Memorial Sloan Kettering Cancer Center

Obesity and Risk of Breast Cancer

Ayca Gucalp, MD
Assistant Attending
Memorial Sloan Kettering Cancer Center
Instructor of Medicine
Weill Cornell Medical College
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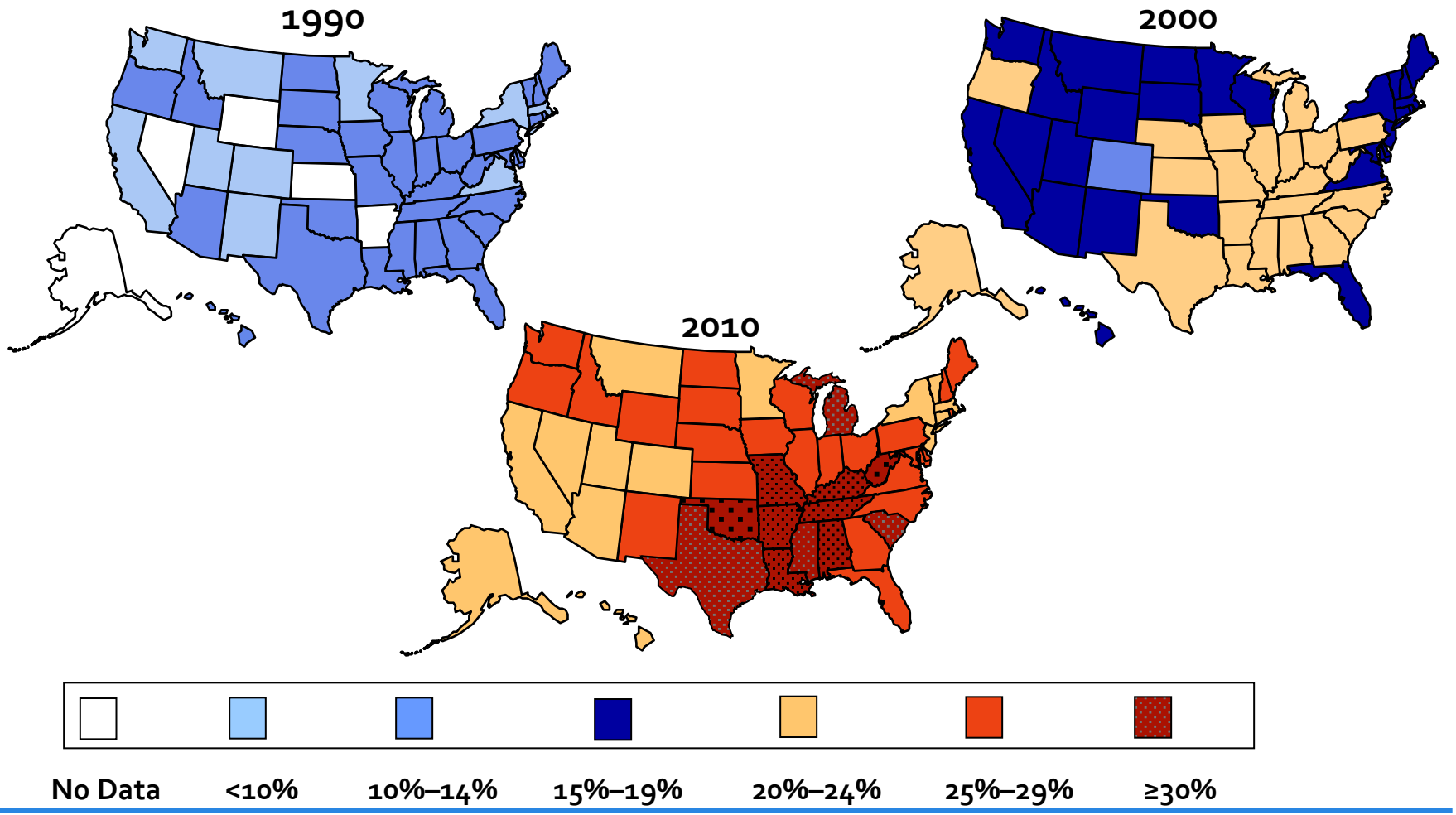
Case

- 64 year old postmenopausal female
- Diagnosed with stage I ER/PR+, HER2- IDC
- Treated with lumpectomy/SLNBx, RT and an aromatase inhibitor
- At 8-month follow up the patient reports hot flashes, vaginal dryness, and weight gain
- Pre-diagnosis: height 163 cm, weight 80 kg , BMI 30
- Current: height 163 cm, weight 83.9 kg , BMI 32

Obesity* Trends Among US Adults

BMI = [weight in kilograms/(height in meters)^2]
(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



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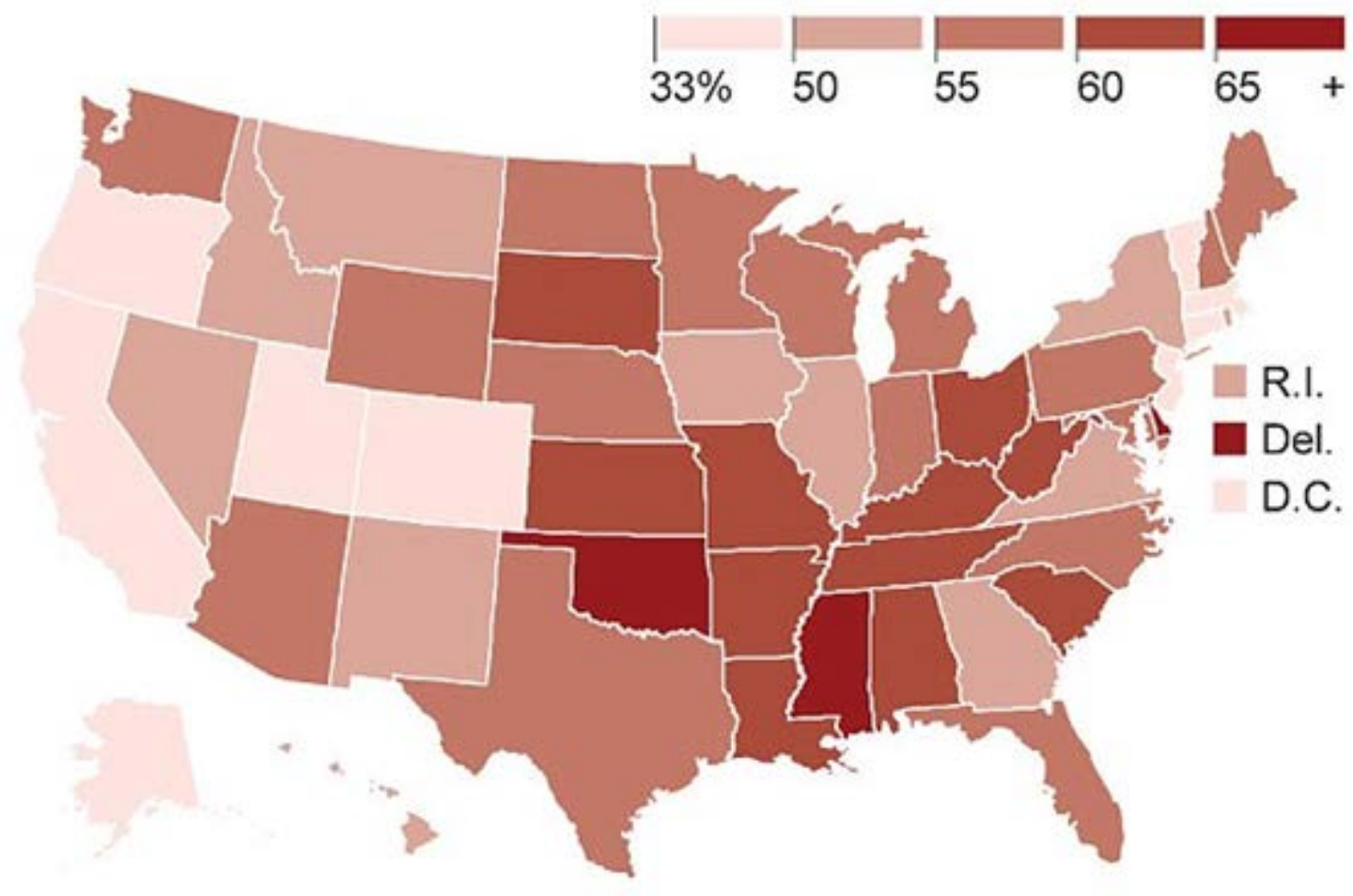
Behavioral Risk Factor Surveillance System; CDC; http://www.cdc.gov/obesity/data/adult.html accessed August 2014.

Projected Obesity As Percentage of State Population by 2030



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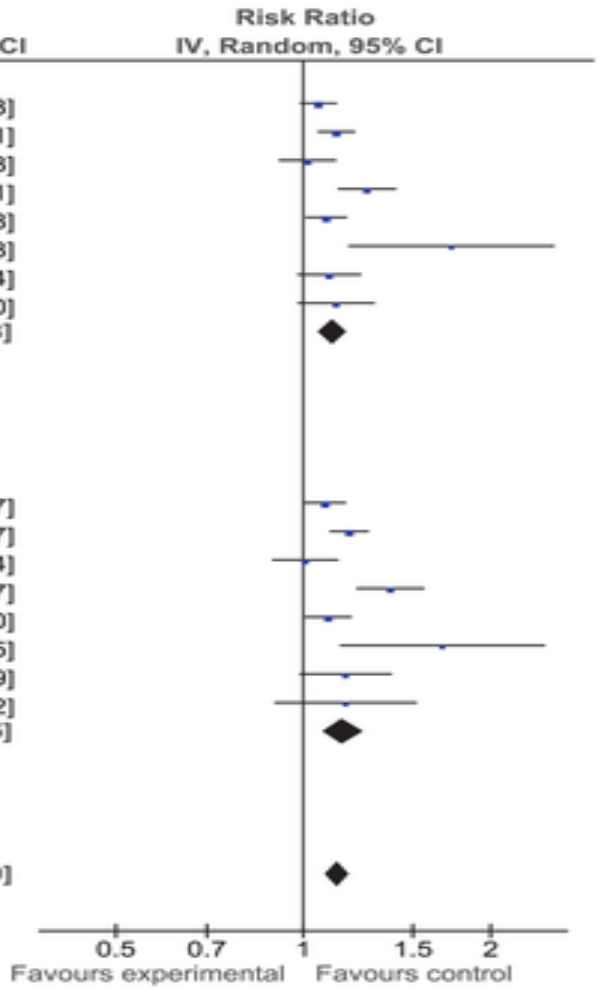
F as in Fat: How Obesity Threatens America's Future 2013; Trust for America's Health, Robert Wood Johnson Foundation ; September 2013.

Increased BMI is Associated with Postmenopausal Breast Cancer

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 Overweight						
Barlow 2006	1408	237278	1864	332255	9.3%	1.06 [0.99, 1.13]
Kerlikowske 2008	1505	93717	1697	119504	9.3%	1.13 [1.06, 1.21]
Lee 2006	542	17154	843	27107	7.0%	1.02 [0.91, 1.13]
Sellers 2002	702	12916	567	13205	7.0%	1.27 [1.14, 1.41]
Setiawan 2009	1053	26172	1488	40272	8.7%	1.09 [1.01, 1.18]
Sonnenschein 1999	47	966	55	1955	1.2%	1.73 [1.18, 2.53]
Suzuki 2006	436	16805	692	29359	6.4%	1.10 [0.98, 1.24]
Tehard 2006	244	9039	735	30744	5.3%	1.13 [0.98, 1.30]
Subtotal (95% CI)		414047		594401	54.2%	1.12 [1.06, 1.18]
Total events	5937		7941			
Heterogeneity: Tau² = 0.00; Chi² = 15.98, df = 7 (P = 0.03); I² = 56%						
Test for overall effect: Z = 3.94 (P < 0.0001)						
1.2.2 Obese						
Barlow 2006	977	160573	1864	332255	8.8%	1.08 [1.00, 1.17]
Kerlikowske 2008	1244	73894	1697	119504	9.0%	1.19 [1.10, 1.27]
Lee 2006	348	11110	843	27107	6.2%	1.01 [0.89, 1.14]
Sellers 2002	381	6428	567	13205	6.0%	1.38 [1.22, 1.57]
Setiawan 2009	729	17983	1488	40272	8.2%	1.10 [1.01, 1.20]
Sonnenschein 1999	48	1020	55	1955	1.2%	1.67 [1.14, 2.45]
Suzuki 2006	156	5659	692	29359	4.2%	1.17 [0.99, 1.39]
Tehard 2006	58	2074	735	30744	2.3%	1.17 [0.90, 1.52]
Subtotal (95% CI)		278741		594401	45.8%	1.16 [1.08, 1.25]
Total events	3941		7941			
Heterogeneity: Tau² = 0.01; Chi² = 20.20, df = 7 (P = 0.005); I² = 65%						
Test for overall effect: Z = 3.92 (P < 0.0001)						
Total (95% CI)		692788		1188802	100.0%	1.14 [1.09, 1.19]
Total events	9878		15882			
Heterogeneity: Tau² = 0.00; Chi² = 37.70, df = 15 (P = 0.0010); I² = 60%						
Test for overall effect: Z = 5.67 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.65, df = 1 (P = 0.42), I² = 0%						



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Cheraghi et al. PLoS One 2012.

Increased BMI is a Poor Prognostic Factor in Patients with Breast Cancer

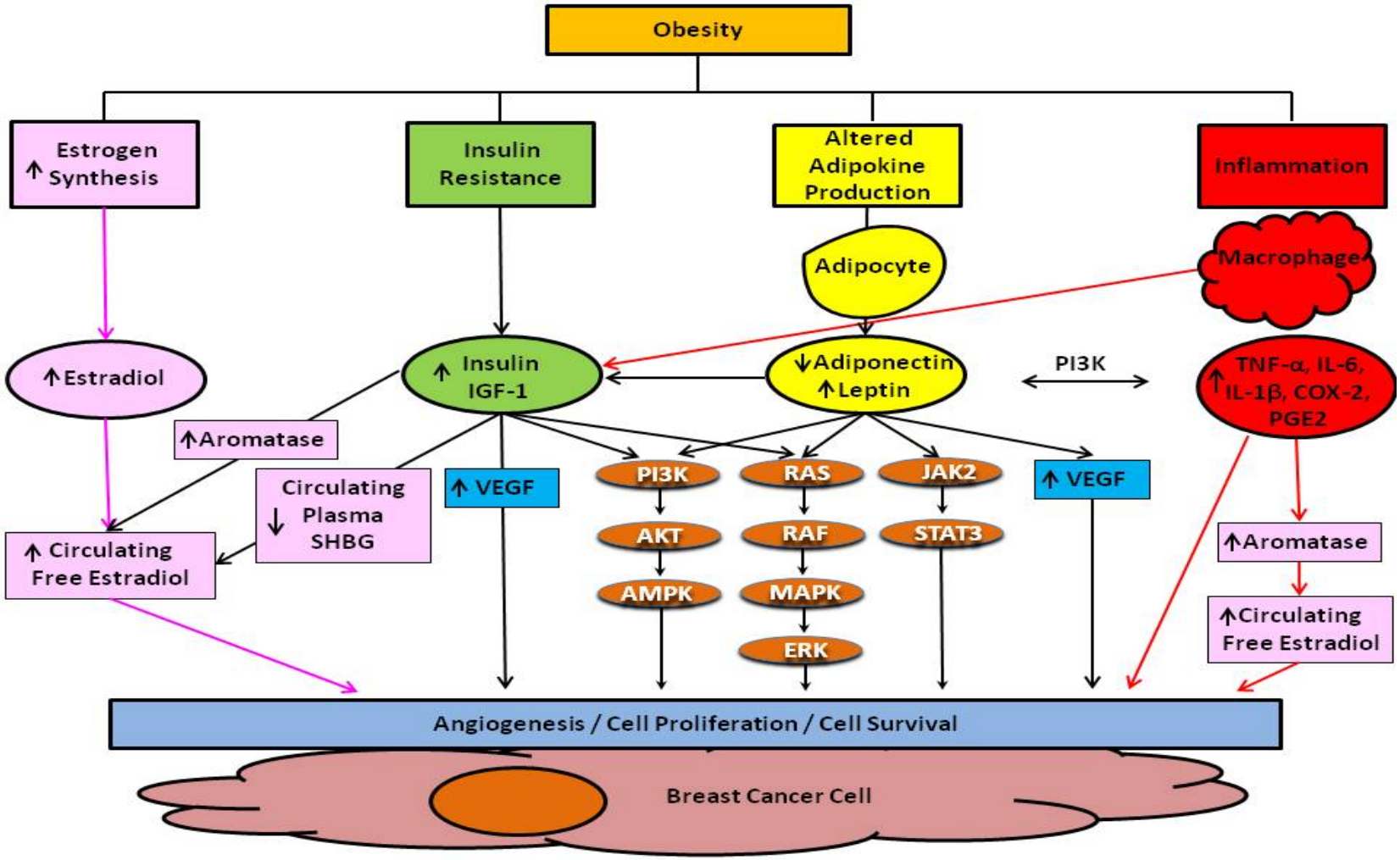
Table 1 Sensitivity analyses of pooled hazard ratios of the effect of obesity on survival in breast cancer patients

Subgroup	No. of estimates	Pooled HR (95% CI)	I^2%	P-value
Survival measure				
All-cause	36	1.33 (1.21–1.47)	73 (62–80)	0.91
Breast cancer specific	19	1.33 (1.19–1.50)	58 (30–75)	
Obesity measure				
BMI	55	1.33 (1.23–1.44)	70 (60–77)	0.96
WHR	6	1.31 (1.14–1.50)	0 (0–75)	
Study design				
Observational cohort	48	1.36 (1.23–1.49)	73 (64–79)	0.53
Treatment cohort	7	1.22 (1.14–1.31)	0 (0–71)	
Menopausal status				
Pre-menopausal	16	1.47 (1.19–1.83)	68 (46–81)	0.25*
Post-menopausal	12	1.22 (0.95–1.57)	70 (47–84)	
Both	36	1.33 (1.23–1.43)	61 (45–73)	
Year of diagnosis				
Pre-1995	30	1.31 (1.16–1.46)	76 (66–83)	0.17
Post-1995	11	1.49 (1.31–1.68)	0 (0–60)	

* P-value for pre- versus post-menopausal women (not including studies which did not stratify by menopausal status)

Protani et al. BCRT 2010.

Pathways Linking Obesity with Breast Cancer

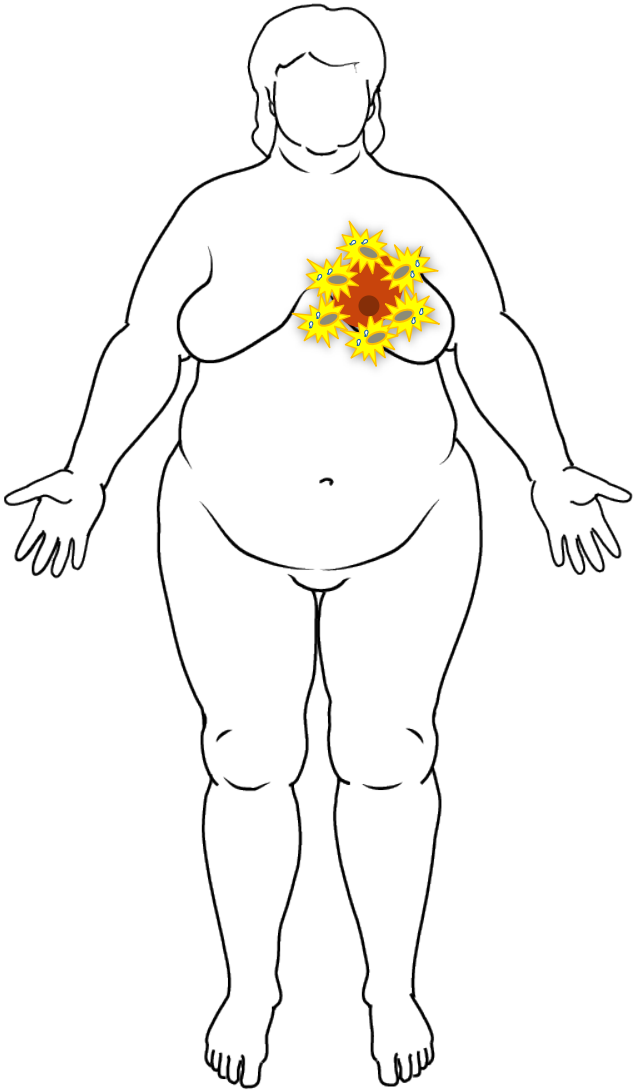


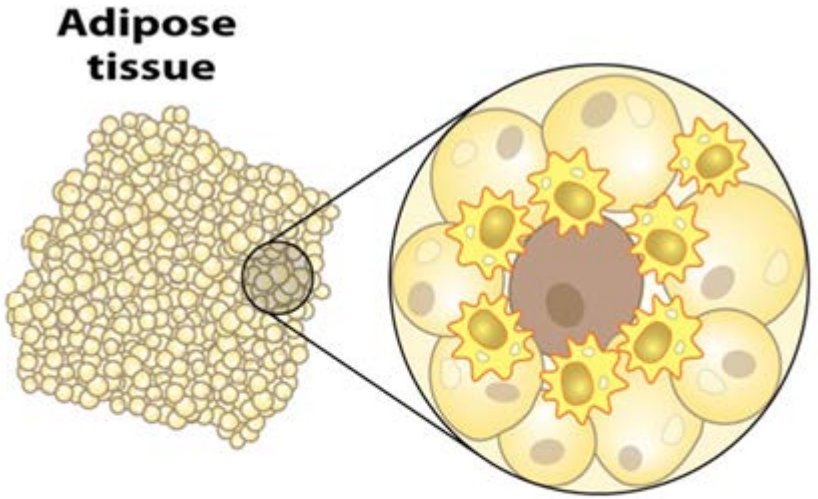
Gucalp et al. Disease of the Breast. 2014.

Obesity, Estrogen, and Increased Risk of Postmenopausal Breast Cancer

- After menopause, peripheral aromatization of androgen precursors in adipose tissue is largely responsible for estrogen synthesis.
- Obesity causes inflammation in both visceral and subcutaneous fat.
- A number of inflammatory mediators (specifically PGE2, TNFa, IL-1β, and IL-6), are all known to induce aromatase.
- A direct link between obesity, breast white adipose tissue inflammation, and aromatase expression was previously unknown.

Obesity Causes An Inflammatory State

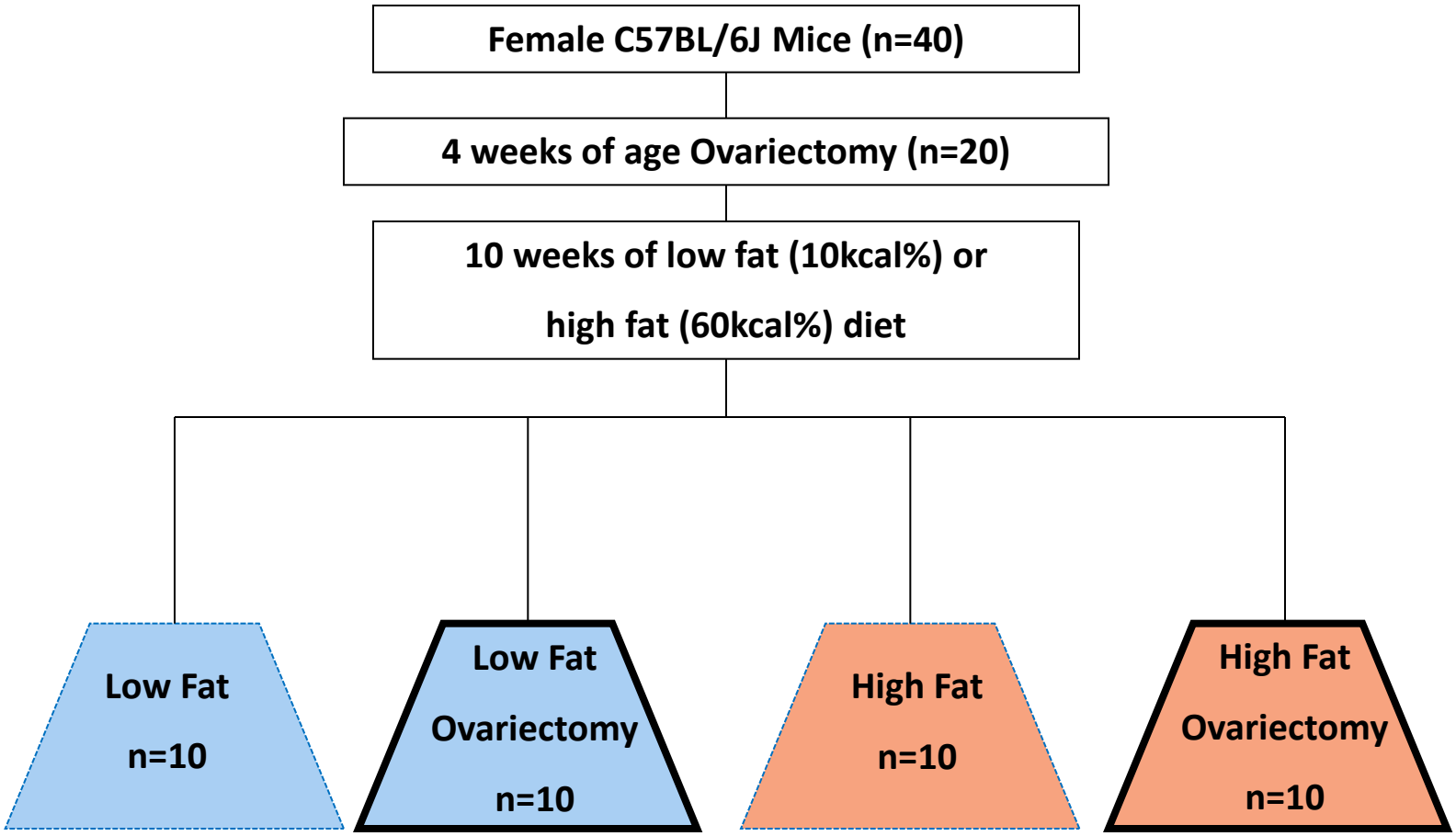




- Adipocyte hypertrophy
- Macrophage recruitment
- Macrophage polarity switch
- Increased cytokine production
- Increased lipolysis

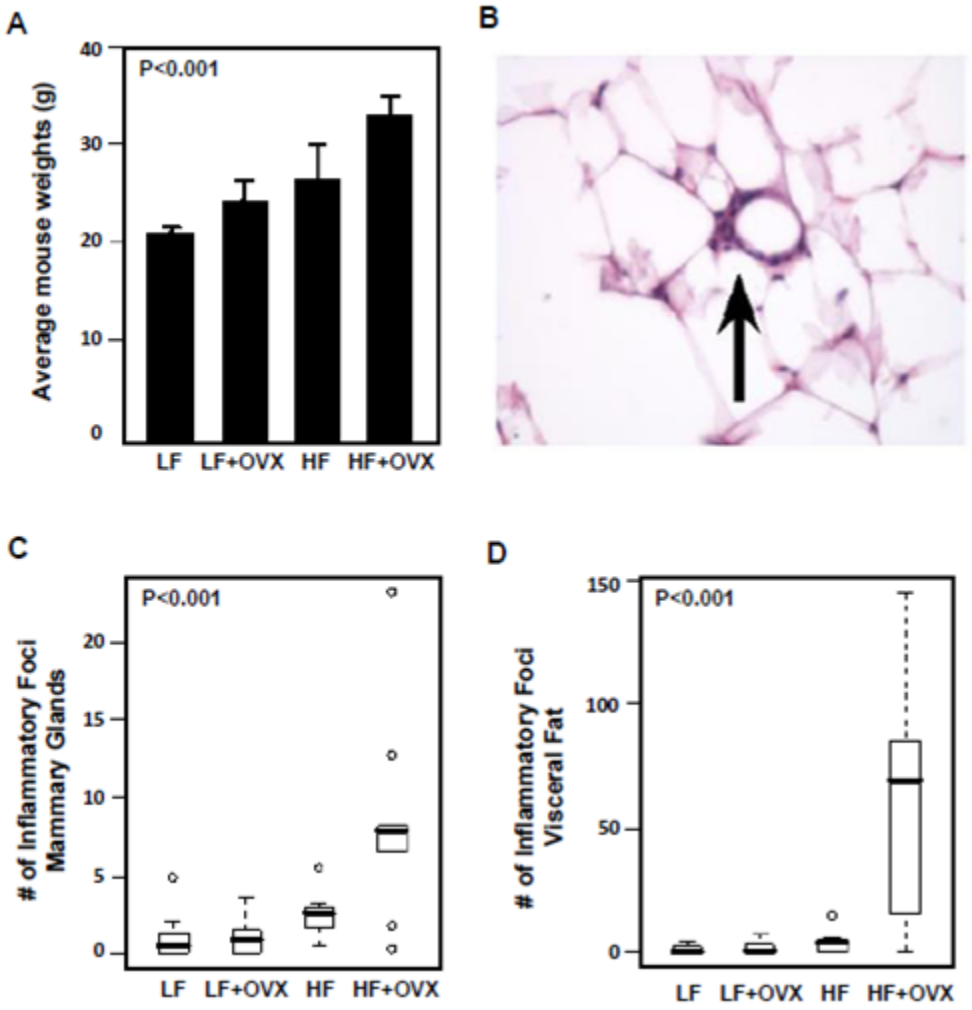
Adapted from Olefsky & Glass. Annu. Rev. Physiol 2010.

Preclinical Study To Investigate the Obesity → Inflammation → Aromatase Axis



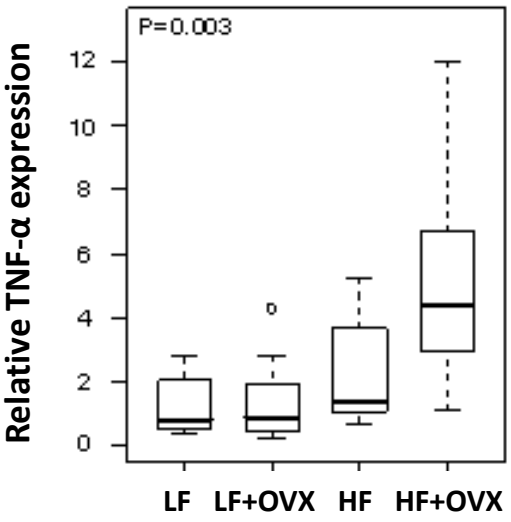
Subbaramaiah, K et al. Cancer Prev Res 2011.

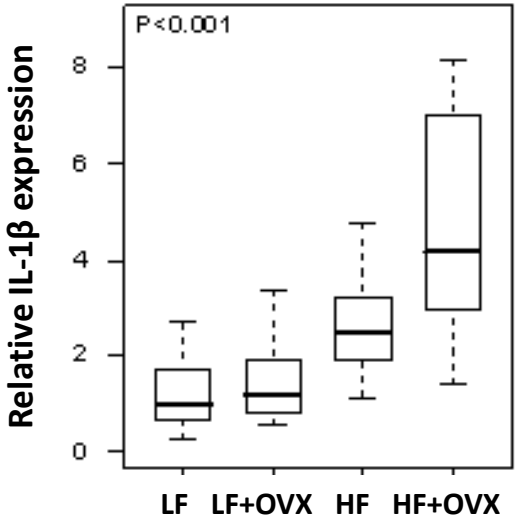
Diet Induced Obesity Causes Inflammation in the Mammary Gland and Visceral Fat

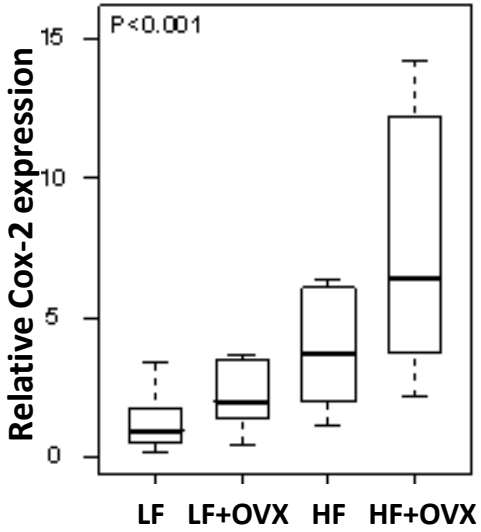


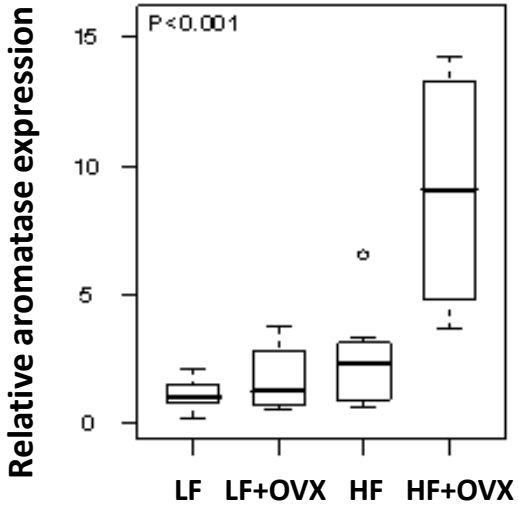
Subbaramaiah, K et al. Cancer Prev Res 2011.

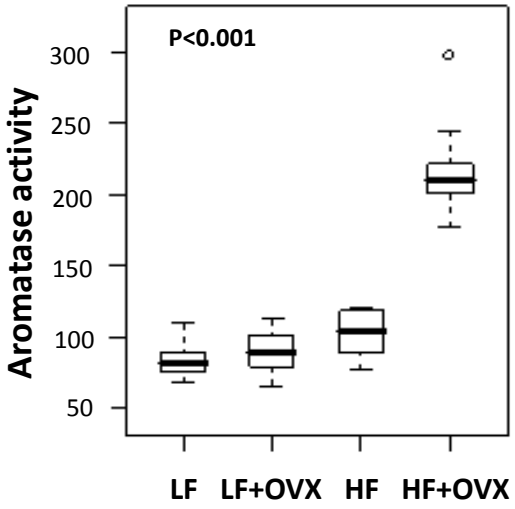
Obesity is Associated with Increased Levels of Pro-inflammatory Mediators and Aromatase





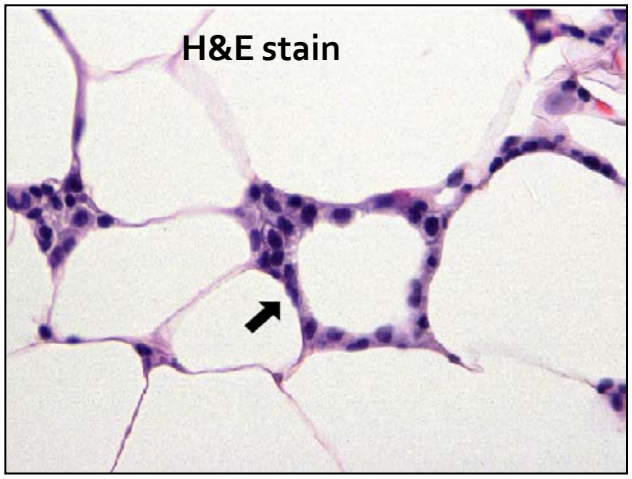


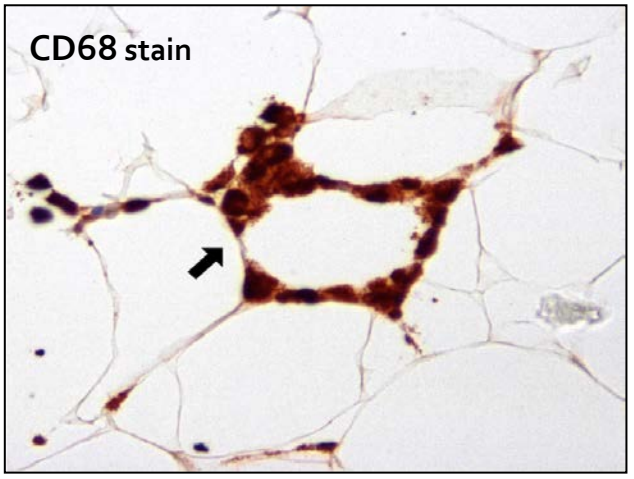


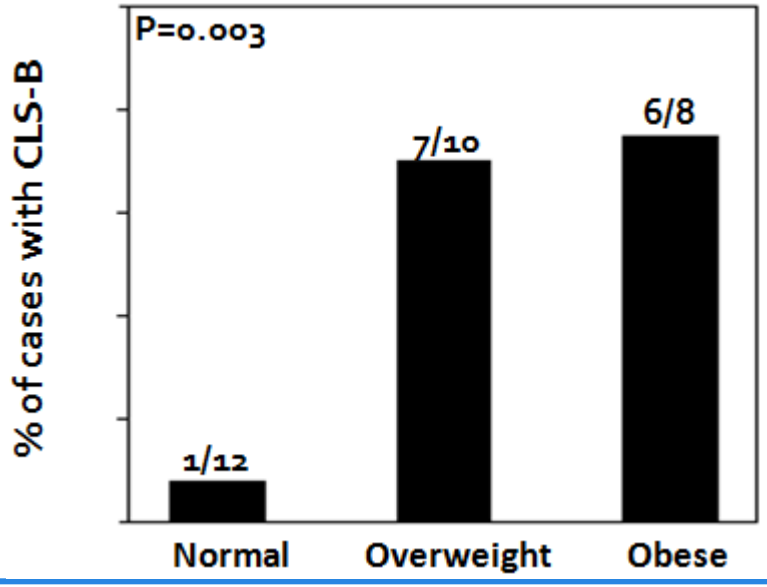


Subbaramaiah, K et al. Cancer Prev Res 2011.

CLS-B are Common in the Breasts of Overweight and Obese Women

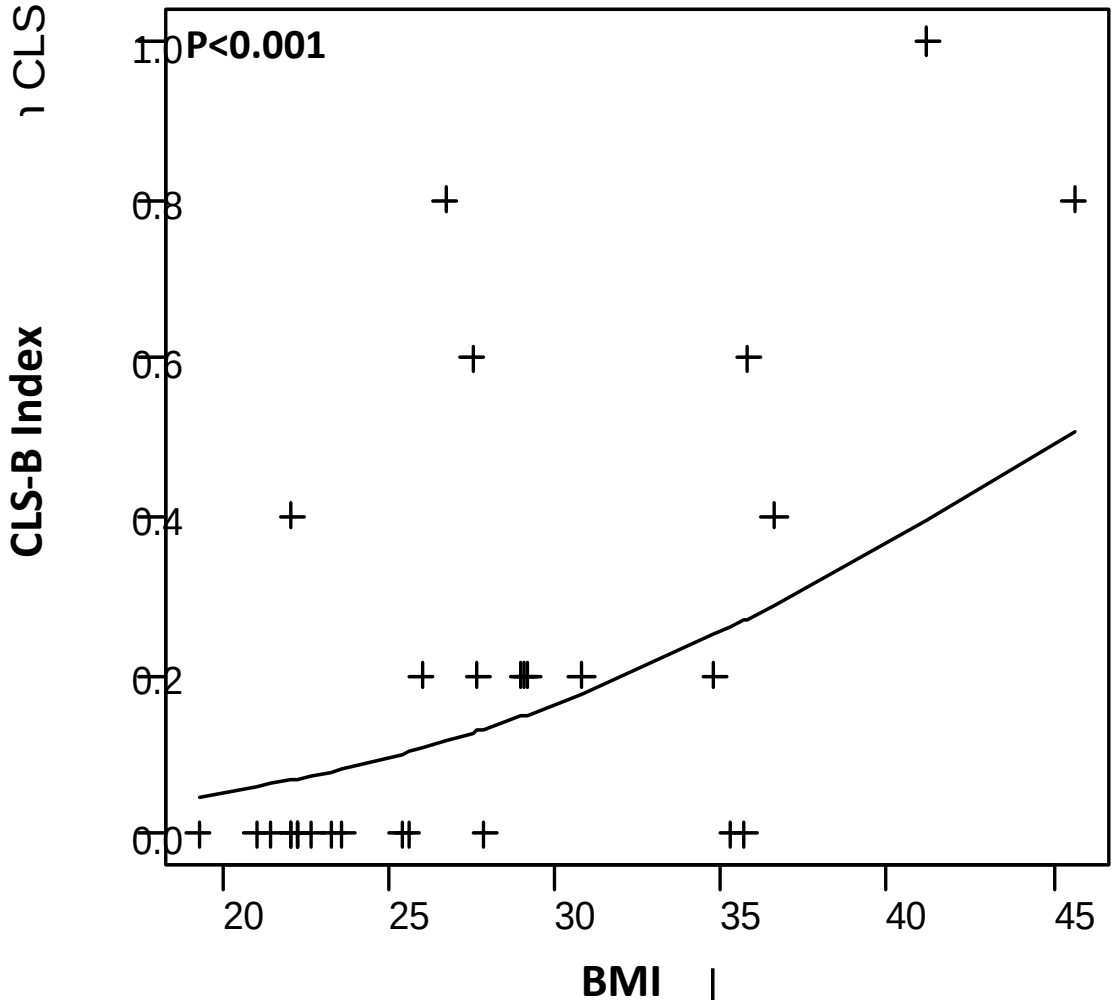






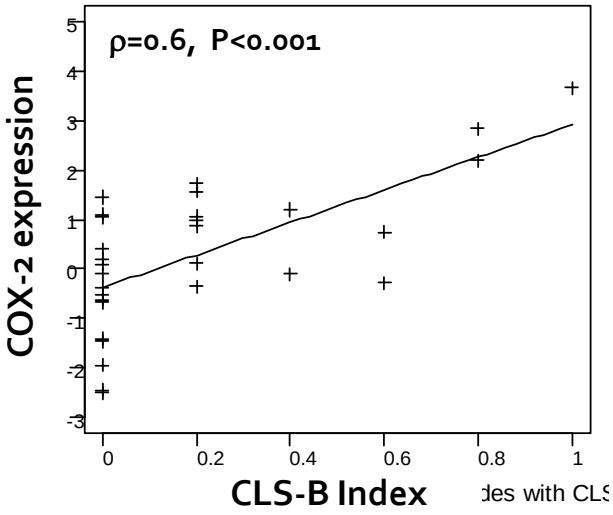
Morris PG et al. Cancer Prev Res 2011.

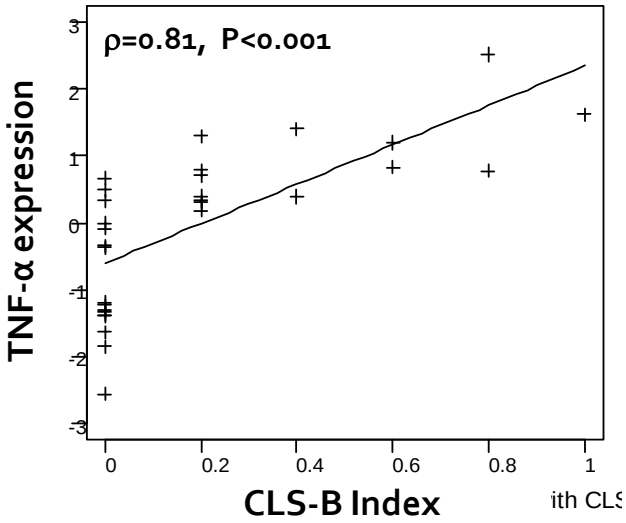
Increasing BMI is Associated with Increased Breast Inflammation

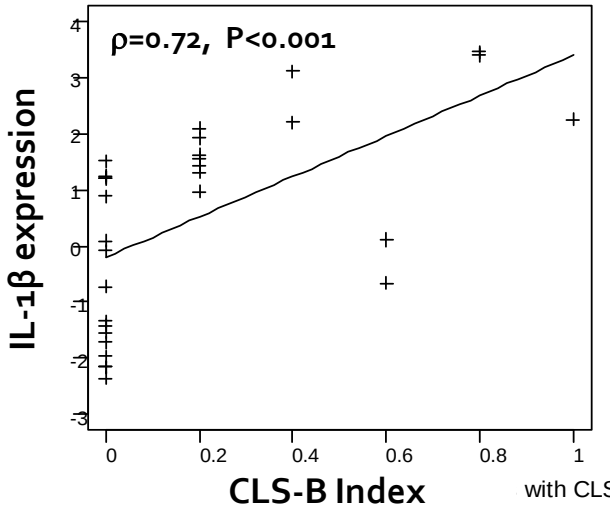


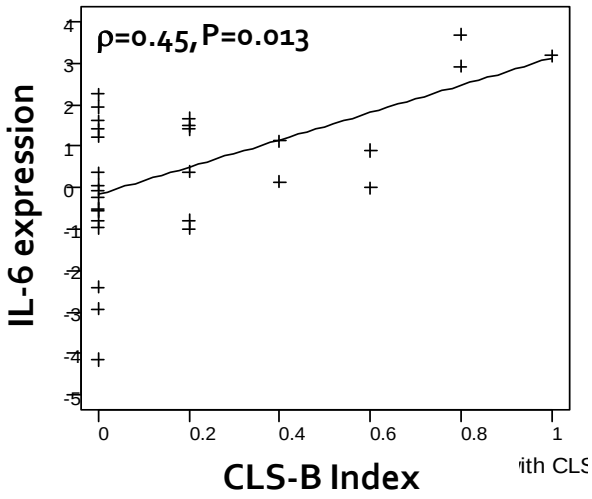
Morris PG et al. Cancer Prev Res 2011.

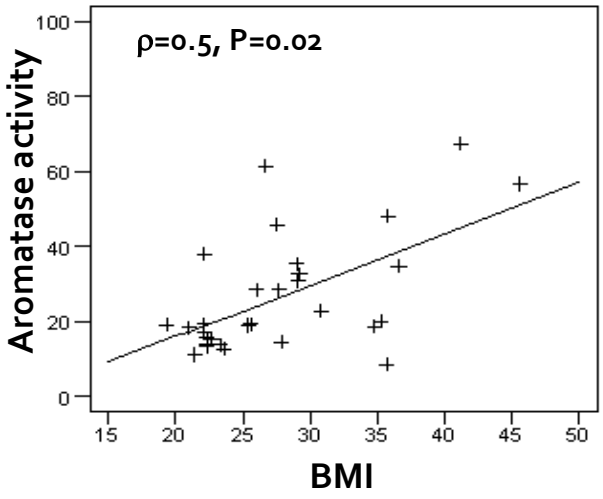
Levels of Pro-inflammatory Mediators and Aromatase are Increased in Inflamed Breast Tissue

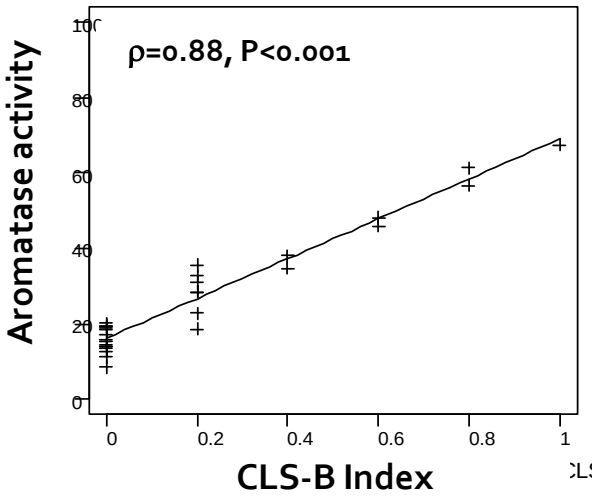












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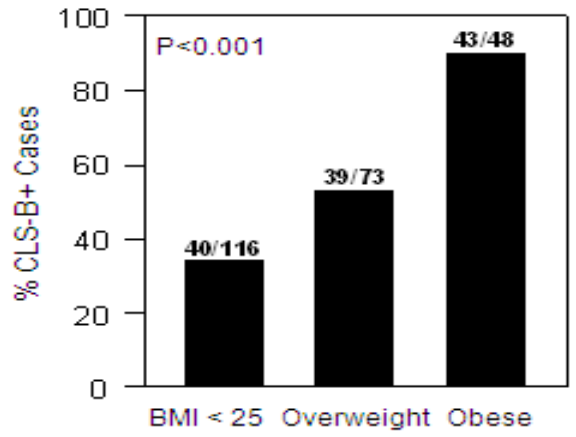
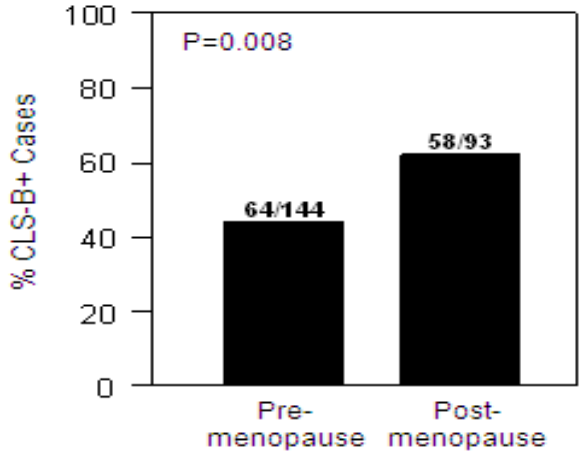
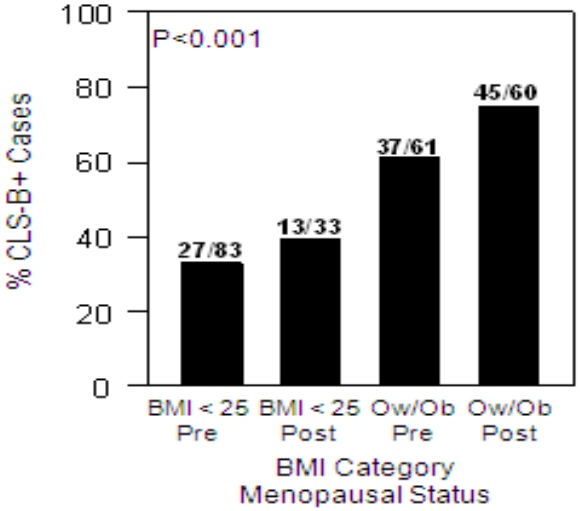
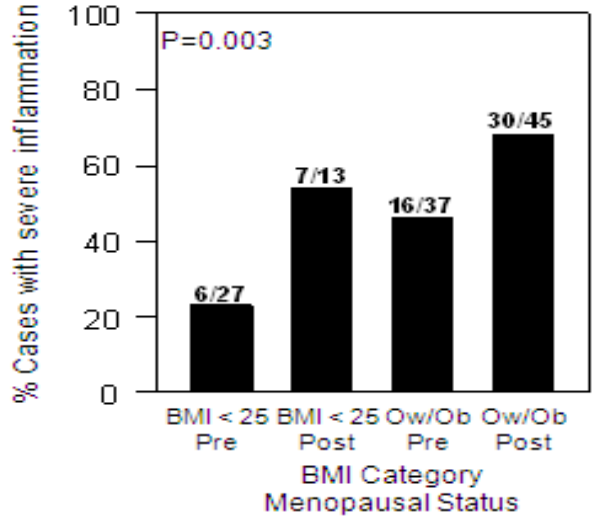
Subbaramaiah K, et al. Cancer Discov 2012.

CLS-B are Associated with BMI and Postmenopausal Status



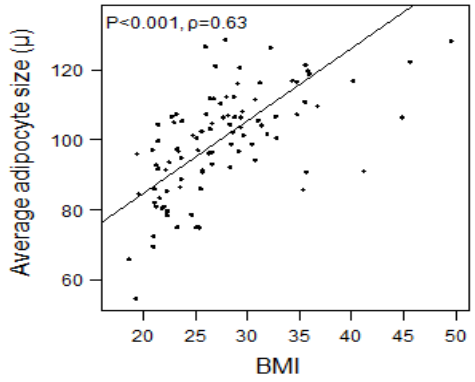


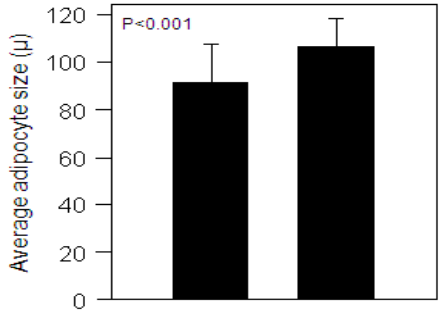


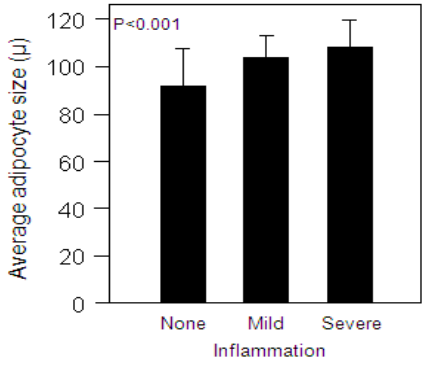


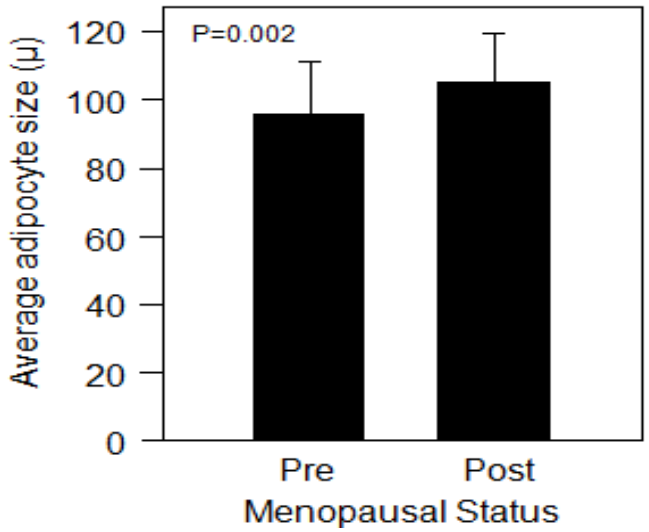
Iyengar et al. ASCO Annual Meeting 2014.

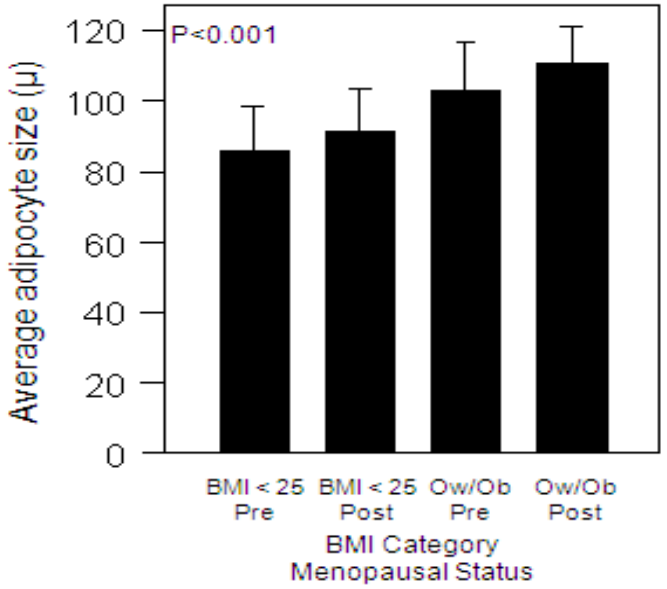
Adipocyte Size Correlates with BMI, Menopausal Status, and CLS-B











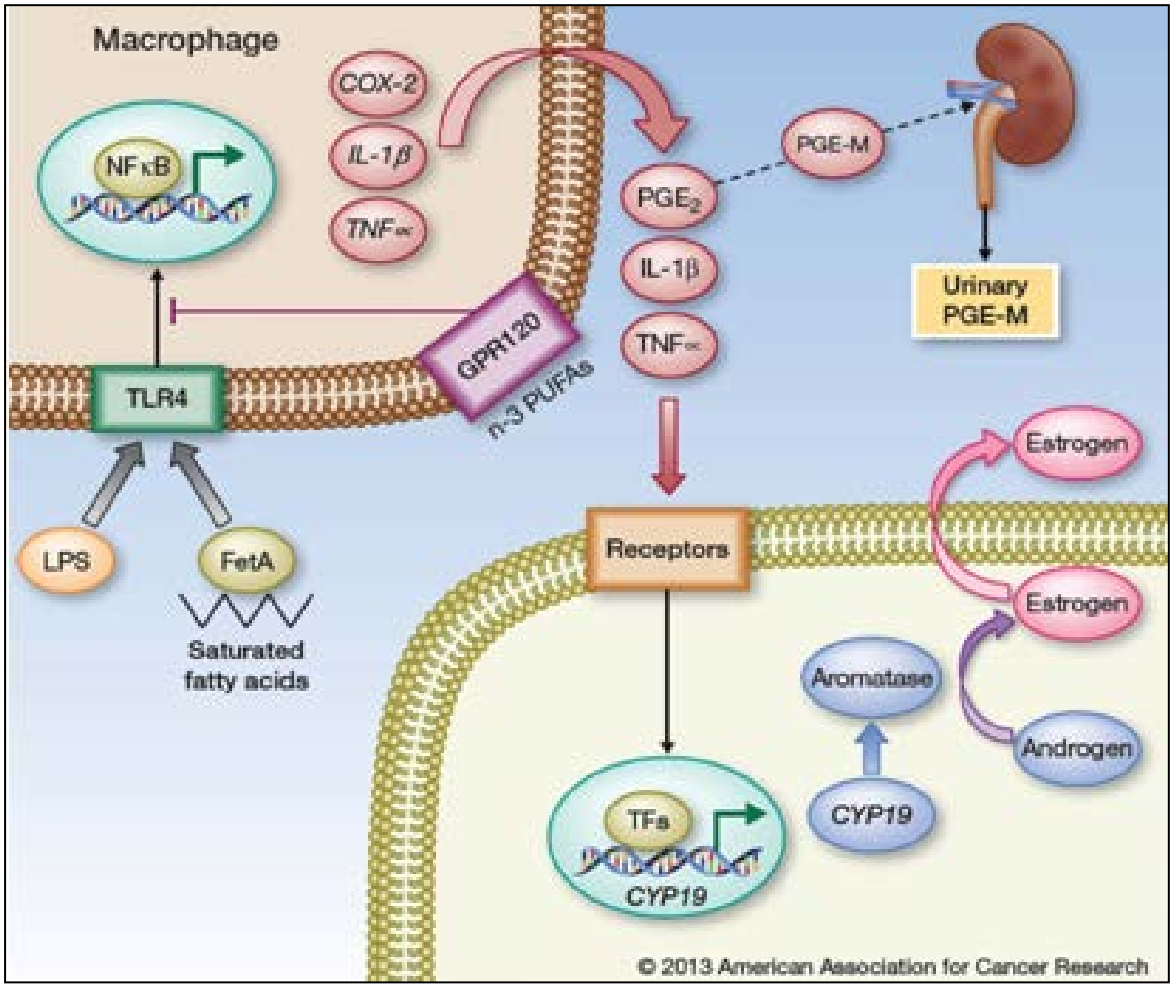
Iyengar et al. ASCO Annual Meeting 2014.

CLS Status is Concordant Between Adipose Depots

Bilateral breast WAT	N (%)
Concordant	**49/63 (78%)**
CLS-B Positive	32/63 (51%)
CLS-B Negative	17/63 (27%)
Discordant	**14/63 (22%)**
Abdominal and breast WAT	
Concordant	**10/13 (77%)**
CLS-B Positive	7/13 (54%)
CLS-B Negative	3/13 (23%)
Discordant	**3/13 (23%)**

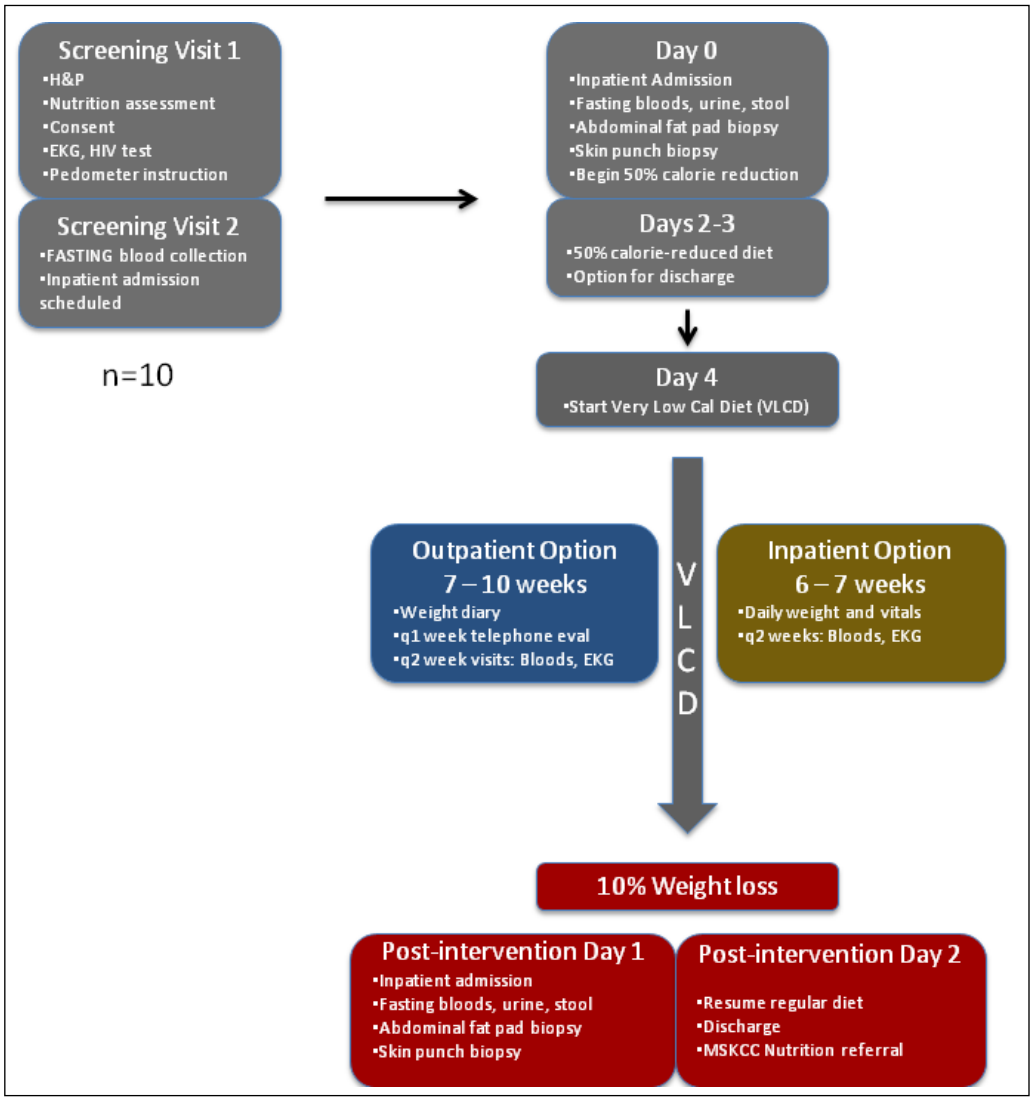
Iyengar et al. ASCO Annual Meeting 2014.

Paracrine Interactions Establish an Obesity → Inflammation → Aromatase Axis

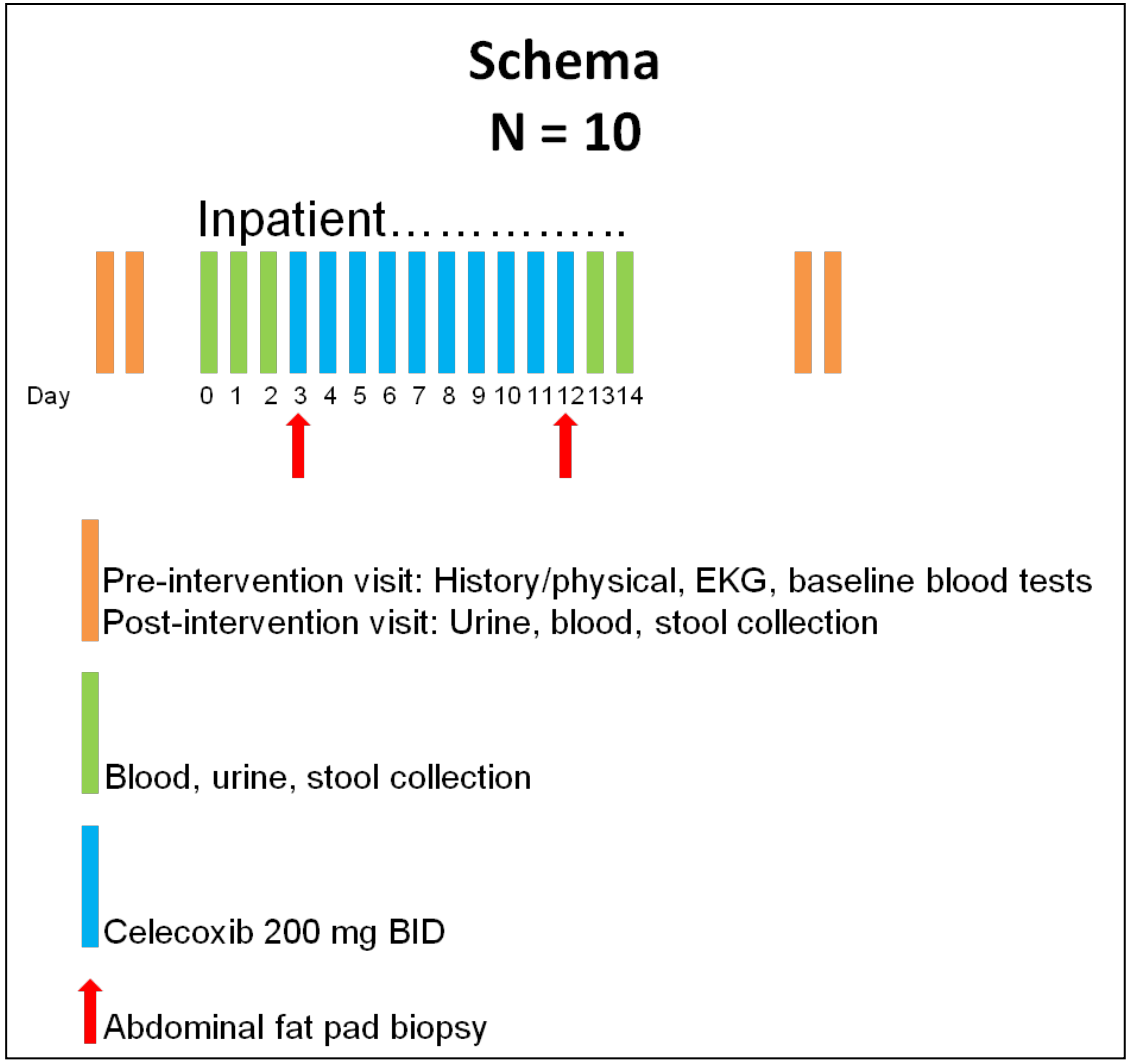


Howe et al. CCR 2013.

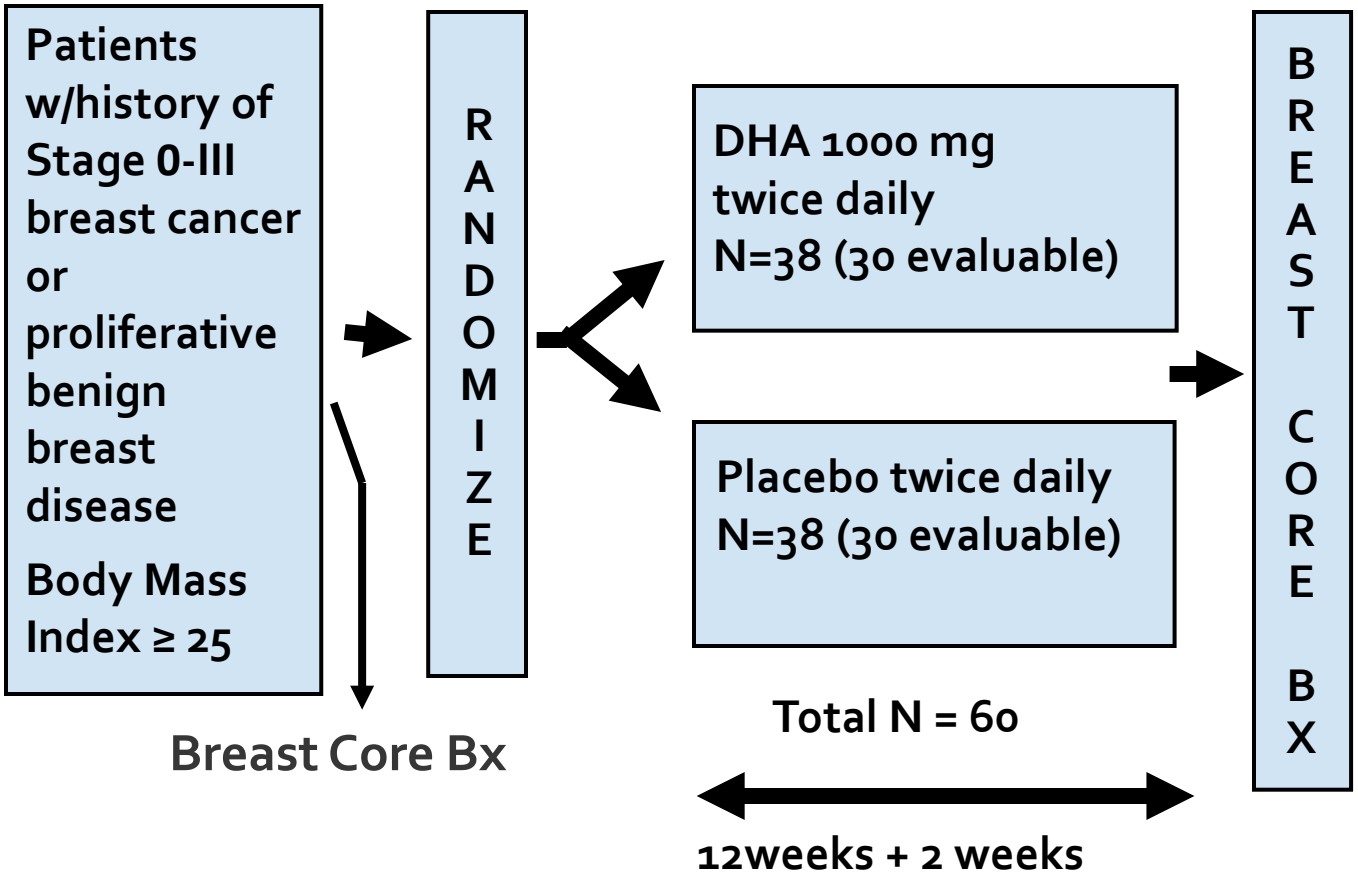
Obesity Weight Loss (OWL) Study



Celecoxib Pilot Study



Docosahexaenoic Acid Intervention Study



Endpoints

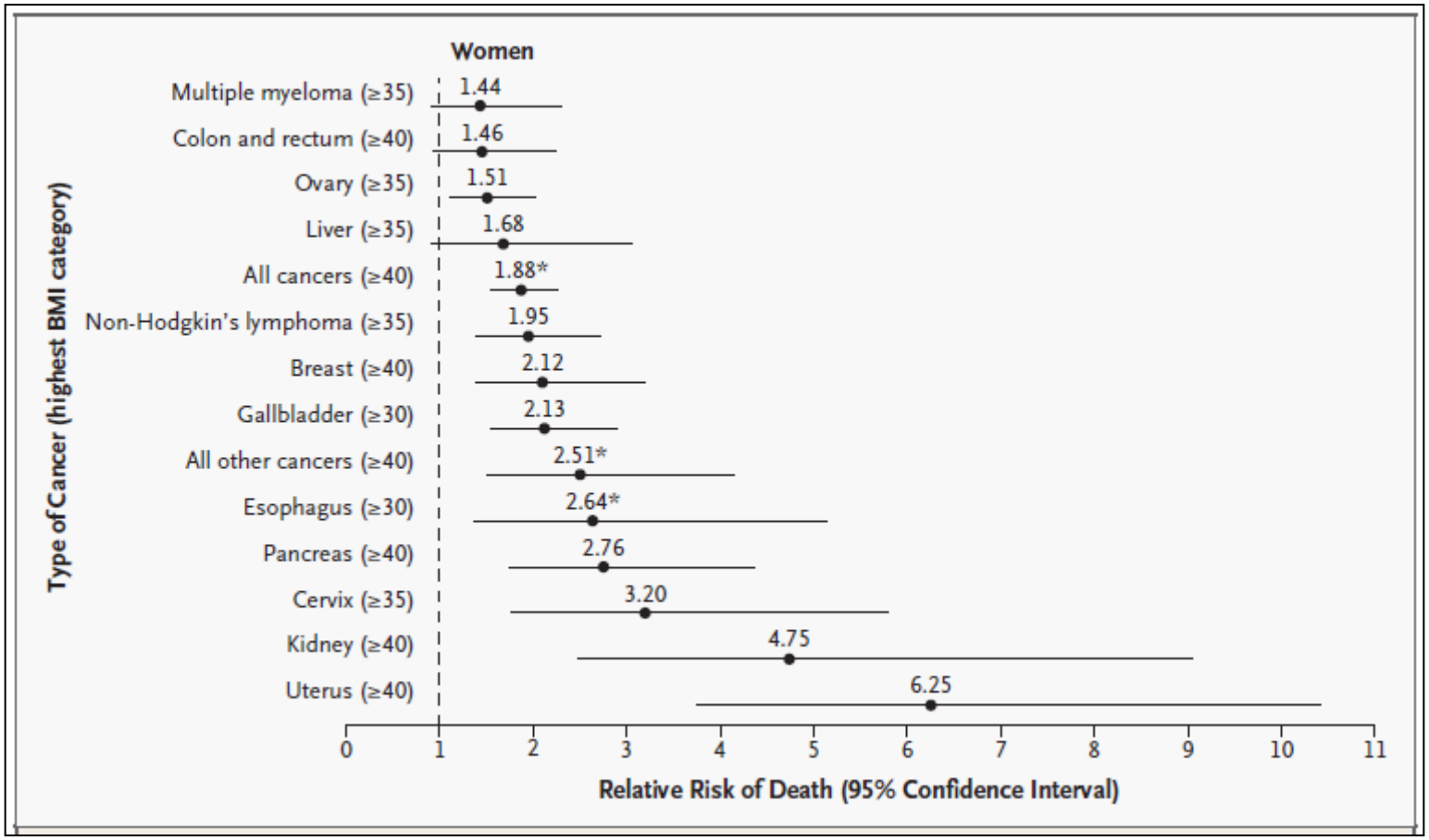
Primary Endpoint: Change in normal breast tissue TNF-α

Secondary Endpoints: Changes in breast tissue: COX-2, IL-1β; Crown-like Structures of the breast (CLS-B), CLS-B index; age as a predictor of CLS-B and inflammatory biomarkers

Being conducted at MDACC, MSK, Dana Farber, Columbia, Cornell, Baylor

Gucalp et al. ASCO Annual Meeting. 2014.

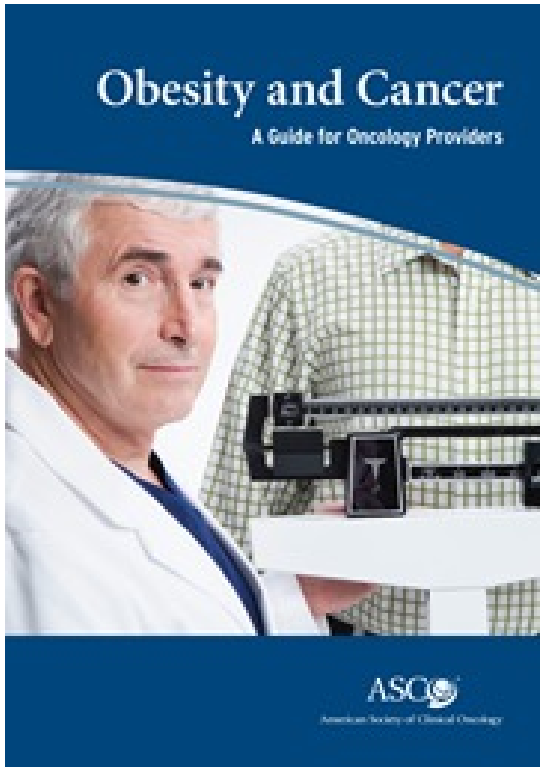
Obesity and Cancer Outcomes

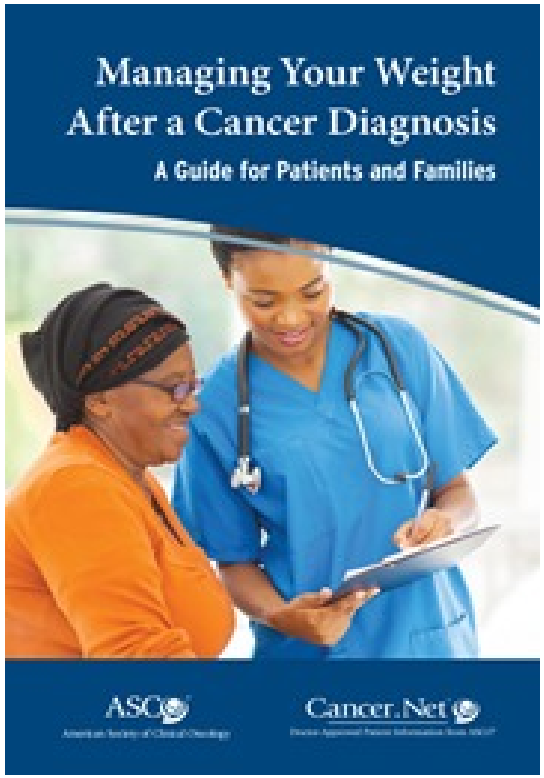


Calle EE, et al. N Engl J Med 2003.

Case

- 64 year old postmenopausal female
- Diagnosed with stage I ER/PR+, HER2- IDC on therapy with adjuvant AI
- BMI > 30





Conclusions & Future Directions

- Obesity is associated with risk and worse prognosis in a growing number of malignancies
- Obesity is associated with systemic inflammation manifest as CLS and circulating proinflammatory mediators
- White adipose tissue inflammation in the breast is associated with menopausal status, BMI, and adipocyte size
- The obesity → inflammation → aromatase axis is active in the breasts of many women

Conclusions & Future Directions

- **Do CLS represent a histologic biomarker of risk and/or prognosis?**
- **Need for non-invasive detection of adipose inflammation**

Acknowledgements

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