BWEL and Beyond:

Examining Diet and Exercise Interventions to Reduce Breast Cancer Recurrence

Jennifer Ligibel, MD

Dana-Farber Cancer Institute

Presented By Jennifer Ligibel at 2019 ASCO Annual Meeting

Objectives

- Review the observational data linking obesity to breast cancer recurrence and mortality
- Discuss existing evidence suggesting that lifestyle change could reduce the risk of breast cancer recurrence and mortality
- Discuss on-going and recently completed trials testing weight loss interventions as a part of breast cancer treatment

Obesity linked to recurrence and mortality in breast cancer survivors

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

Is there any evidence that lifestyle change could reduce the risk of breast cancer recurrence?

The impact of lowering dietary fat after diagnosis on breast cancer recurrence has been tested in 2 RCT's

Women's Interventional Nutrition Study

- Randomized 2437 women to low-fat diet intervention or control group
- Eligibility:
  - Stage I-III breast cancer
  - At least 20% calories from fat
- Dietary goals: reduce fat to 15% of total calories

Women's Healthy Eating and Living Study

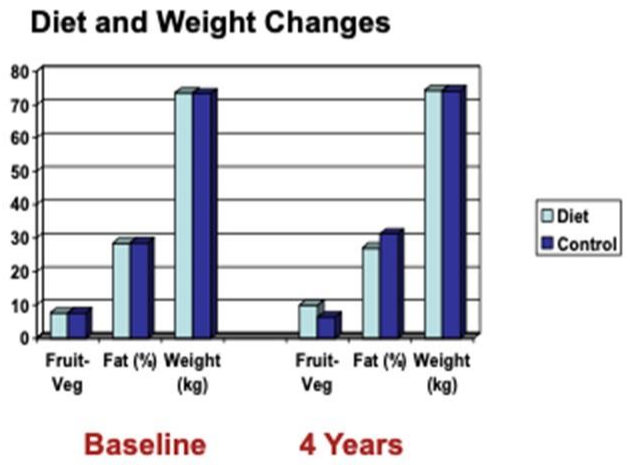
- Randomized 3088 women to diet intervention or control group
- Eligibility
  - Stage I-III breast cancer
  - No dietary criteria
- Dietary goals:
  - Increase fruits and vegetables
  - Lower fat
  - Increase fiber

Chlebowski et al, JNCI 2006: 98: 1767-76; Pierce et al., JAMA 2007; 298: 289-98.

Intervention Adherence

Women's Interventional Nutrition Study ***Women's Healthy Eating and Living Study***

- 10% absolute reduction in fat intake
- 2.3 kg weight loss in diet group

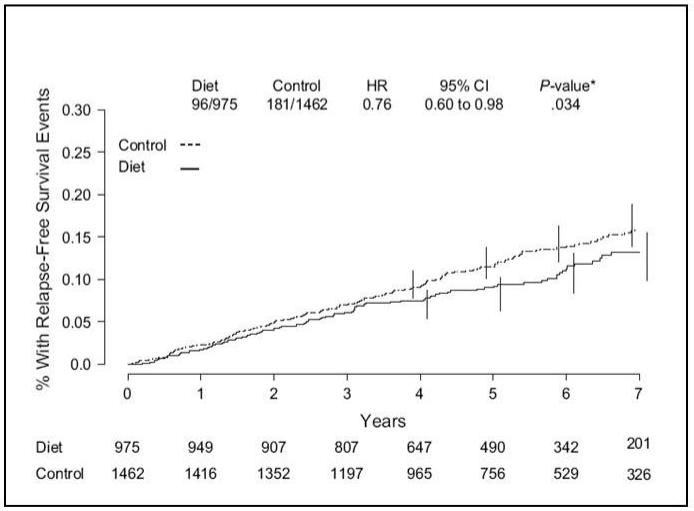


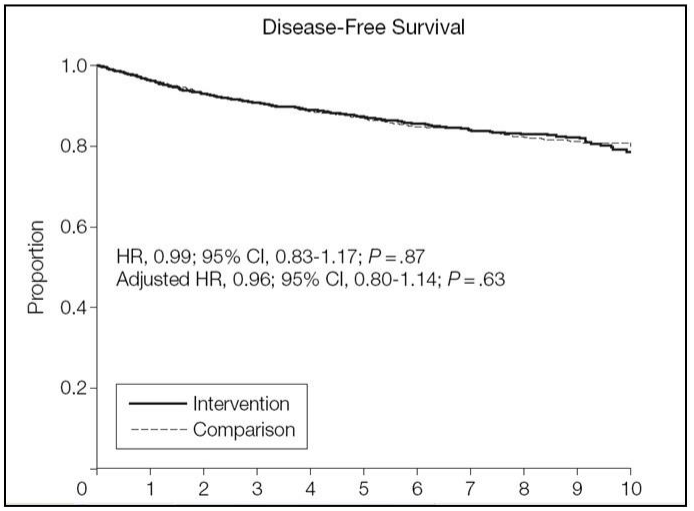
Chlebowski et al, JNCI 2006: 98: 1767-76; Pierce et al., JAMA 2007; 298: 289-98..

Study Results

Women's Interventional Nutrition Study ***Women's Healthy Eating and Living Study***

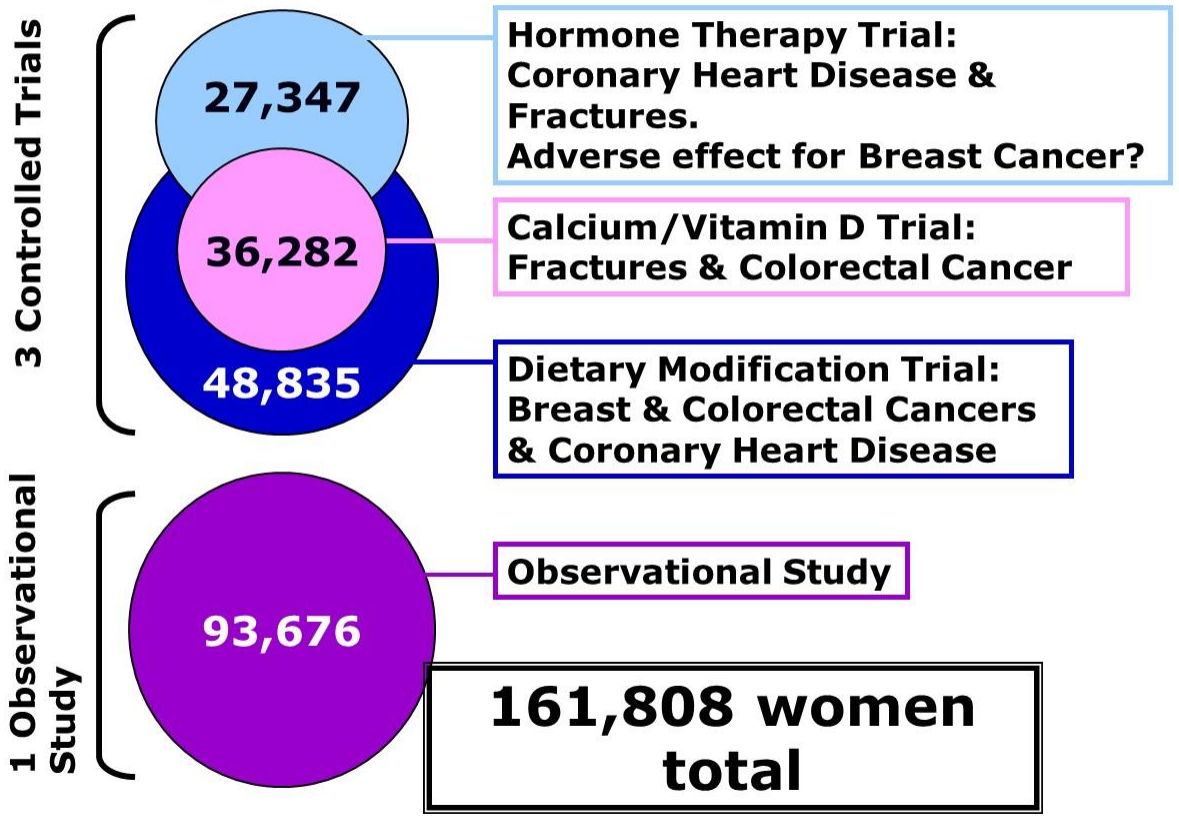
- 24% reduction in recurrence in diet group
- Majority of benefits seen in ER- pts





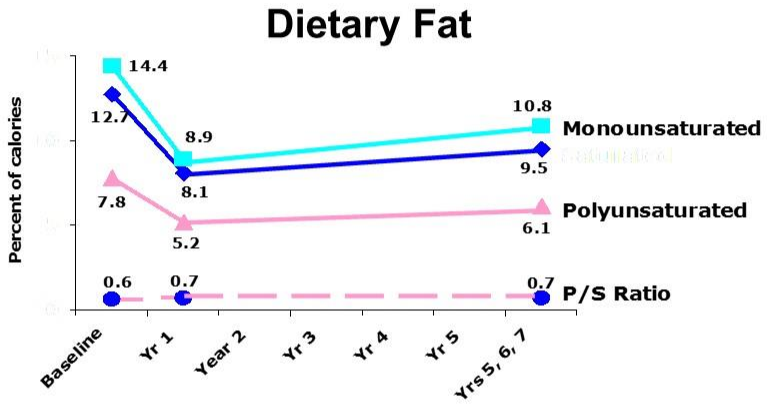
Chlebowski et al, JNCI 2006: 98: 1767-76; Pierce et al., JAMA 2007; 298: 289-98..

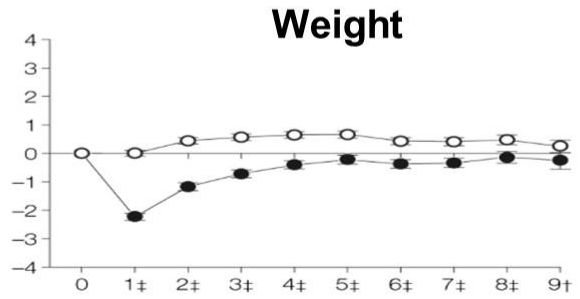
The Women's Health Initiative (WHI)



Women's Health Initiative Low-Fat Dietary Intervention Study

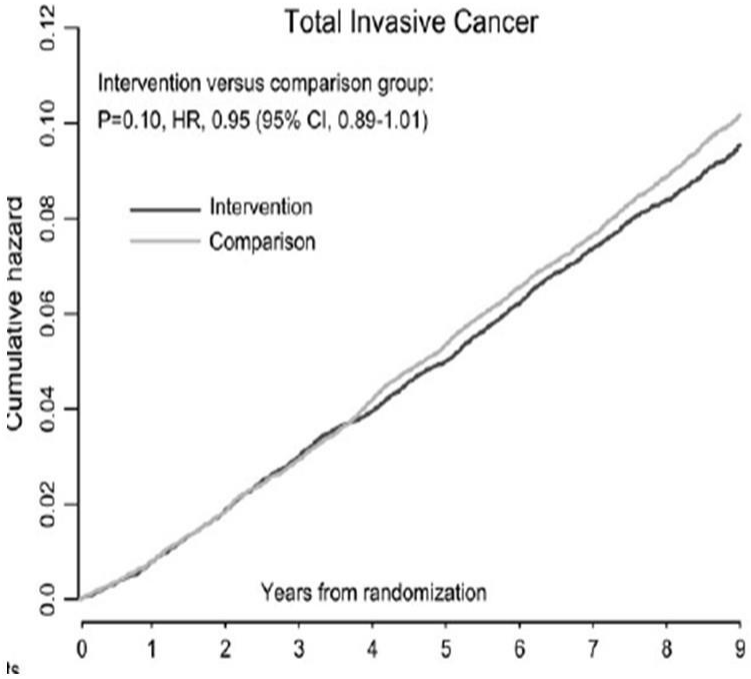
- Randomized 48,835 postmenopausal women to low-fat diet intervention or control
- Intervention goals:
  - Decrease dietary fat to 20% of calories
  - Increase fruits, vegetable and grains
- Endpoints:
  - Breast and colorectal cancer
  - Ovarian, endometrial and total cancer
- Eligibility: ≥ 32% of calories from fat





Prentice et al, JNCI 2007.

Results of WHI Low-Fat Diet Intervention Study

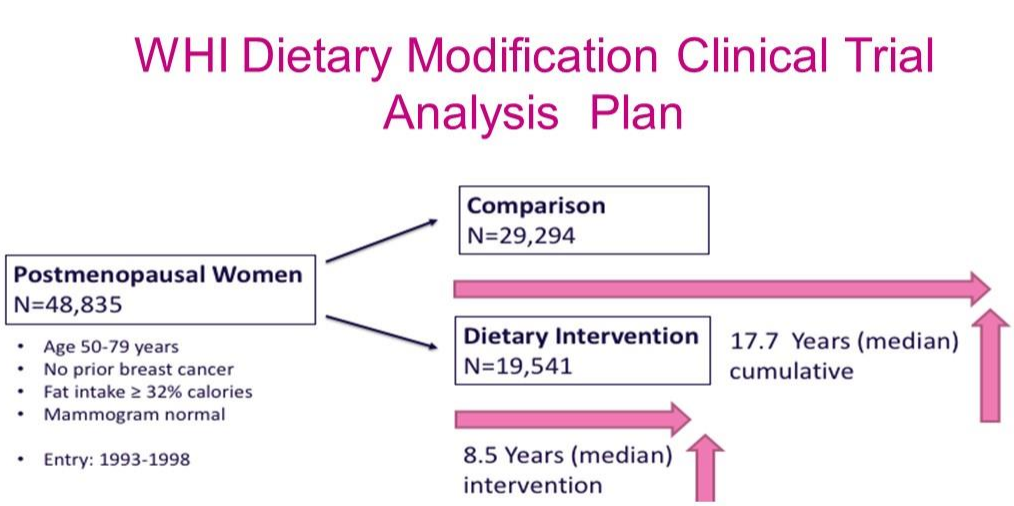


Cancer site	Incidence per 1000 person-years (No. of cases) Intervention	Comparison	P†	HR (95% CI)‡
Ovary	0.36 (57)	0.43 (103)	.03	0.83 (0.60 to 1.14)
Endometrium	0.79 (125)	0.71 (170)	.18	1.11 (0.88 to 1.40)
Breast	4.15 (655)	4.52 (1072)	.09	0.91 (0.83 to 1.01)
Colorectal	1.27 (201)	1.18 (279)	.29	1.08 (0.90 to 1.29)
All other sites	4.56 (720)	4.81 (1140)	.30	0.95 (0.86 to 1.04)
Total cancer	10.69 (1687)	11.22 (2661)	.10	0.95 (0.89 to 1.01)

No difference in rates of total cancer….

Presented By Jennifer Ligibel at 2019 ASCO Annual Meeting

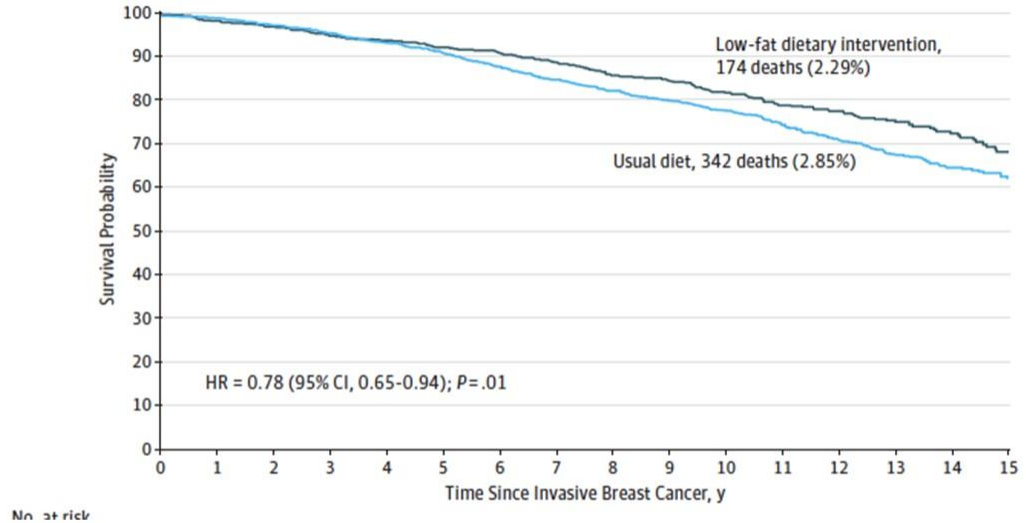
Mortality in women who developed breast cancer during WHI dietary intervention period



- 1764 breast cancers occurred during intervention period
  - Lower proportion of patients with ER+/PR- cancers
- 3437 total cancer-related deaths during the 17.7 year follow up period
  - 327 deaths from breast cancer

Chlebowski et al. JAMA *Oncol.* Published online May 24, 2018

Association between dietary intervention and mortality in women who developed breast cancer



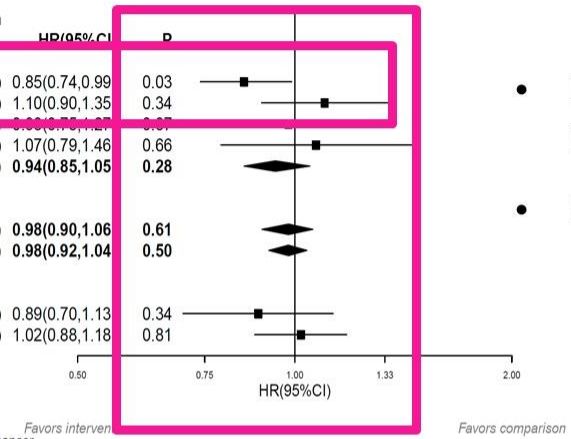
- Diet arm vs control:
  - Significant reduction in CVD death: HR 0.62 (95% CI 0.39-0.99)
  - Non-sig reduction in breast cancer death: HR 0.86 (95% CI 0.64-1.17)
  - Association between diet arm and lower mortality only seen with high waist circumference

Chlebowski et al. JAMA *Oncol.* Published online May 24, 2018

Presented By Jennifer Ligibel at 2019 ASCO Annual Meeting

Association between dietary intervention and mortality

	Intervention N(%)	Comparison N(%)	HR(95%CI)	P
Primary analysis				
Death after breast cancer	280(0.098)	507(0.12)	0.85(0.74,0.99	0.03
Death after colorectal cancer	164(0.057)	228(0.052)	1.10(0.90,1.35	0.34
Death after endometrial cancer	69(0.042)	98(0.039)	1.07(0.79,1.46	0.66
Death after protocol identified cancers*	**583(0.20)**	**944(0.22)**	**0.94(0.85,1.05**	**0.28**
Secondary analysis				
Death after other cancers^	**997(0.35)**	**1565(0.36)**	**0.98(0.90,1.06**	**0.61**
Death after total cancers	**1506(0.52)**	**2361(0.54)**	**0.98(0.92,1.04**	**0.50**
Exploratory analysis				
Death after pancreatic cancers	102(0.036)	179(0.041)	0.89(0.70,1.13	0.34
Death after lung cancers	290(0.10)	440(0.10)	1.02(0.88,1.18	0.81

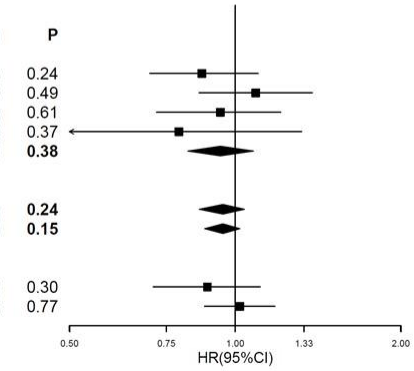


* Protocol identified cancers include: breast, colorectal, ovarian, and endometrial cancer.
^ Includes those cancers, listed above, that were not identified in the protocol.

- Lower all-cause mortality in women with breast cancer in low fat diet arm
- No association in other cancer

- No significant association between intervention arm and cancer mortality (to date)

	Intervention N(%)	Comparison N(%)	HR(95%CI)	P
Primary analysis				
Death from breast cancer	120(0.036)	207(0.042)	0.87(0.70,1.10)	0.24
Death from colorectal cancer	116(0.035)	160(0.032)	1.09(0.86,1.38)	0.49
Death from ovarian cancer	93(0.028)	148(0.030)	0.94(0.72,1.21)	0.61
Death from endometrial cancer	23(0.012)	43(0.015)	0.79(0.48,1.32)	0.37
Death from protocol identified cancers*	**352(0.11)**	**559(0.11)**	**0.94(0.82,1.08)**	**0.38**
Secondary analysis				
Death from other cancers^	**738(0.22)**	**1175(0.24)**	**0.95(0.86,1.04)**	**0.24**
Death from total cancers	**1090(0.33)**	**1734(0.35)**	**0.95(0.88,1.02)**	**0.15**
Exploratory analysis				
Death from pancreatic cancers	117(0.035)	201(0.041)	0.89(0.71,1.11)	0.30
Death from lung cancers	311(0.094)	457(0.092)	1.02(0.88,1.18)	0.77



* Protocol identified cancers include: breast, colorectal, ovarian, and endometrial cancer.
^ Includes those cancers, listed above, that were not identified in the protocol.

What do these studies tell us about lifestyle change and breast cancer recurrence?

- WINS provides the only available evidence that a lifestyle intervention after diagnosis could affect recurrence

- WHI showed lower risk of mortality in women who developed breast cancer during/after participation in a low-fat diet intervention
    - Low rate of breast cancer mortality
    - ? Public health message as there was not a reduction in overall breast cancer mortality in the population (to date)

- Preliminary evidence that weight loss could impact breast cancer recurrence
    - WINS participants lost weight, presumably through caloric restriction, and had lower risk of recurrence; WHEL participants did not lose weight or improve outcomes

A number of RCT's are testing impact of weight loss on breast cancer recurrence

	LISA	SUCCESS C	DIANA 5	BWEL
N	2200*	2292	1241	3136
Location	Canada (+ few US sites)	Germany	Italy	US + Canada
Eligibility •Stage •BMI (kg/m^2) •Other	I-III 24-40	II-III 24-40	I-III None ↑ testosterone/insulin Metabolic syndrome or ER - cancer	II-III ≥ 27 kg/m^2
Intervention	2-yr Weight Loss	2-yr Weight Loss	4+ yr Med Diet + Exercise	2-yr Weight Loss
1° End point	IDFS	DFS	IDFS	IDFS

* Accrual terminated after 338 women due to funding issues

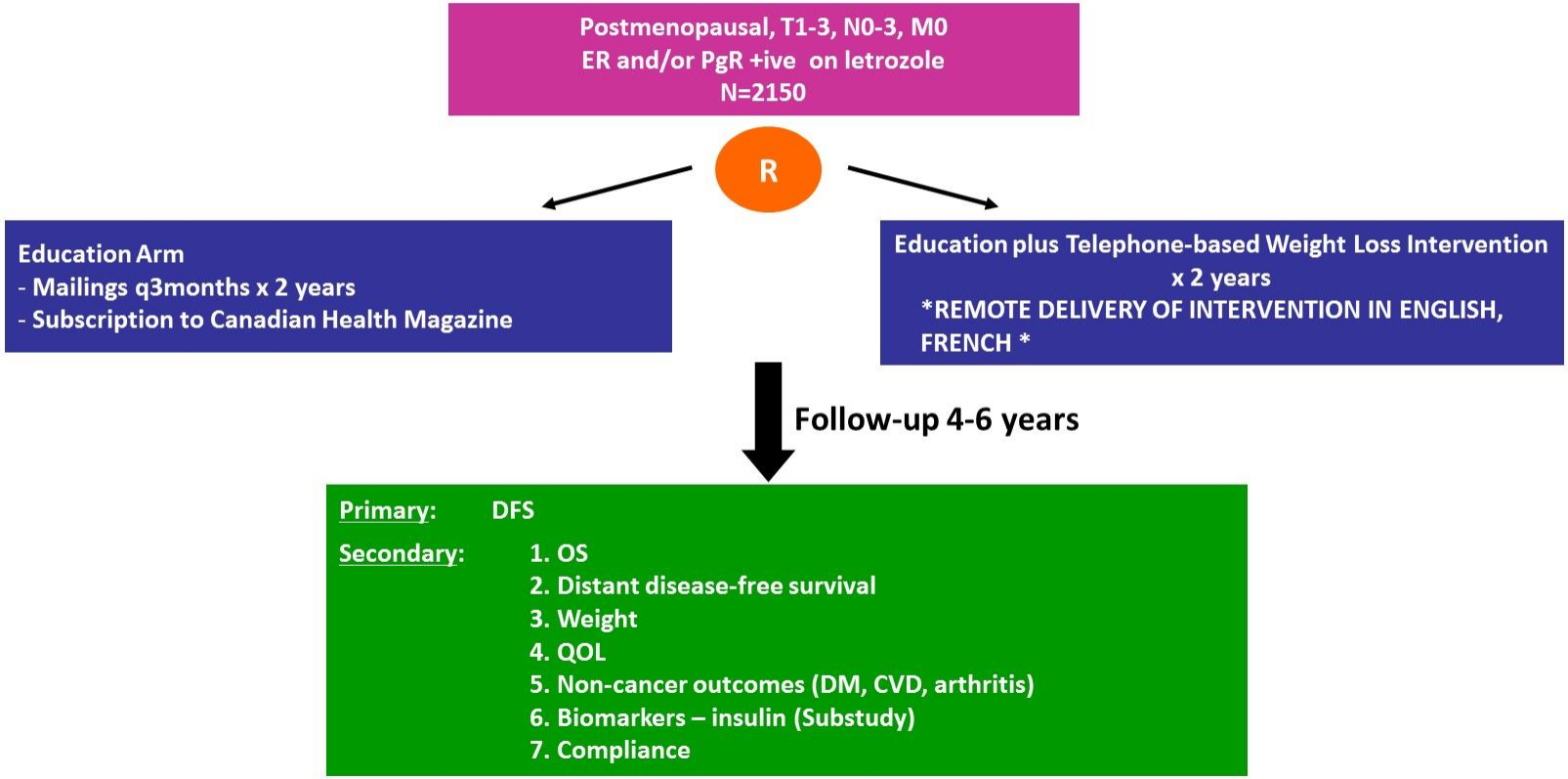
Presented By Jennifer Ligibel at 2019 ASCO Annual Meeting

A number of RCT's are testing impact of weight loss on breast cancer recurrence

	LISA	SUCCESS C	DIANA 5	BWEL
N	2200*	2292	1241	3136
Location	Canada (+ few US sites)	Germany	Italy	US + Canada
Eligibility •Stage •BMI (kg/m^2) •Other	 I-III 24-40	 II-III 24-40	 I-III None ↑ testosterone/insulin Metabolic syndrome or ER - cancer	 II-III ≥ 27 kg/m^2
Intervention	2-yr Weight Loss	2-yr Weight Loss	4+ yr Med Diet + Exercise	2-yr Weight Loss
1° End point	IDFS	DFS	IDFS	IDFS

* Accrual terminated after 338 women due to funding issues

LISA study tested impact of weight loss on disease outcomes in postmenopausal women on AI



* Coordinated by Ontario Clinical Oncology Group *

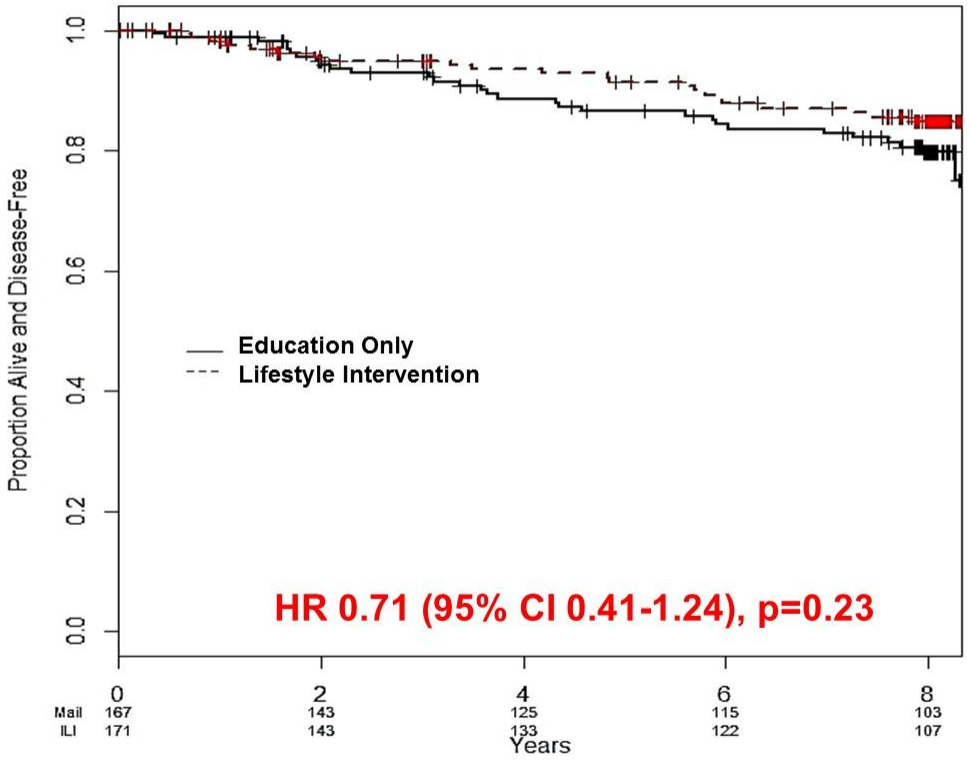
Presented By Jennifer Ligibel at 2019 ASCO Annual Meeting

LISA Weight Loss

Weight (kg)		Weight Loss Intervention		Educational Intervention		T-test
		n	Mean	n	Mean	P value
Baseline		171	82.7	167	81.7	
6-mos.	% Change from Baseline	161	-5.2	155	-0.7	<.001
12-mos.	% Change from Baseline	142	-5.4	147	-0.7	<.001
18-mos.	% Change from Baseline	135	-4.6	144	-1.0	<.001
24-mos	% Change from Baseline	133	-3.7	131	-0.4	<.001

Goodwin et al. JCO 2014.

SABCS 2018: LISA Trial Final DFS Analysis



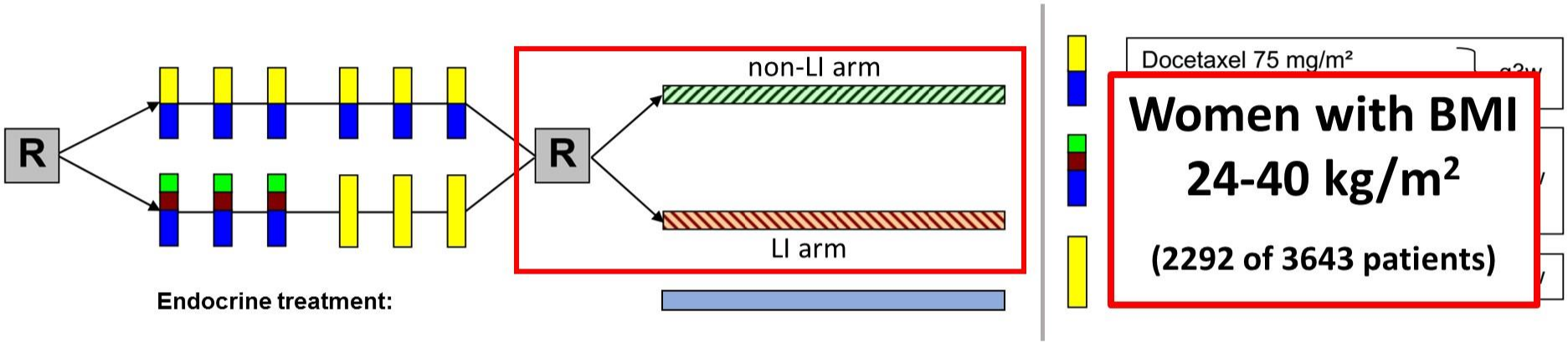
Intervention produced significant weight loss (-3.7% vs. -0.4% at 2 years)

Weight loss not maintained at 8 years (-0.3% vs -2.8% at 8 years)

Disease-free survival comparisons not statistically significant; favored the lifestyle intervention

Goodwin et. Al, SABCS 2018 with permission

SUCCESS C



First randomization:
3 cycles FEC100 followed by 3 cycles docetaxel vs. 6 cycles docetaxel/ cyclophosphamide

Second randomization:

- **LI arm: Intensified lifestyle intervention program to reduce body weight comprising individual weight loss, diet and physical activity goals in the framework of a 2-year standardized and structured telephone and mail-based intervention**
- **non-LI arm: General recommendations for healthy lifestyle**

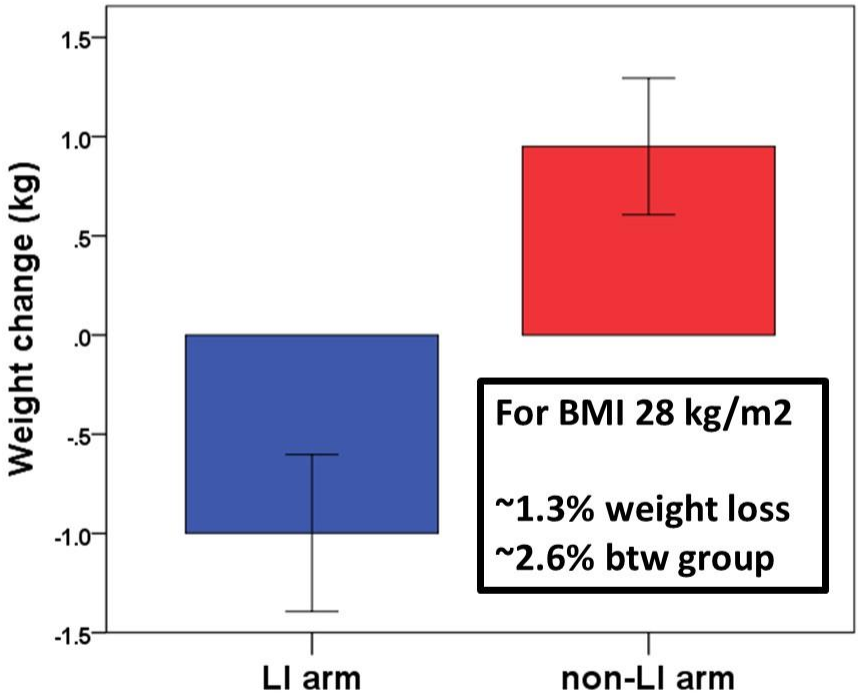
Rack et al. Breast Care, 2010

Weight change by lifestyle intervention arm

Baseline BMI ~28kg/m^2

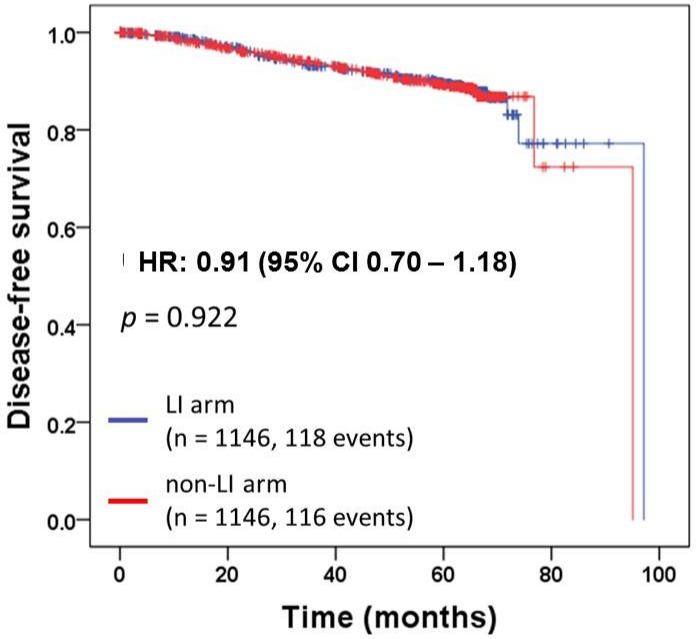
Weight loss by study arm:

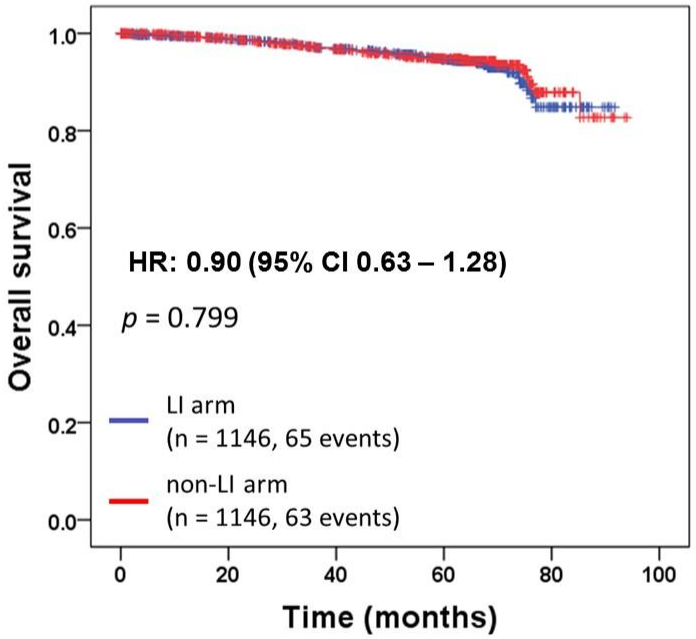
- LI arm (n = 828): weight **loss 1.0 kg** (95% CI -0.60 to -1.39)
- non-LI arm (n = 816): weight **gain 0.95 kg** (95% CI 0.61 to 1.30)



Janne et al. San Antonio Breast Cancer Symposium 2018 (with permission)

Preliminary results: Disease-free survival (DFS) and overall survival (OS) by lifestyle intervention arm (ITT)





Attrition:

- **51.8% of intervention arm**
- **19.3% of control arm**

Janne et al. San Antonio Breast Cancer Symposium 2018

Patient characteristics completer/non-completer LI arm (n = 1146)

There were slight, but significant differences between completers and non-completer for age (p = 0.013), Grading (p = 0.043) and hormone receptor status (p = 0.004)

Patient and tumor characteristics*		completer (n = 552)		non-completer (n = 594)	
Age (years) §		56.0	30 – 78	58.0	28 – 77
Body mass index (kg/m^2)		28.0	24.0 – 39.8	28.3	23.7 – 40.2
Tumor size (n, %)	*pT1*	245	44.4	222	37.4
	pT2	272	49.3	322	54.2
	pT3/pT4	35	6.3	50	8.4
Nodal stage (n, %)	*pN0*	207	37.5	248	41.8
	pN+	345	62.5	346	58.3
Histological grading § (n, %)	*G1*	48			
	G2	284			
	G3	220			
Histological type (n, %)	*ductal*	441			
	lobular	73	13.2	78	13.1
	other	38			
Hormone receptor status § (n, %)	*negative*	106			
	positive	446			
Menopausal status (n, %)	*premenopausal*	191			
	postmenopausal	361	65.4	416	70.0
Adjuvant chemotherapy (n, %)	*FEC-Doc*	281	50.9	296	49.8
	DocC	271	49.1	298	50.2

Grade 3: 39.9 % completer
46.3 % non-completer

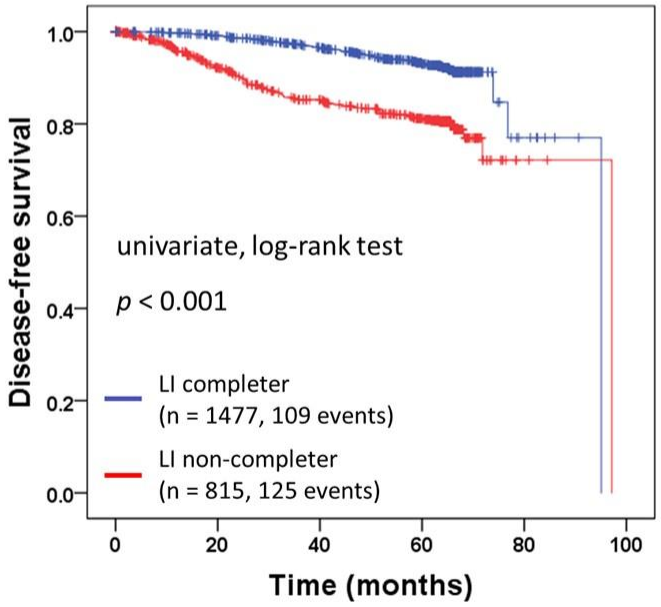
ER/PR-: 19.4 % completer
26.2 % non-completer

* missing data in some categories

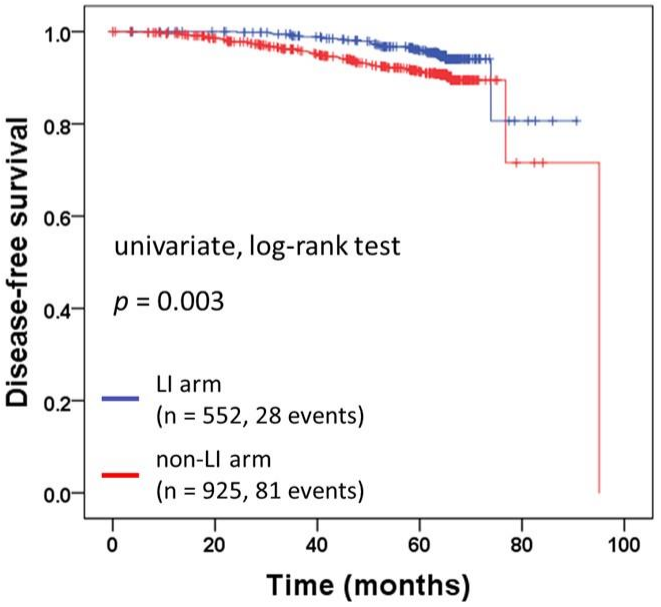
§ significant differences (p<0.01)

Exploratory subset analyses in patients who completed the 2-year intervention period

DFS LI Completers vs non-completers



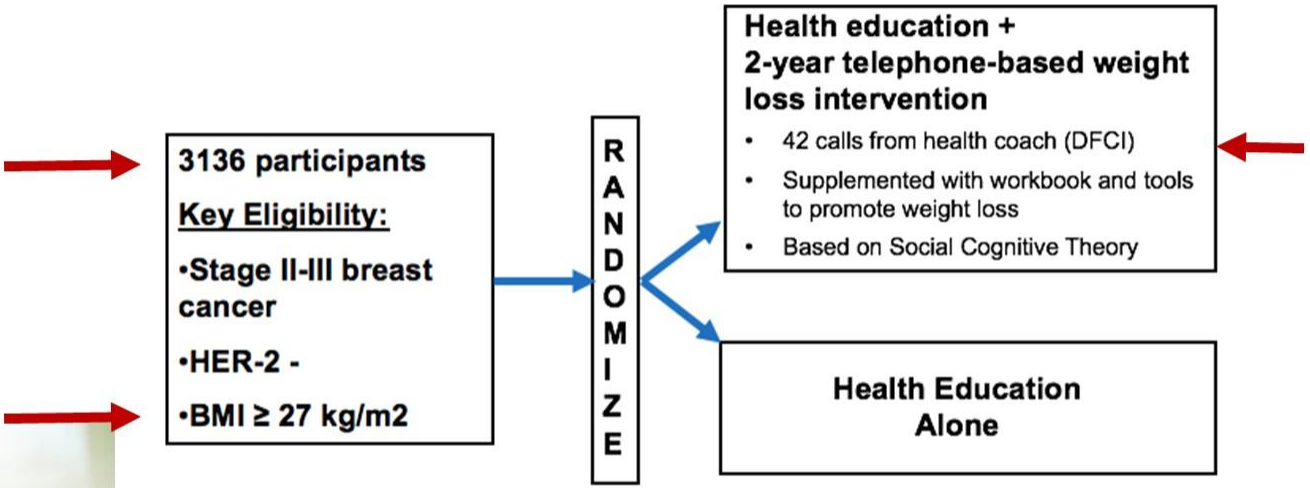
DFS LI vs control in completers



HR 0.51 (95% CI 0.33-0.78)

The Breast Cancer Weight Loss Trial

NCT02750826



- **Primary Outcome: Invasive Disease Free Survival**
- **Statistical considerations:**
  - 85% power to detect HR 0.80
  - 4.1% absolute reduction in recurrence

Study Status

- **Trial activated August 29, 2016**
- **Current participating sites:**
  - >1127 US sites
  - 20 Canadian sites

- **Enrollment: 2092 patients randomized**
  - 49 states
  - 1st Canadian participant enrolled November, 2017
  - Study opened to Spanish-speaking participants March, 2018

BWEL Study Timeline

- **BWEL passed weight loss interim analysis March 2019**
- **Accrual anticipated to be completed in summer 2020**
- **Last patient will complete the intervention period summer 2022**
- **Primary results anticipated early 2024**

Diet and exercise interventions to prevent breast cancer recurrence

- Observational evidence demonstrates consistent associations between obesity and breast cancer mortality
- Somewhat conflicting evidence regarding role of a low fat diet in improving breast cancer outcomes
- Limited evidence that weight loss could reduce risk of breast cancer mortality; but on-going trials will provide more information in coming years

Acknowledgements

- All the patients who have volunteered for our studies!

- Dana-Farber
  - Eric Winer
  - Winnie Ng
  - Rinath Jeselsohn
  - Kathiana Amazan
  - Tari King
  - Anita Giobbie-Hurder
  - Bill Barry
  - Liz Frank
  - Deborah Dillion
  - Eric Winer
  - Ann Partridge
  - Justin Brown
  - Jeff Meyerhardt
  - Stuart Schnitt
  - Tula Mahl
  - Jay Oppenheim
  - Reem Jabr
  - Judy DiPaolo
  - Wendy Kemp
  - Valerie Abrigo
  - Sheila Purdie
  - Janine Gilard
  - Barb Fargnoli
  - Christina Conte
  - Lynne Smith
  - Nancy Campbell

- Collaborators
  - Melinda Irwin (Yale)
  - Pam Goodwin (Univ of Toronto)
  - Anne McTiernan (FHCRC)
  - Tom Wadden (Penn)
  - Linda Delahanty (MGH)
  - Catherine Alfano (ACS)
  - Cyndi Thomson (UA)
  - Marian Neuhouser (FHCRC)
  - Patty Spears (UNC)
  - Dawn Hershman (Columbia)

- Funding:
  - Susan G Komen Foundation/SWHR
  - AICR
  - NIH, NCI and NCI TREC
  - CALGB and Alliance
  - ASCO
  - Breast Cancer Research Foundation