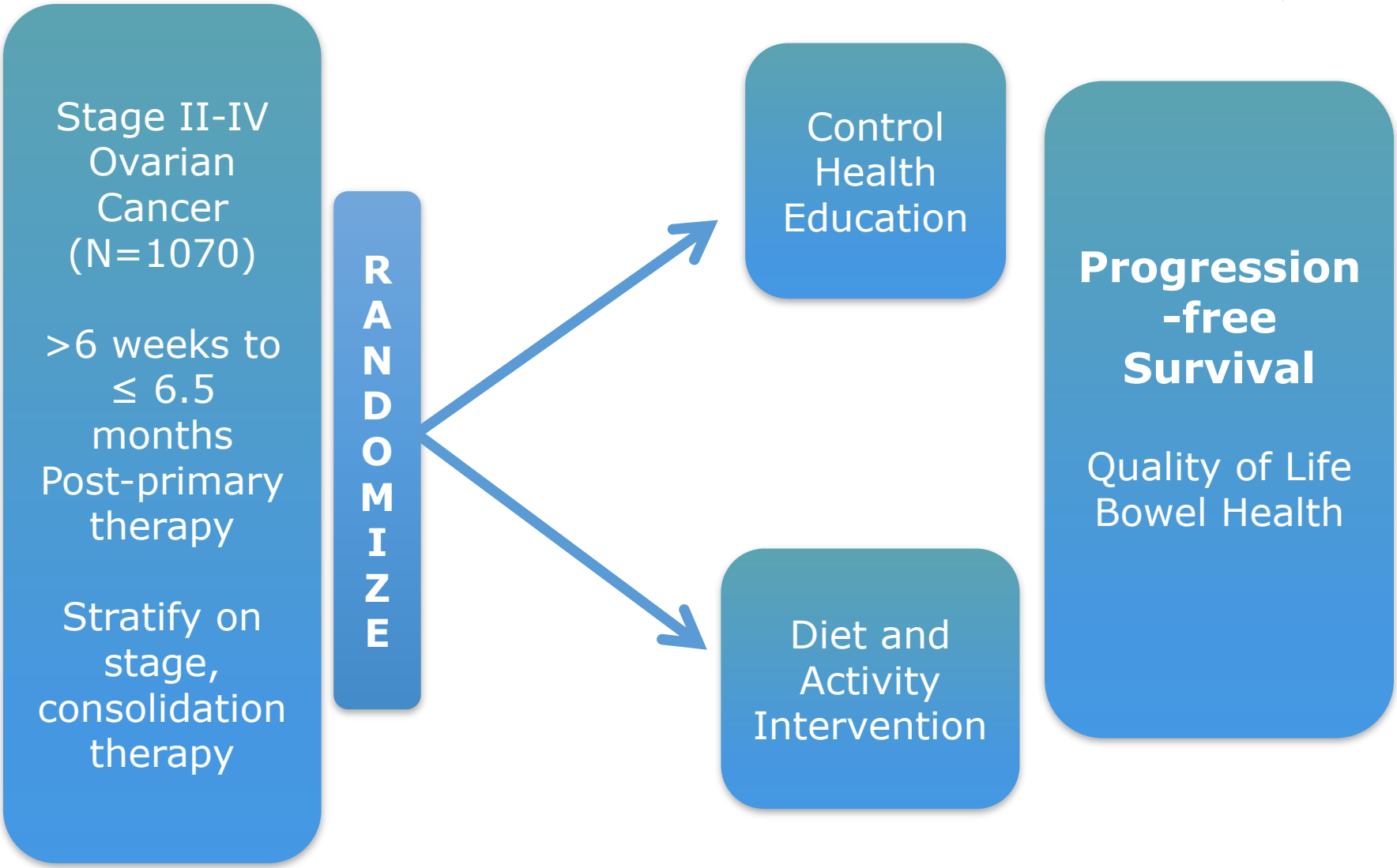
GAP4 Study-Metastatic Prostate Cancer

Figure 2. Study Design



Slide courtesy of Kerry Courneya

Study Schematic for GOG 0225 – LIVES study



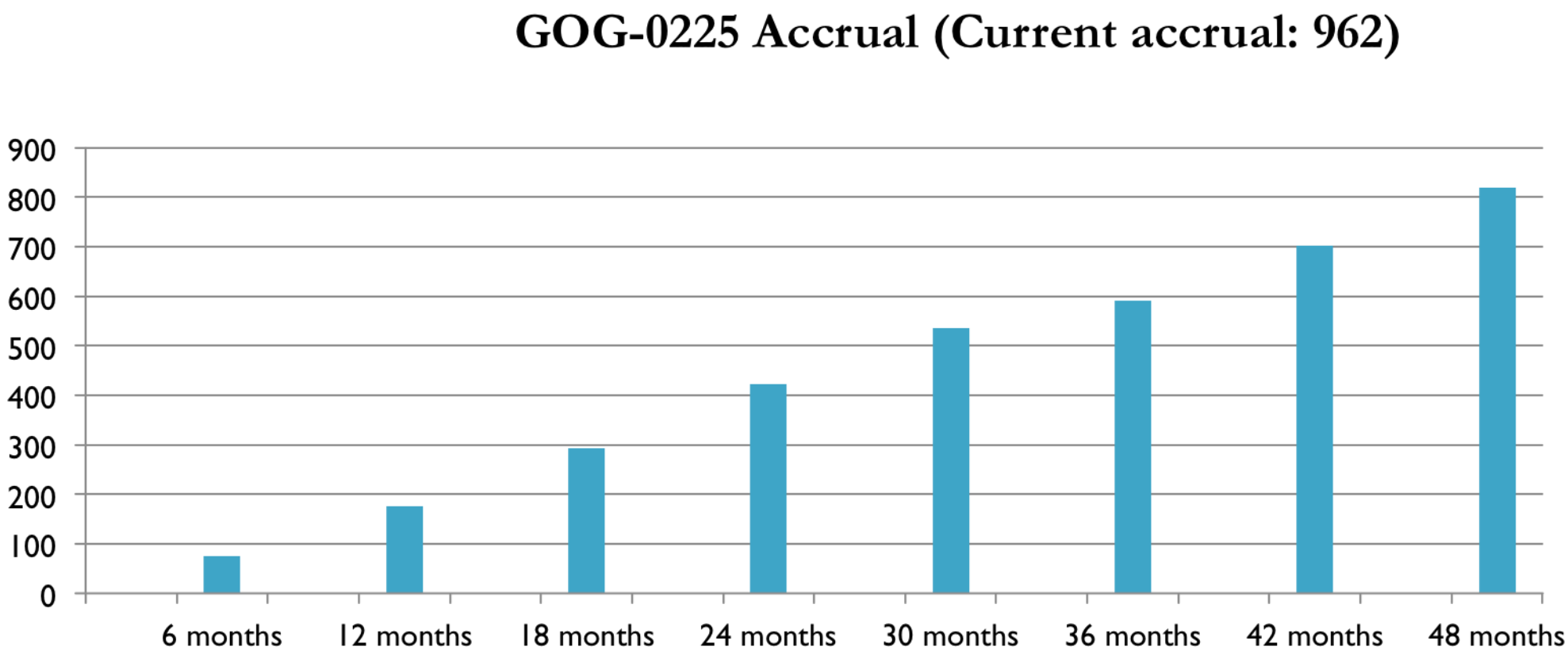
PI: Thomson and Alperts

Lifestyle Intervention for Ovarian Cancer Enhanced Survival

- Centralized telephone coaching
  - English and Spanish
- Multi-modal intervention
  - Telephone, print, SMS, email, blog
- Participant centered intervention
  - Grounded in Social Cognitive Theory utilizing Motivational Interviewing
- Promotion of high vegetable, fiber and fruit diet with low fat and +4000 steps daily
- Control: attention control health education group

LIvES
Lifestyle Intervention for oVarian cancer Enhanced Survival

RECRUITMENT



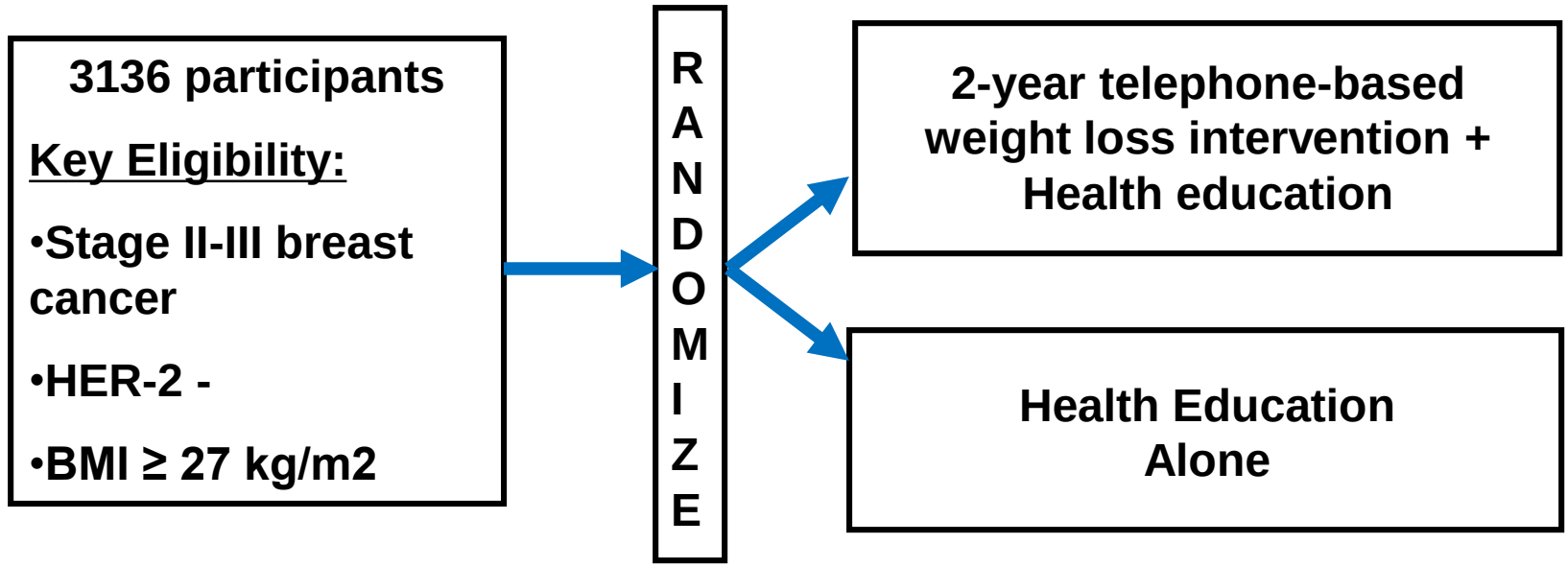
Patient Characteristics, first 529 patients

Characteristic	N (%)
Age	
≤50	100 (18.8%)
51-60	171 (32.2%0
61-70	181 (34.1%)
71+	70 (14.9%)
Race/ethnicity	
Non-Hispanic White	459 (86.8%)
Non-Hispanic Black	22 (4.2%)
Hispanic	30 (5.6%)
Body Mass Index	
<25 kg/m2	197 (37.2%)
25-29.9 kg/m2	177 (33.5%)
≥30kg/m2	149 (28.2%)
Disease Stage	
II	82 (15.4%)
III	376 (70.8%)
IV	72 (13.8%)

The Breast Cancer Weight Loss Trial A011401

PI's: Ligibel and Goodwin

BWEL Study Schema



Objectives

- **Primary:** Assess the impact of the weight loss intervention on iDFS
- **Secondary:**
  - Assess impact of intervention upon:
    - OS, DDFS
    - Comorbidities
    - Weight, diet and exercise
  - Correlative science and PRO

Weight Loss Intervention Overview

- **Centralized, 2 year telephone-based weight loss program**

- **Each patient paired with a weight loss coach, based at DFCI**
  - Patients receive 42 phone calls over 2 years
  - Receive a workbook to accompany calls, tools to help increase exercise and reduce calories (Fitbit, wireless scale, food scale, protein shakes)

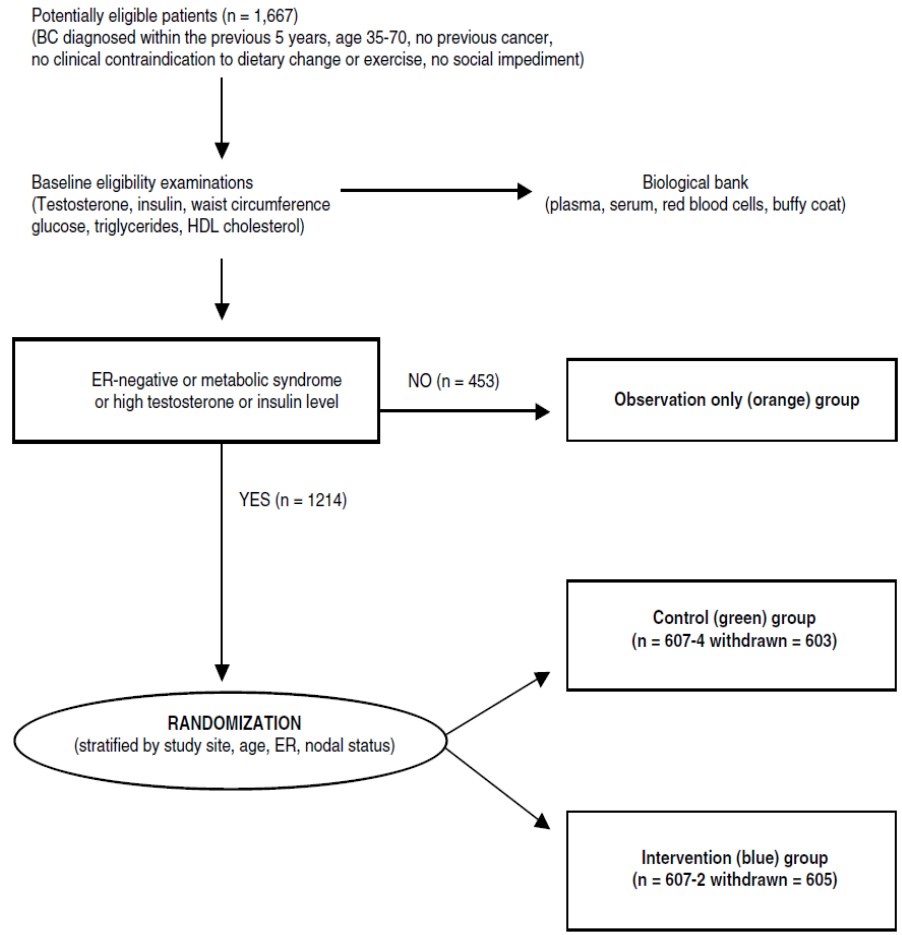
- **Intervention goals:**
  - **10% weight loss**
  - **500-1000 kcal/day deficit**
    - » Portion control -- meal replacements, structured menus
    - » Basic diet stresses fruits, vegetables, whole grains, lower in fat
  - **Increased physical activity**
    - – **1**50-200 minutes moderate-intensity activity in first 6 months
    - – Goal of 45-60 minutes of activity/day in maintenance phase

BWEL Study Update

- Protocol activated August 29, 2016
- Currently open in 897 sites in US
- Two step registration/randomization process for first 514 patients to allow for detailed diet and exercise data
  - 292 patients registered
  - 234 patients randomized
- Next steps
  - Activation in Canadian centers planned for early spring 2017
  - Additional of Spanish version of intervention planned summer 2017

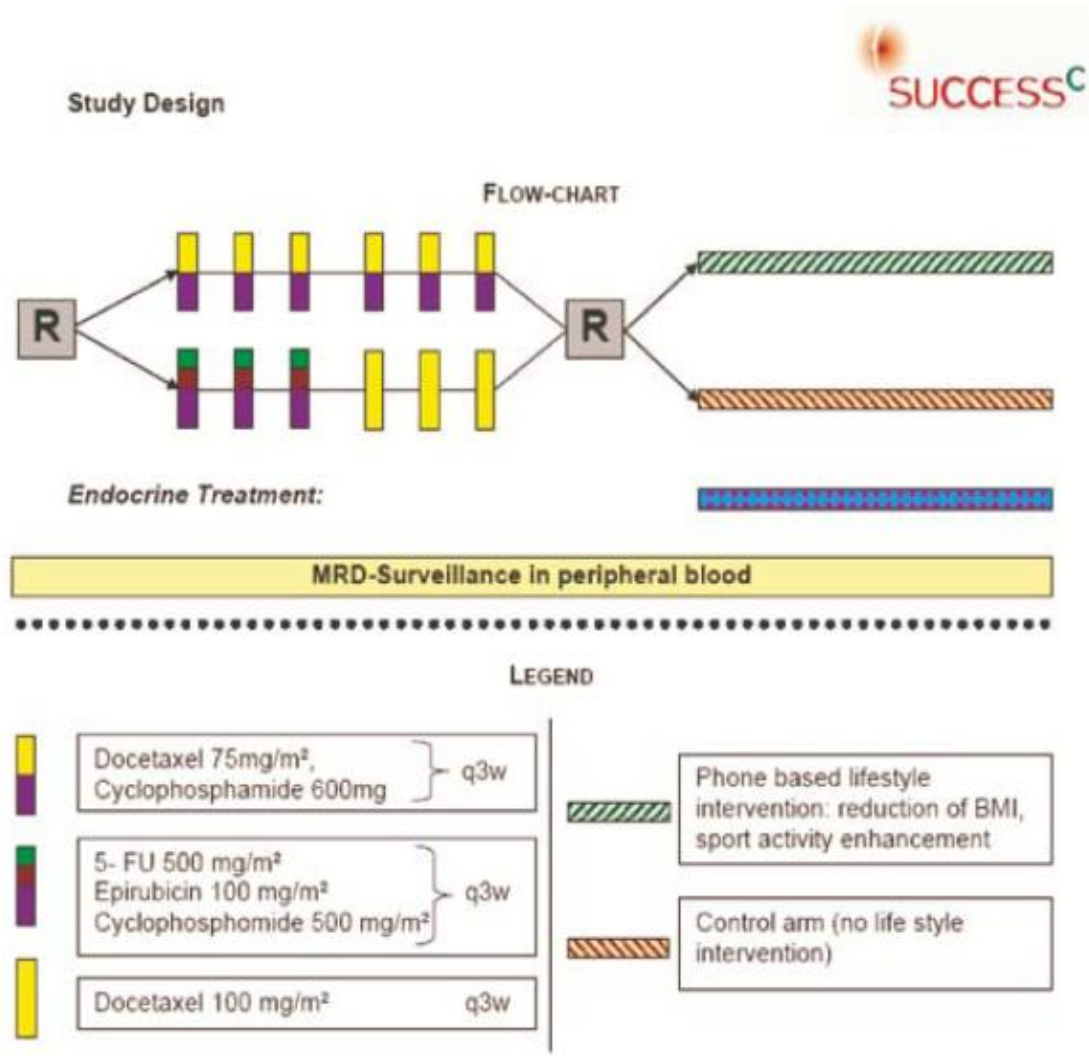
Other ongoing trials testing lifestyle change on breast cancer outcomes

Diana-5: Calorie restricted Mediterranean diet + Increased PA vs control



Villarini et al. Tumori. 2012;98 (1)

SUCCESS-C


Study Design
SUCCESS C
FLOW-CHART
R
R
Endocrine Treatment:
MRD-Surveillance in peripheral blood
LEGEND
Docetaxel 75mg/m², Cyclophosphamide 600mg
q3w
5- FU 500 mg/m²
Epirubicin 100 mg/m²
Cyclophosphomide 500 mg/m²
q3w
Docetaxel 100 mg/m²
q3w
Phone based lifestyle intervention: reduction of BMI, sport activity enhancement
Control arm (no life style intervention)

Summary of RCT's with disease recurrence/ mortality end points

	BWEL	CHALLENGE	DIANA 5	GAP4	LIVES	SUCCESS C
N	3136	962	1241	866	1040	~1400
Disease	Breast	Colon	Breast	Prostate	Ovarian	Breast
Stage	II-III	II-III	I-III	IV	II-IV	II-III
Intervention	2-yr Weight loss	3-yr Ex	4+ yr Med diet + Ex	2-yr Ex	2-yr Diet + Ex	2-yr Weight loss
1º End point	IDFS	DFS	IDFS	OS	PFS	DFS
Correlative	Blood Tissue	Blood	Blood	Blood	Blood	Blood

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Intervention	2-yr Weight loss	3-yr Ex	4+ yr Med diet + Ex	2-yr Ex	2-yr Diet + Ex	2-yr Weight loss
1º End point	IDFS	DFS	IDFS	OS	PFS	DFS
Correlative	Blood Tissue	Blood	Blood	Blood	Blood	Blood

Will these trials fill the evidence gaps?

- Studies will test impact of lifestyle change after cancer diagnosis on recurrence and mortality in common malignancies

- Each trial examines impact of a specific intervention on recurrence/mortality in a single malignancy
    - Some trials are large enough to evaluate the impact of interventions on subsets of patients defined by tumor or host characteristics

- Can these trials help answer other unresolved questions?

- Can we generalize the information learned from these studies to other malignancies?

Correlative science

- Each of the on-going large-scale trials include biospecimen collection
  - Serial collection of fasting blood for biomarker analysis
  - Baseline collection of tumor and benign tissue
  - DNA
- Assessment of predictors of intervention benefit
  - Potentially define population to whom intervention should be prescribed
- Development of potential intermediate biomarkers
  - Provide a way to determine whether an intervention is “working”
  - Streamline future research
  - Enhance interpretation of prior studies

Lifestyle interventions affect metabolic and inflammatory pathways

Nutrition and Exercise Study for Women (NEW Trial)

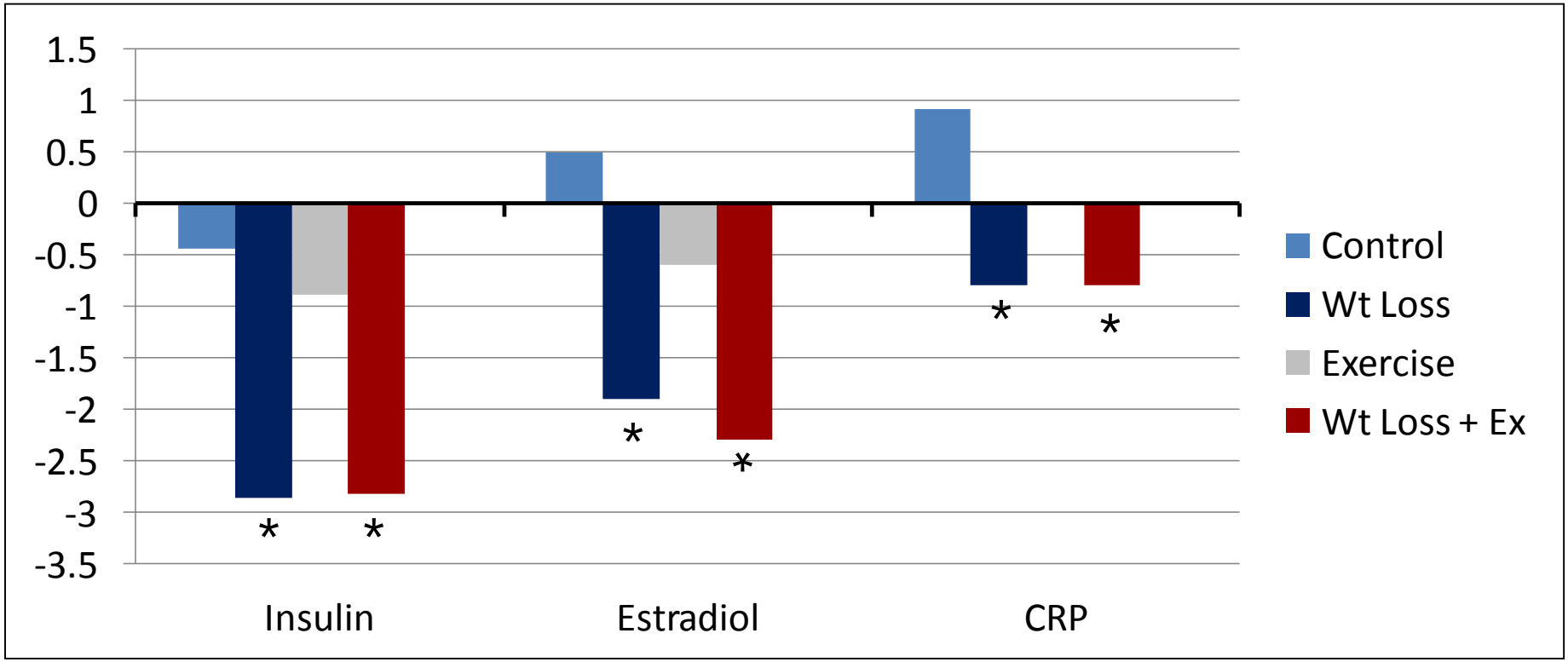
- Designed to evaluate the impact of dietary weight loss and exercise upon biomarkers linked to breast cancer risk

- 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

Weight loss led to significant reductions in metabolic and inflammatory biomarkers



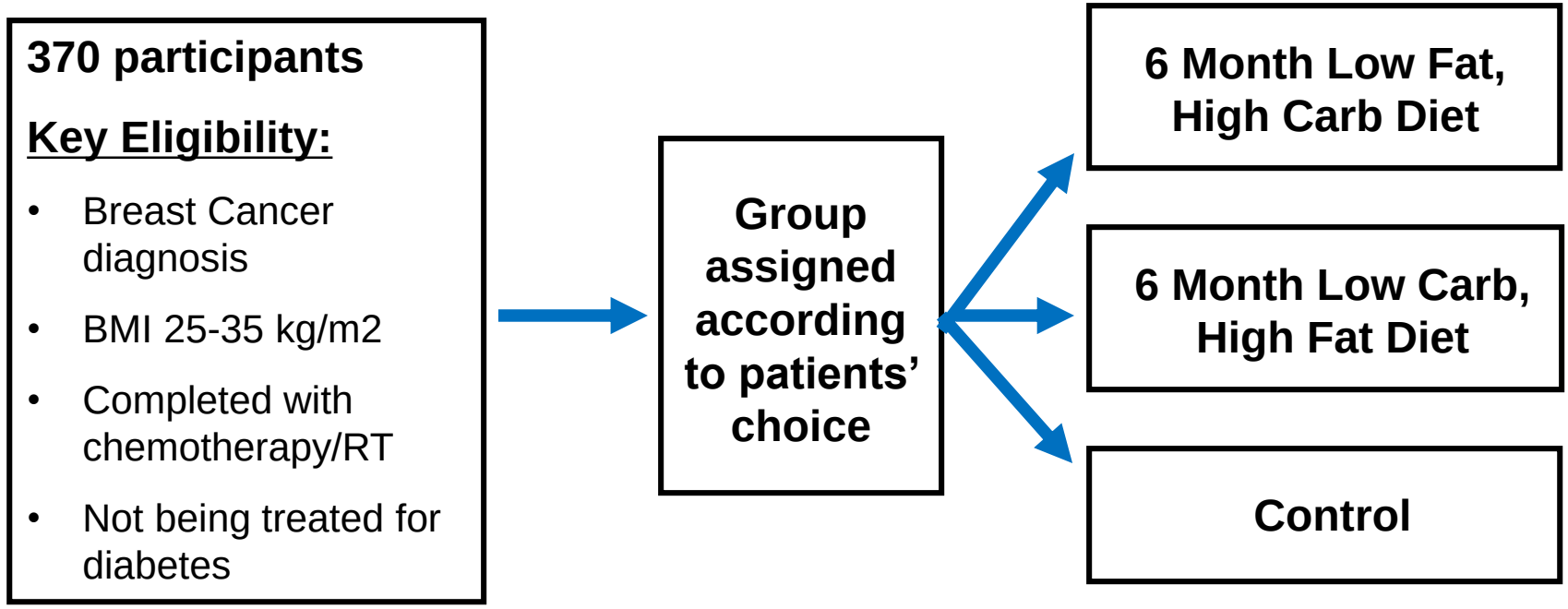
* P<0.001

Weight Change:

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

Mason et al. A J Prevent Med 2011. Imayma et al. Cancer Research 2012.

CHOICE Study: Impact of low fat vs. low carb diet on biomarkers in breast cancer survivors

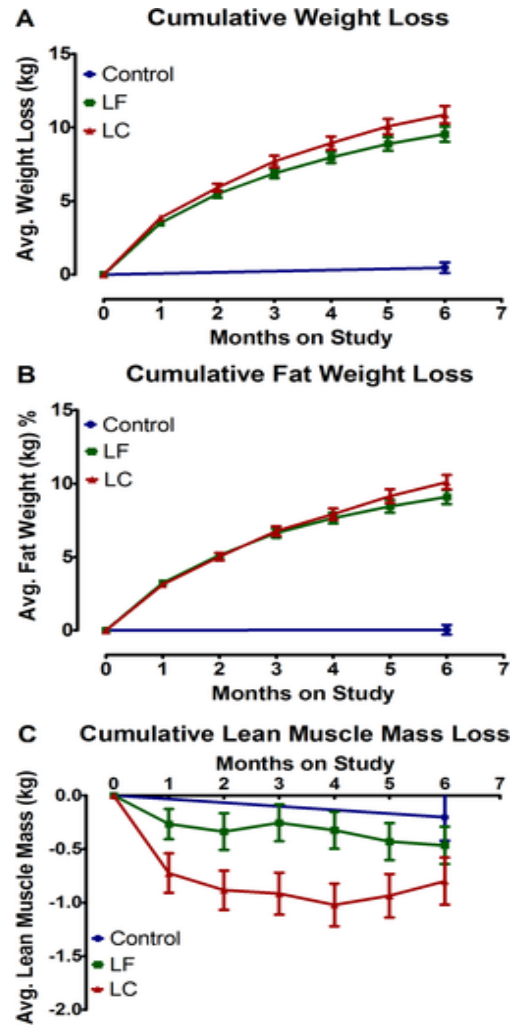


Primary Question: How does fat loss achieved by different dietary approaches impact biomarkers of breast cancer risk?

- Glucose Homeostasis
- Inflammation
- Cellular oxidation
- Sex steroid metabolism

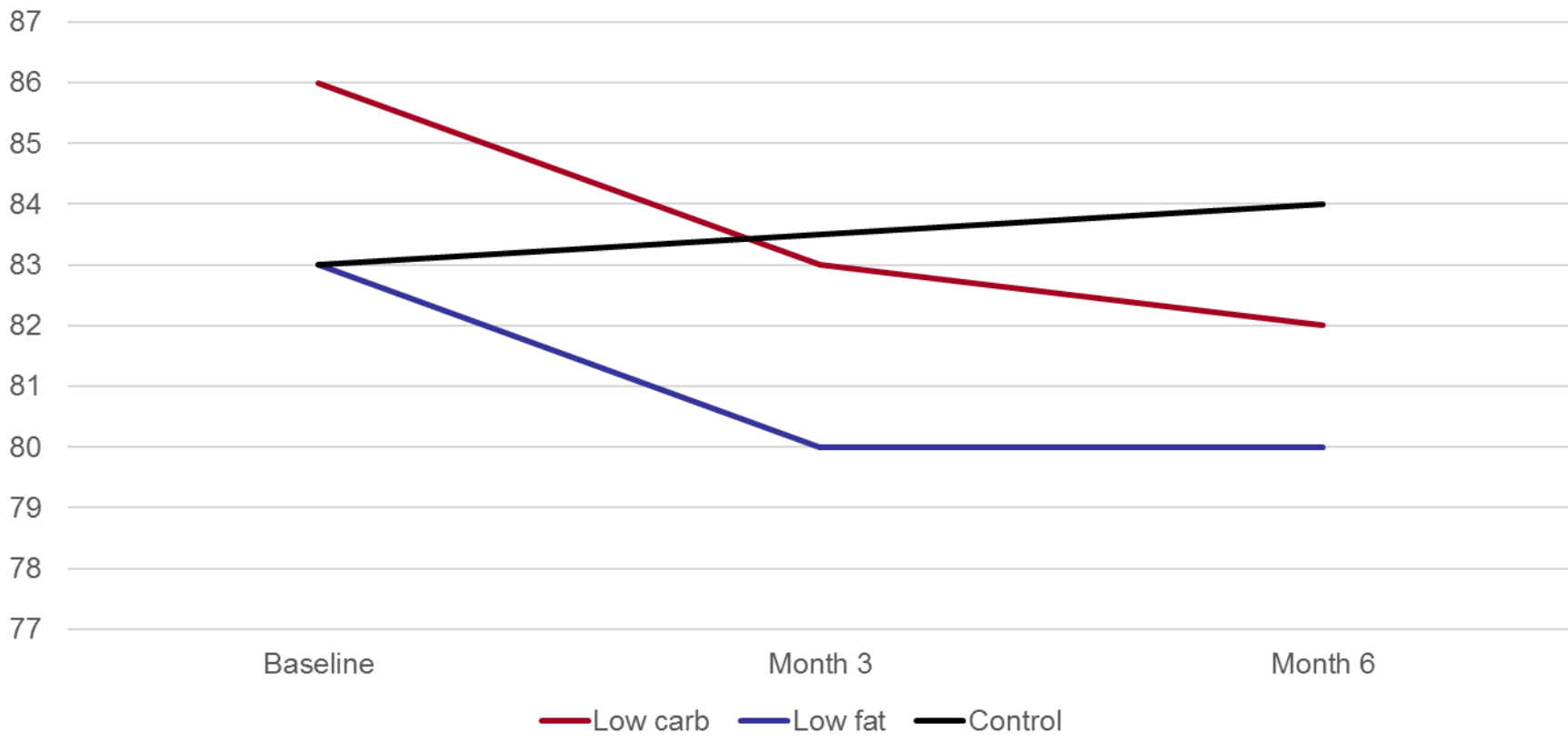
Sedlacek et al. BMC Cancer 2011; 11

Cumulative Loss of Body Weight, Body Fat, and Lean Body Mass According to Study Group



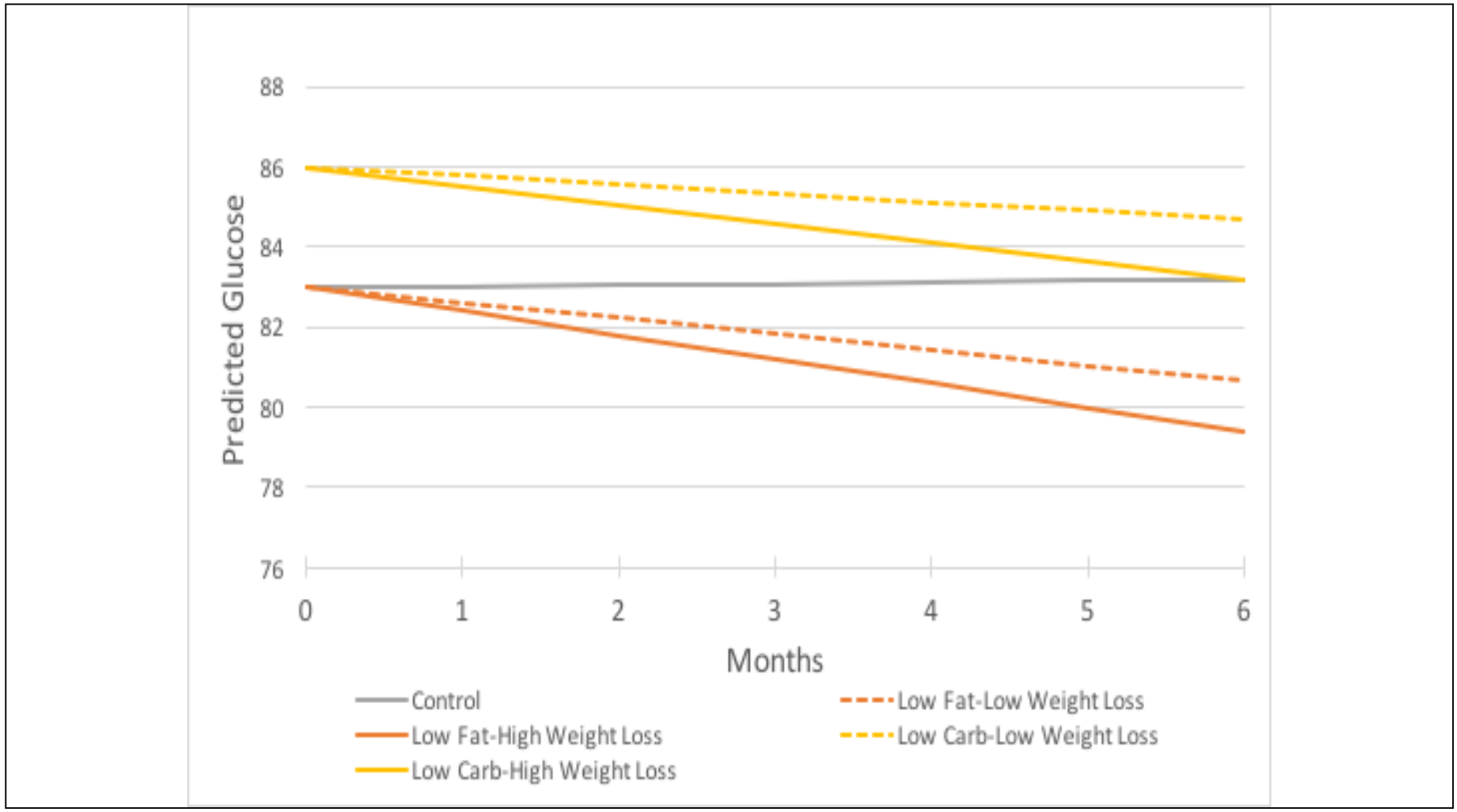
Thompson HJ, et al. (2015) PLOS ONE 10(5): e0127366. doi:10.1371/journal.pone.0127366

Change in fasting glucose by diet group



Thompson et al. Breast Cancer Res. 2012; 14 (1)

Change in glucose by arm and weight change (high vs. low)



Do on-going trials provide a path to wide-spread dissemination in cancer survivors?

	BWEL	CHALLENGE	DIANA 5	GAP 4	LIVES	SUCCESS C
Recruitment sites	Cooperative group	Cooperative group	Individual clinics	Individual clinics	Cooperative group	Cooperative group
Intervention	Weight Loss	Exercise	Dietary change + Exercise	Exercise	Dietary change + exercise	Weight Loss
Intervention delivery	Telephone-based	Supervised, clinic-based	Group, clinic-based	Supervised, clinic-based	Telephone-based	Telephone-based

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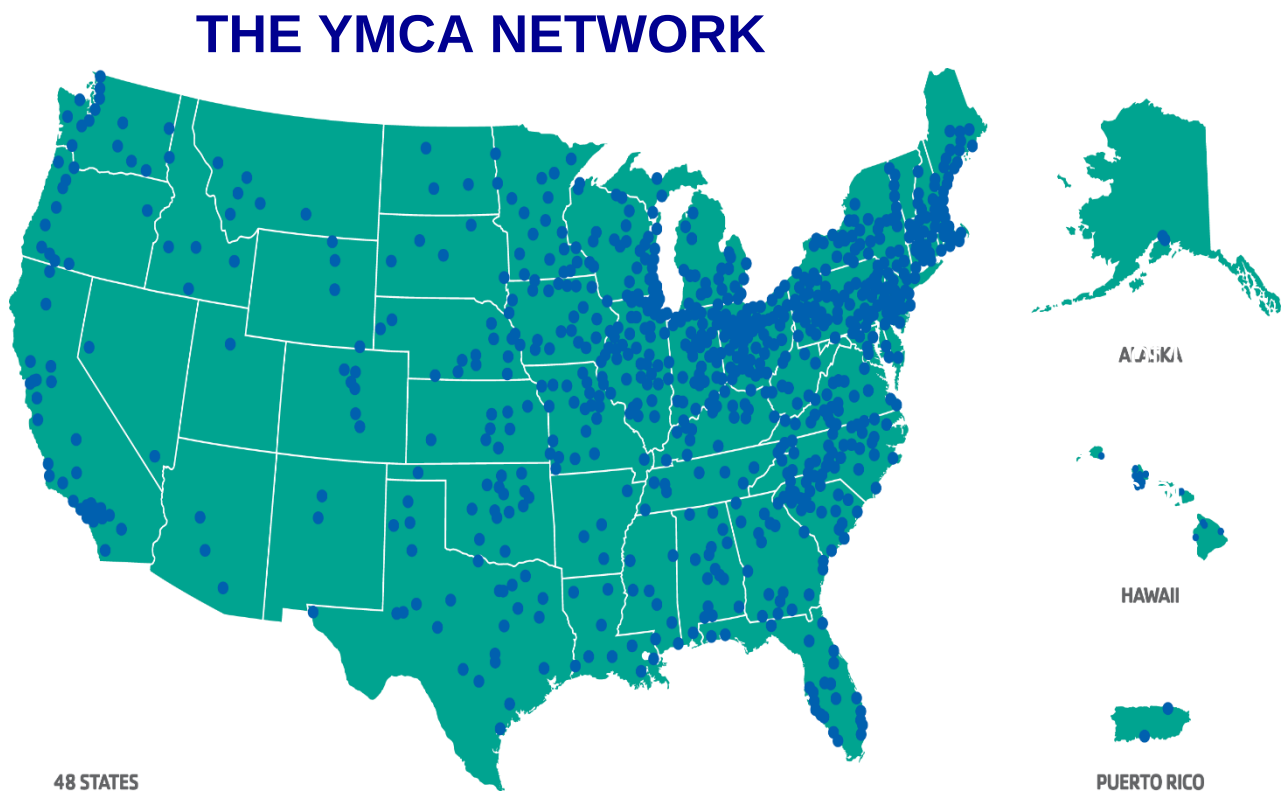
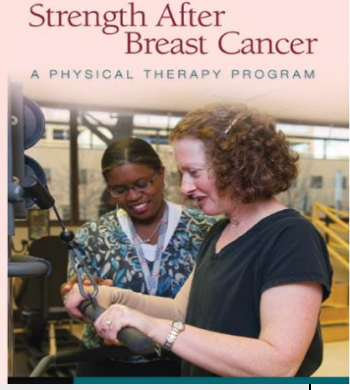
Potential avenues for implementation of exercise interventions in cancer survivors

80% OF U.S. HOUSEHOLDS WITHIN 5 MILES OF A YMCA



SERVING MORE THAN **22 MILLION MEMBERS**
EACH YEAR IN MORE THAN **10,000 COMMUNITIES.**



After Referral to Outpatient Rehabilitation

Visit 1
PT Evaluation And Clearance

Visit 2
Lymphedema Education Session

Visit 3
Teach Warm-up, cool down, teach 2-3 exercises

Visit 4
Have pt repeat Visit 3 activities, answer questions, teach 2-3 exercises

Visit 5
Have pt repeat visit 4 activities, answer questions, teach 2-3 exercises

Visit 6
Discharge Day
Pt. demonstrates complete protocol.

Discharge may only occur when the pt demonstrates understanding of:

1. Good form with exercises
2. Progression
3. Deconditioning
4. Overall arm work
5. Monitoring symptoms
6. When to call for a follow-up appt

Additional visits will be scheduled for pts not ready for discharge at visit 6.

Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6

Week 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Home Exercise

2x weekly
Practice warm-up, cool down, and 2-3 exercises until visit 4

Home Exercise

2x weekly
Practice warm-up, cool down, and 5-6 exercises until visit 5

Home Exercise

2x weekly
Practice warm-up, cool down, and 8-10 exercises until visit 6

Home Exercise

2x weekly
Full protocol, on an ongoing basis, monitoring for symptom changes

Home Exercise Continues 2x weekly
Patient calls PT for evaluation upon noticing any change in symptoms that lasts a week or longer

Resistance delivered to home or purchased by patient.

New technologies may allow for development of distance-based exercise interventions

- Wearable activity monitors allow for transmission of objective activity and biometric data to trainers/investigators

- Mobile platforms allow for delivery of content in real-time and also allow for individualized coaching from afar

- More work is needed

- On-going work will explore balance of technology and traditional coaching methods

Can we generalize information from on-going trials to other diseases/populations?

- Observational data connects obesity and inactivity to increased risk of cancer recurrence and related mortality in many diseases
- On-going trials focus on a small sub-set of these cancers
- Trials also need to focus on a single intervention in a narrow subset of patients to keep sample size feasible
- As oncology treatments become more “personalized”, focusing on development of individual treatment plans for subsets of patients within a particular disease, path to broader generalization of trial results remains unclear

Which evidence gaps will be addressed by current trials?

- Evidence from on-going trials will provide information about the impact of weight loss and increased physical activity on cancer recurrence and mortality

- Trials address specific interventions in individual diseases

- Correlative work may provide tools to extend the knowledge gained from these studies
    - Predictive markers: define populations most likely to benefit
    - Intermediate biomarkers: facilitate work to compare different interventions and doses

- Still significant unanswered questions
    - Best ways to disseminate interventions to diverse groups of cancer survivors, especially exercise interventions
    - Unclear how much generalization can occur across diseases

BWE Study team

- **PI: Jennifer Ligibel**
- **Co-Chairs**
  - **Correlative Science Co-Chair: Pam Goodwin (Co-PI)**
  - **Health Behaviors Co-Chair: Dawn Hershman (SWOG)**
  - **Community Oncology Co-Chair: Judy Hopkins**
  - **Health Disparities Co-Chair: Electra Paskett**
  - **Breast Committee Chairs: Eric Winer & Cliff Hudis**
- **Statistics: Bill Barry, Linda McCourt, Amylou Dueck**
- **Advocates: Patty Spears and Liz Frank**
- **Funding: CTEP, DCP, DCCPS, ACS, Komen**

- **Intervention Oversight Committee:**
  - **Chair: Tom Wadden**
  - **Behavioral Science: Catherine Alfano**
  - **Exercise Physiology: Melinda Irwin**
  - **Nutrition: Marian Neuhouser**
  - **Call Center: Linda Delahanty**
  - **Remote Intervention Delivery: Cyndi Thomson**
- **Steering Committee Members**
  - **Vered Stearn (ECOG)**
  - **Julia White (NRG)**
  - **Rachel Ballard (NIH)**
  - **Worta McCaskill-Stevens (NCI)**
  - **Linda Nebeling (NCI)**
  - **Vanessa Bernstein**