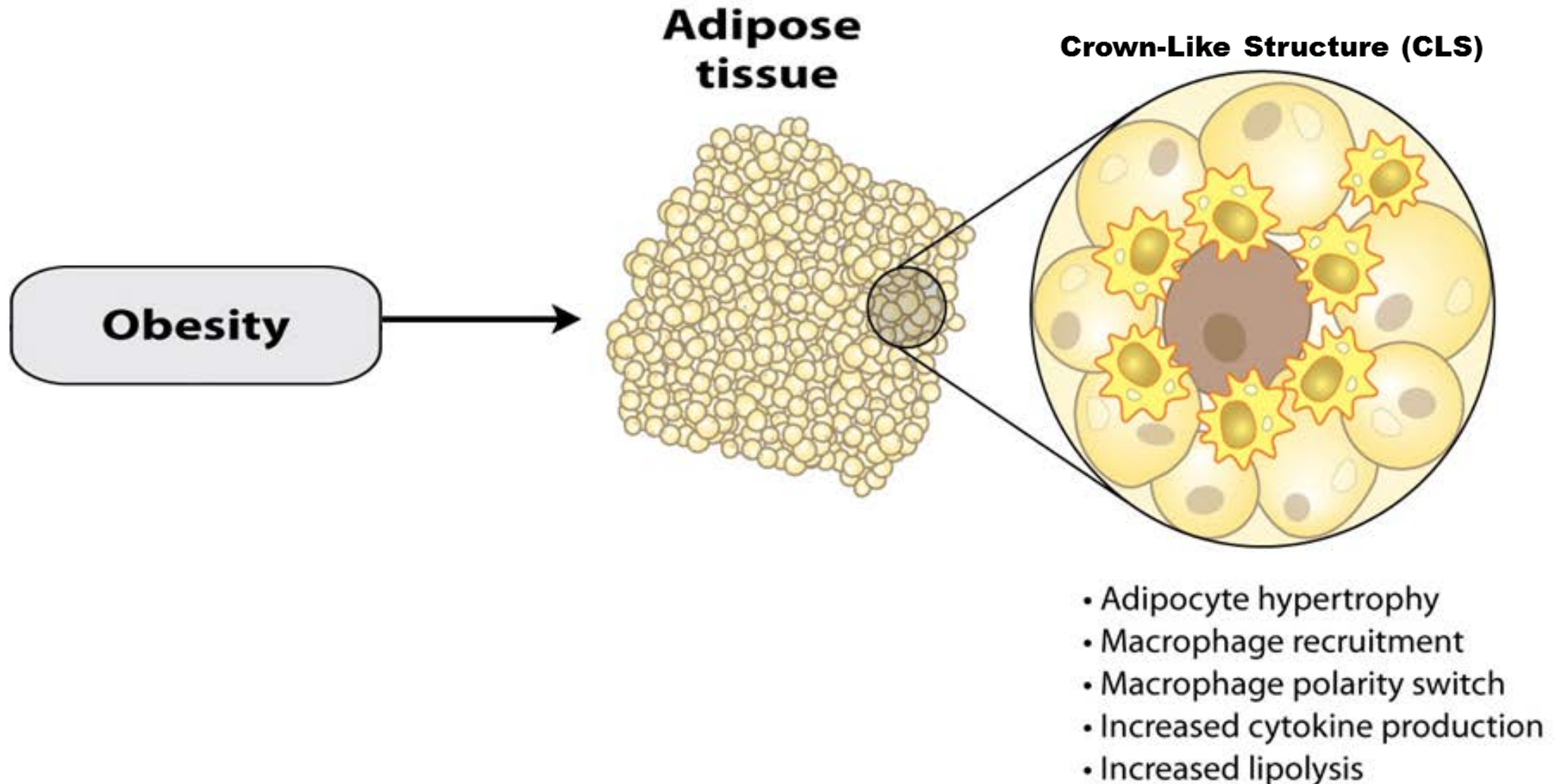# Obesity and Breast Cancer

- Risk factor for development of hormone receptor-positive breast cancer in postmenopausal women.

- Poor prognostic factor for breast cancer patients.

Pathways Linking Obesity with Breast Cancer
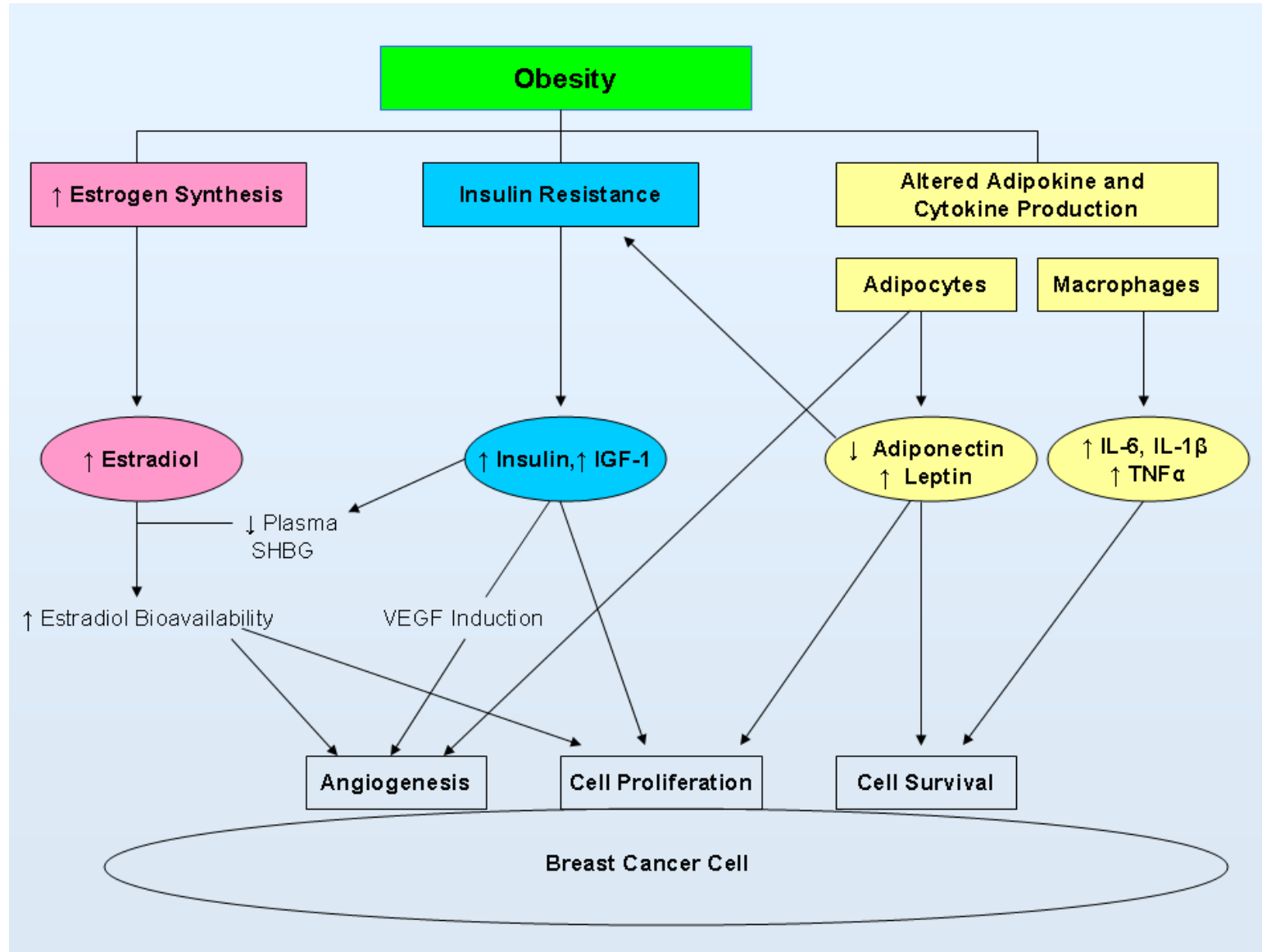
Obesity Causes An Inflammatory State

Adipose tissue

Obesity

Crown-Like Structure (CLS)

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

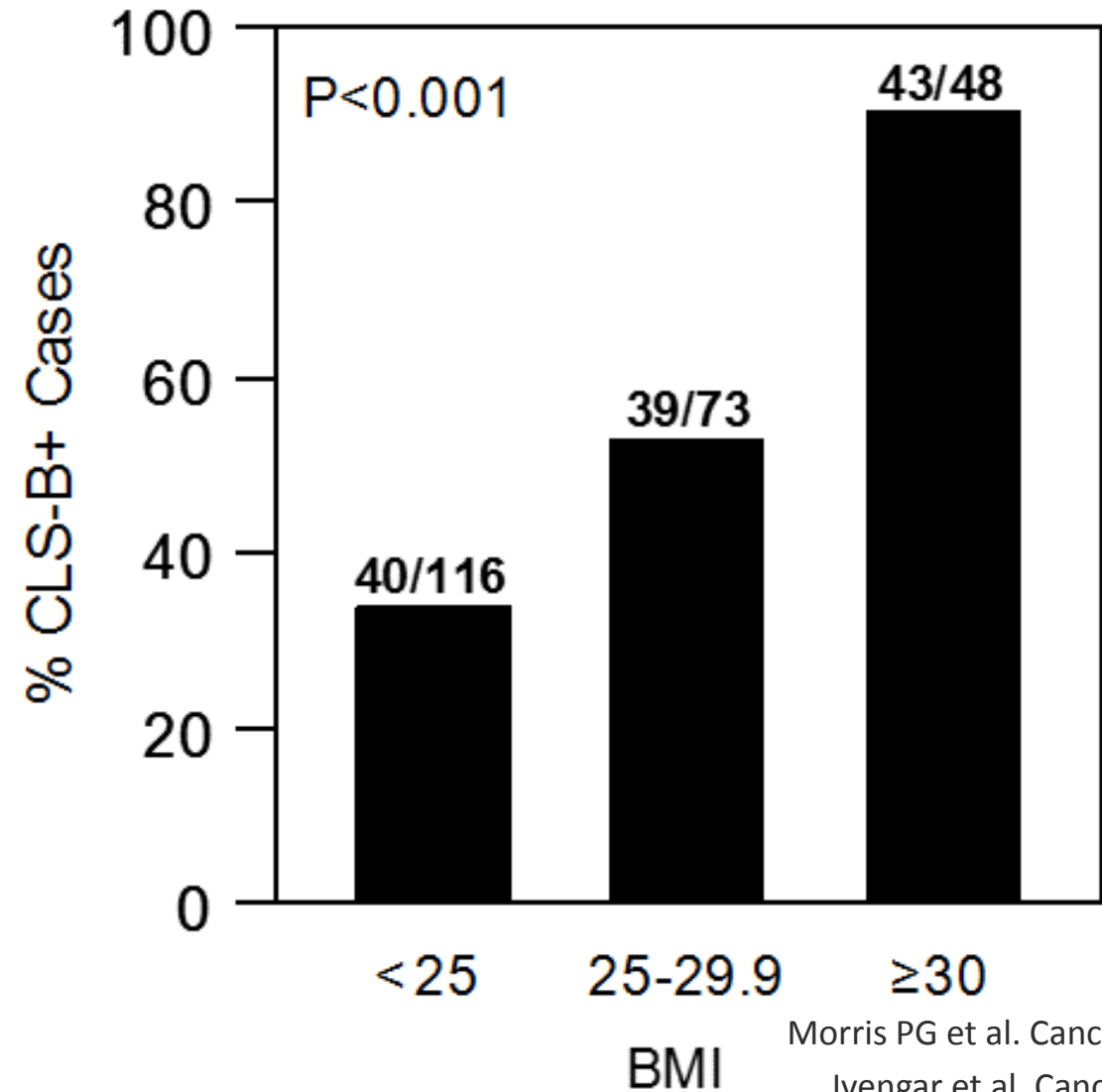Adapted from Olefsky & Glass. Annu. Rev. Physiol. 2010
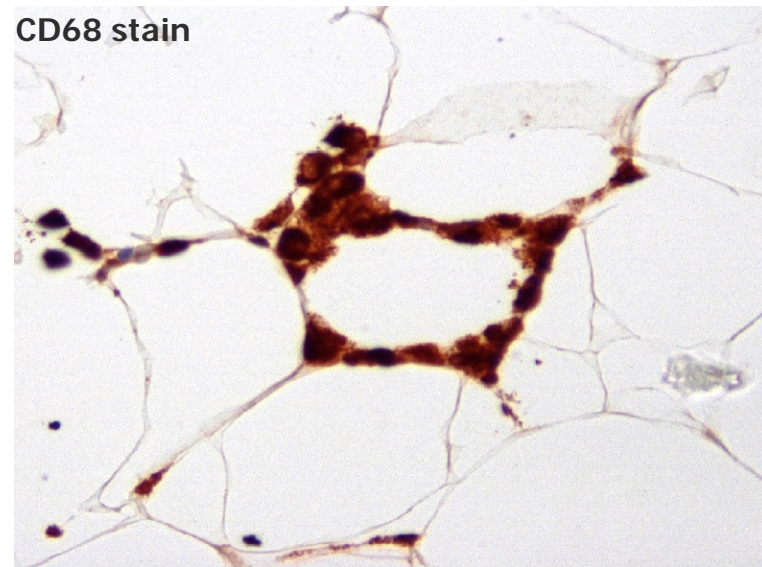
Objective

- To determine if CLS of the breast (CLS-B) exist in women and correlate with BMI.

Study Design

- Breast tissue was obtained from women who underwent mastectomy.

- Routine H&E staining and CD68 IHC was performed.

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

H&E stain

CD68 stain
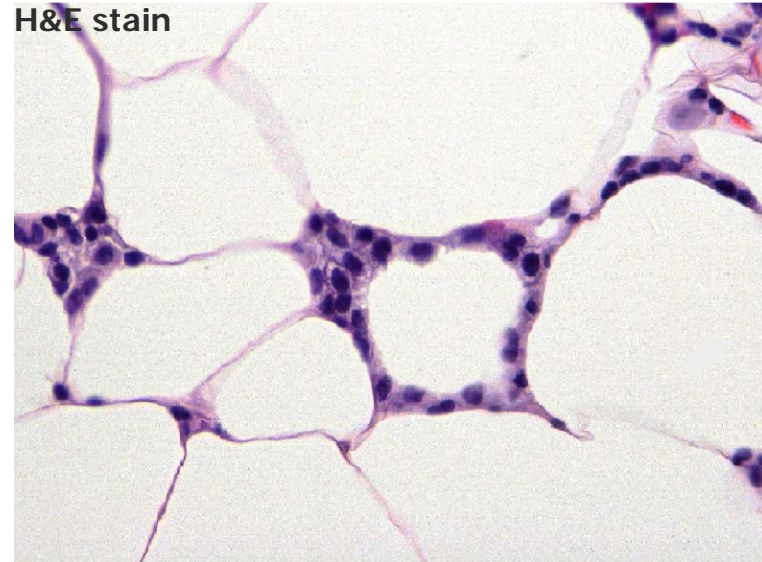
Morris PG et al. Cancer Prev Res 2011

Iyengar et al. Cancer Prev Res 2015

Adipocyte Size Correlates with BMI and CLS-B Status

A

ρ=0.63, P<0.001

Mean adipocyte size (μ)

BMI

B

P<0.001

Mean adipocyte size (μ)

CLS-B −   CLS-B +

Iyengar et al. Cancer Prev Res 2015
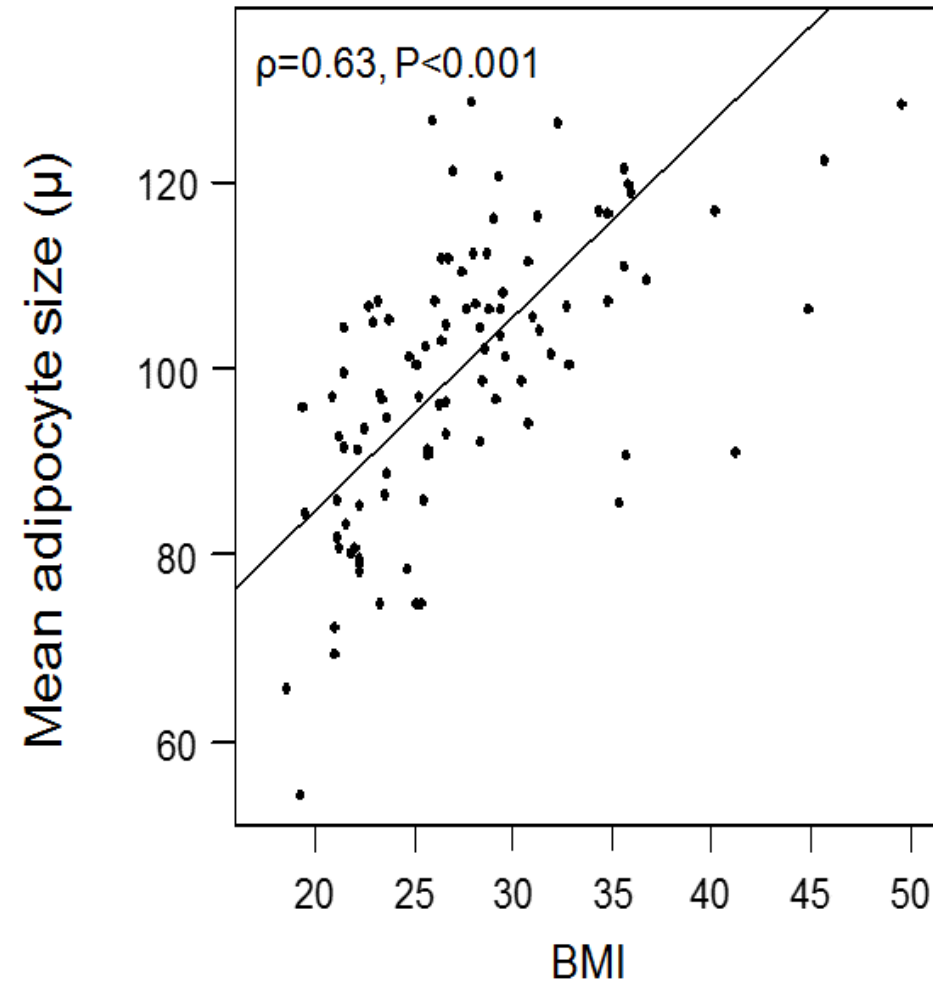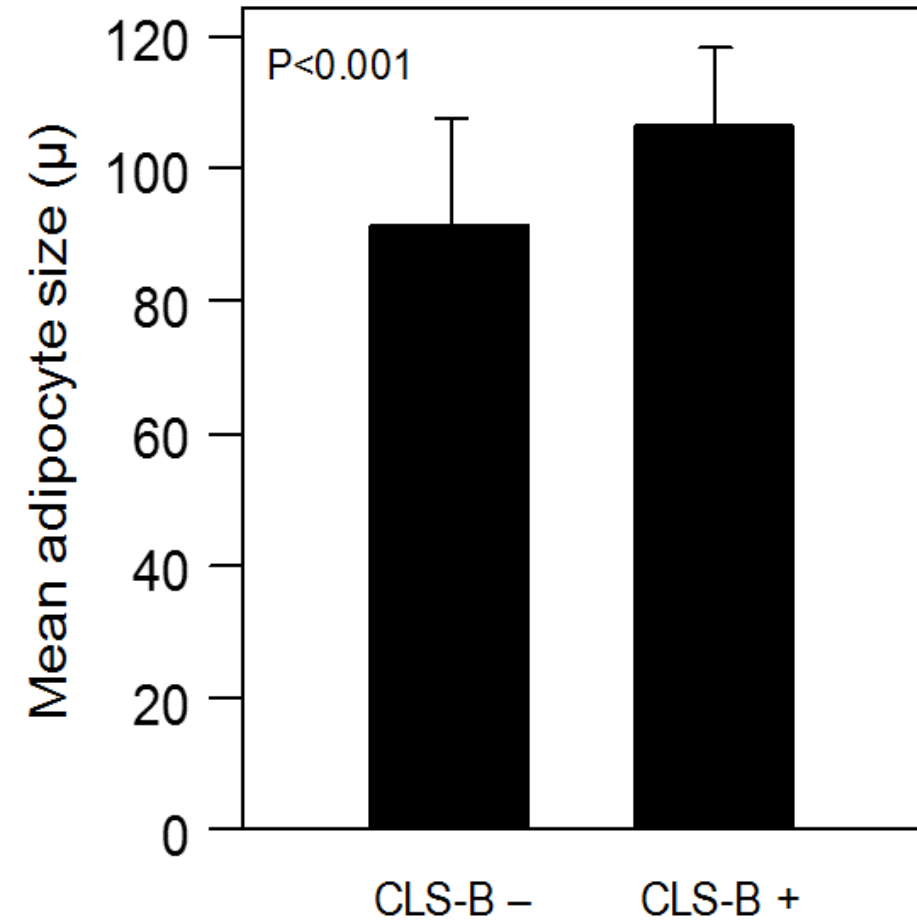
Objective

- To determine whether breast white adipose tissue inflammation (WATi) manifested as CLS-B is associated with shortened recurrence free survival in women who develop metastatic breast cancer.

Clinicopathologic Characteristics in Patients with

| Variables	All (n=127)	CLS-B neg (n=75)	CLS-B pos (n=52)	P
Age. Dx				
Median (range)	50 (32, 84)	44 (32,78)	53.5 (35,84)	<0.001
BMI category, n (%)				
Normal/Underweight	43(33.86%)	33 (44%)	10 (19.23%)	
Overweight	43(33.86%)	29 (38.67%)	14 (26.92%)	
Obese	41(32.28%)	13 (17.33%)	28 (53.85%)	<0.001
Menopause, n (%)				
Pre	65(51.18%)	47 (62.67%)	18 (34.62%)	
Post	62(48.82%)	28 (37.33%)	34 (65.38%)	0.002
Hyperlipidemia, n (%)				
No	108(85.04%)	68 (90.67%)	40 (76.92%)	
Yes	19(14.96%)	7 (9.33%)	12 (23.08%)	0.04
Hypertension, n (%)				
No	97(76.38%)	63 (84%)	34 (65.38%)	
Yes	30(23.62%)	12 (16%)	18 (34.62%)	0.02
DM, n (%)				
No	115(90.55%)	73 (97.33%)	42 (80.77%)	
Yes	12(9.45%)	2 (2.67%)	10 (19.23%)	0.003

CLS-B and Distant Recurrence-free Survival
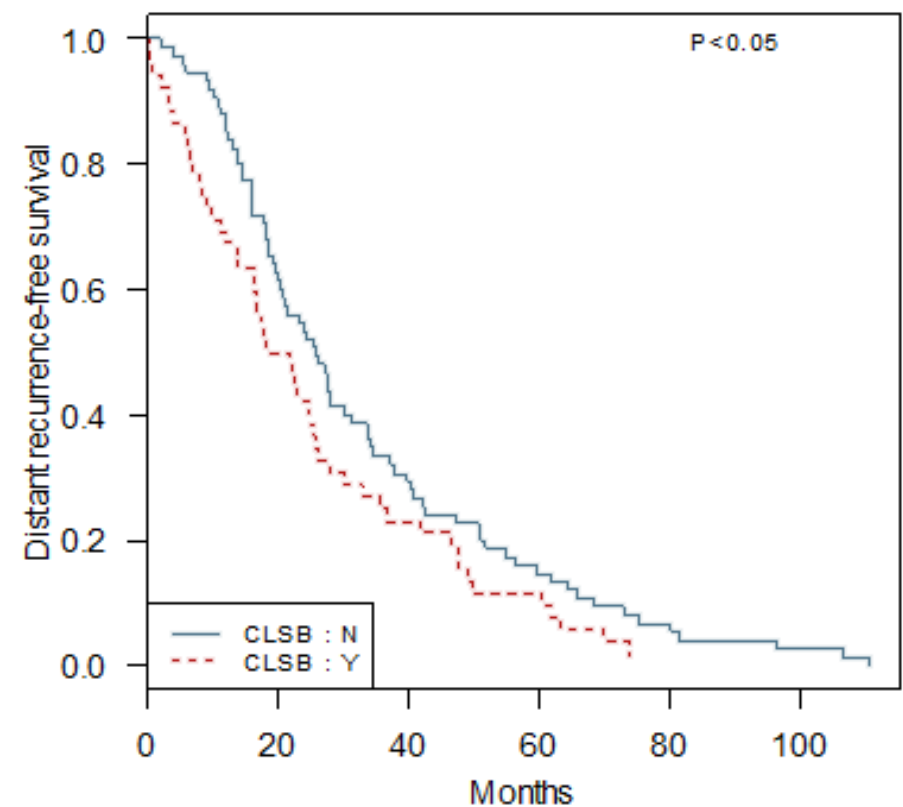
Early Breast Cancer (n=127)	CLS-B- (n=75)	CLS-B+ (n=52)
Median, mths	26 (20 to 34)	20 (16 to 26)
Univariate	Referent	1.44 (95% CI, 1.00 to 2.06)
Adjusted*	Referent	1.83 (95% CI, 1.07 to 3.13)

*adjusted for age, race, BMI, breast cancer subtype, grade, T stage, N stage, hyperlipidemia, hypertension, DM, NeoadjChemo, AdjChemo, AdjEndo, AdjTrast, AdjRT.

Iyengar NM et al. Clin. Cancer Res. 2016

Conclusions

- Breast WAT inflammation is a/w metabolic syndrome.

- In patients who develop metastasis, WAT inflammation is associated with shortened distant recurrence free survival.

- Whether WAT inflammation promotes the progression of breast cancer via local effects, systemic mechanisms, e.g., hyperinsulinemia or both is uncertain.

Is WATi a/w Local or Systemic Effects that Promote Breast Cancer?

- Assess CLS-B status in 100 women with varying BMI

- RNA-seq on nontumorous breast tissue

- Fasting serum/plasma used to quantify:

  - hsCRP, IL-6, insulin, glucose

Patient Characteristics by CLS-B Status

Variables	All (n=100)	No CLS-B (n=48)	CLS-B (n=52)	p.value
Age				
Median (range)	47 (27, 70)	45 (31, 62)	49 (27, 70)	**0.013**
Race,n (%)				
Asian	7 (7.1%)	3 (6.2%)	4 (7.8%)	
Black	7 (7.1%)	2 (4.2%)	5 (9.8%)	
White	85 (85.9%)	43 (89.6%)	42 (82.4%)	0.683
BMI				
Median (range)	25.4 (17.5, 50.0)	23.2 (17.5, 31.4)	27.3 (18.4, 50.0)	**<0.001**
Menopausal, n (%)				
Pre	65(65%)	39 (81.3%)	26 (50%)	
Post	35(35%)	9 (18.7%)	26 (50%)	**0.002**
HTN, n (%)				
No	88(88%)	45 (93.7%)	43 (82.7%)	
Yes	12(12%)	3 (6.3%)	9 (17.3%)	0.13
DM, n (%)				
No	96(96%)	48 (100%)	48 (92.3%)	
Yes	4(4%)	0 (0%)	4 (7.7%)	0.12
Dyslipidemia, n (%)				
No	85(85%)	47 (97.9%)	38 (73.1%)	
Yes	15(15%)	1 (2.1%)	14 (26.9%)	**<0.001**

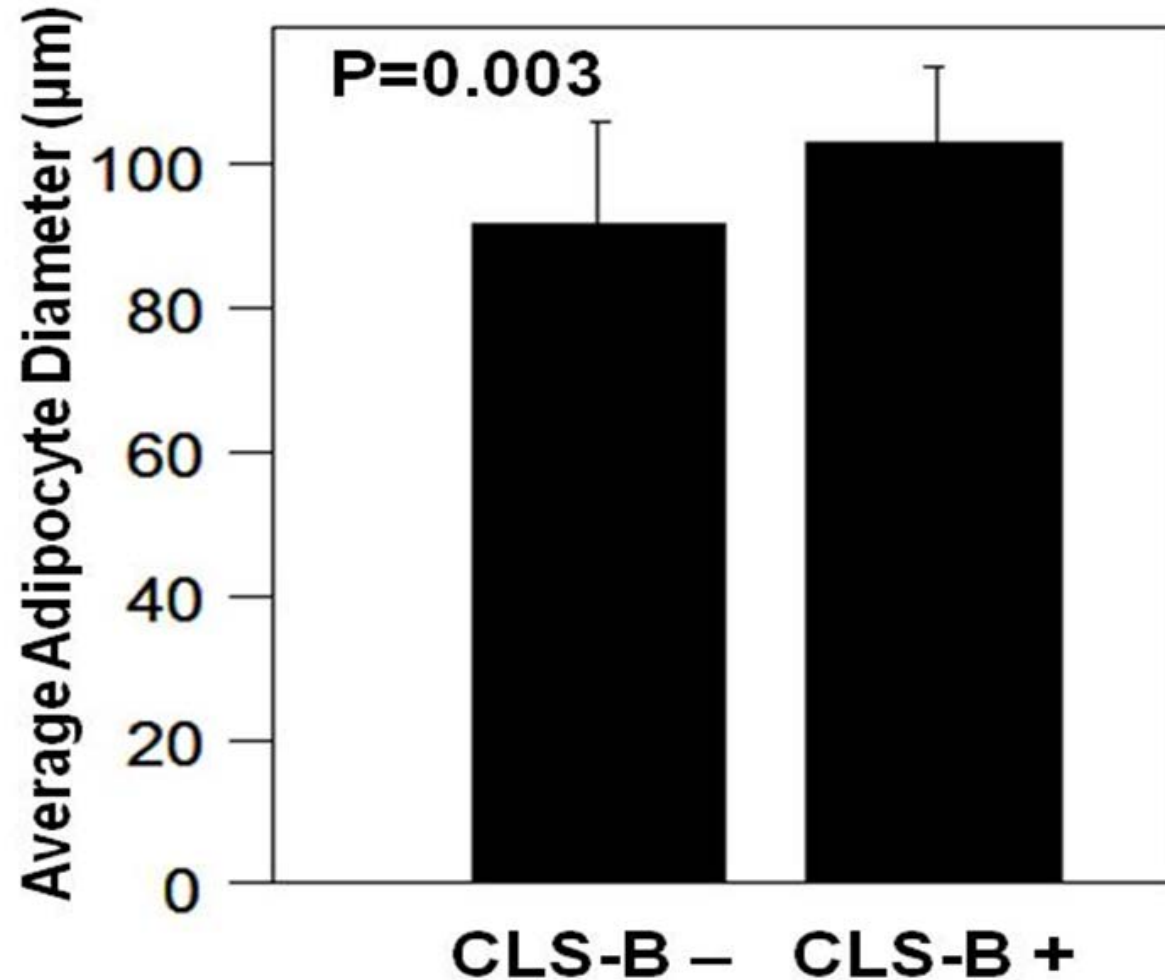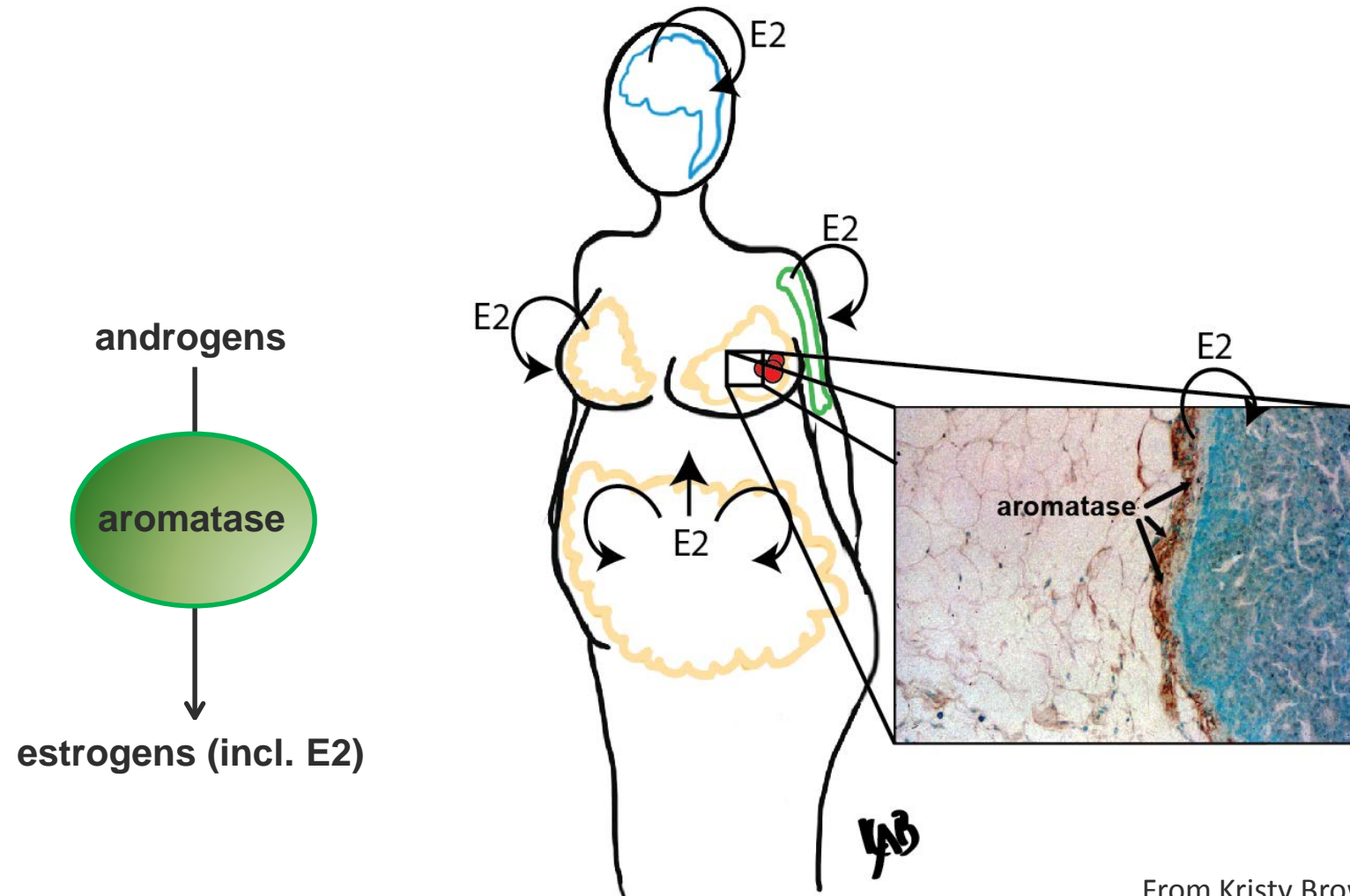# Breast WATi is a/w Elevated hsCRP, IL-6, Insulin and Glucose
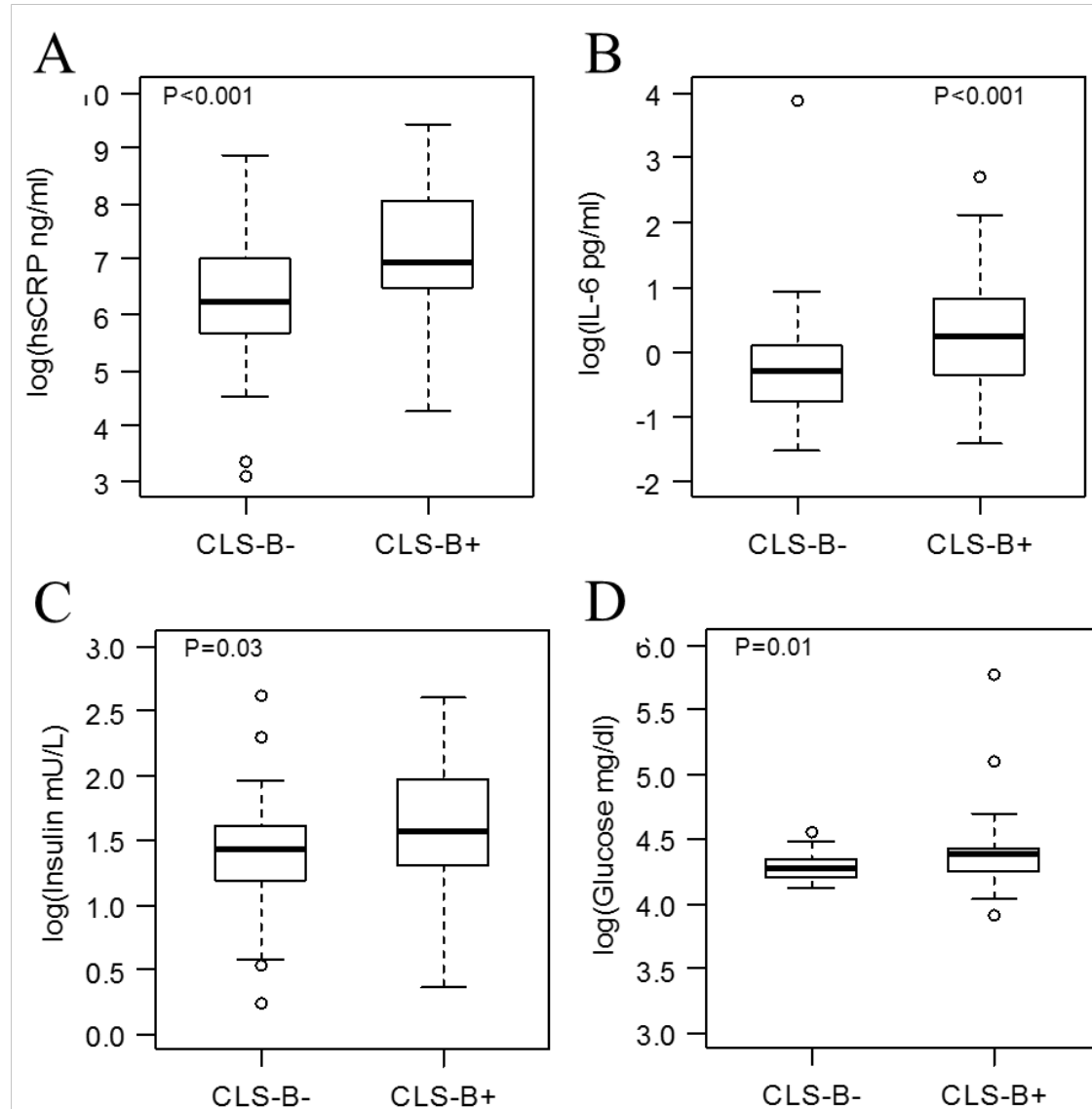
Breast WAT Inflammation Occurs in Women with Normal BMI
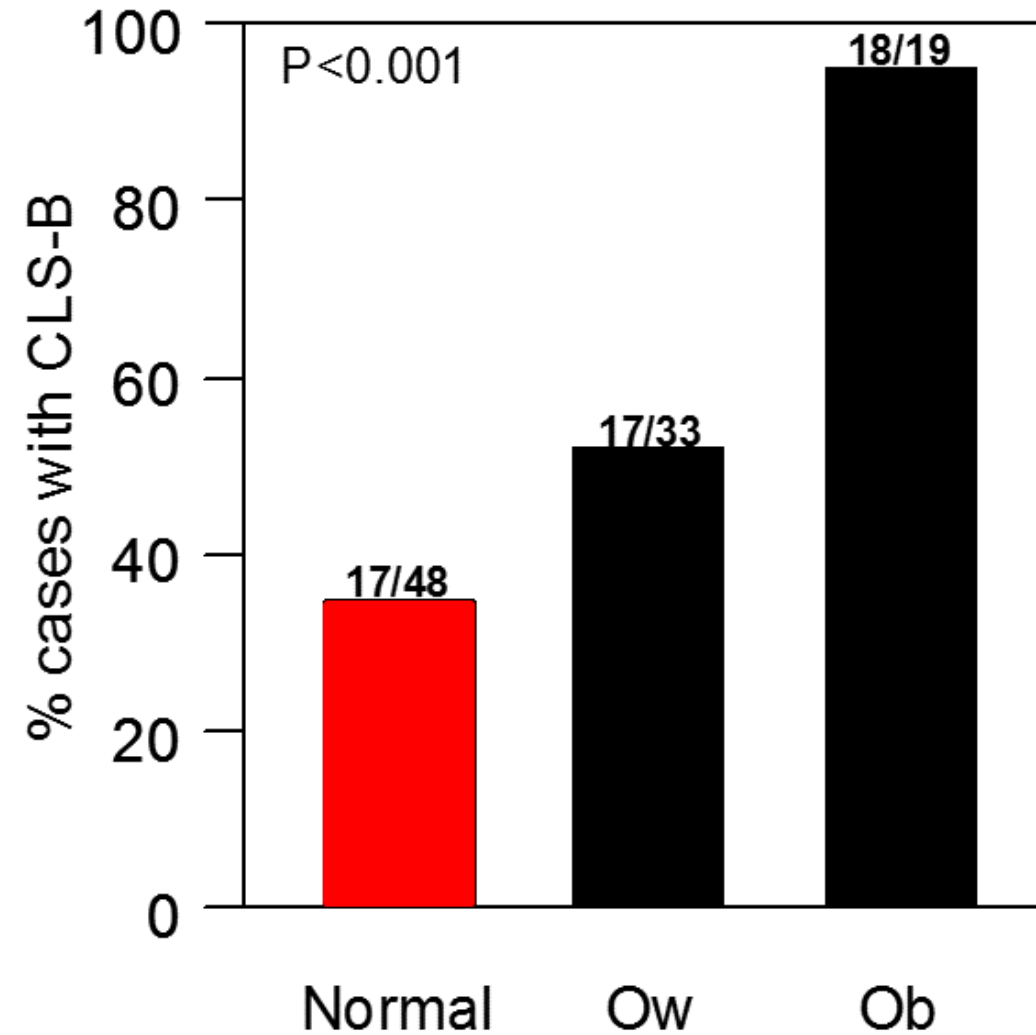
WAT Inflammation is a/w Breast Adipocyte Hypertrophy in Normal BMI Women
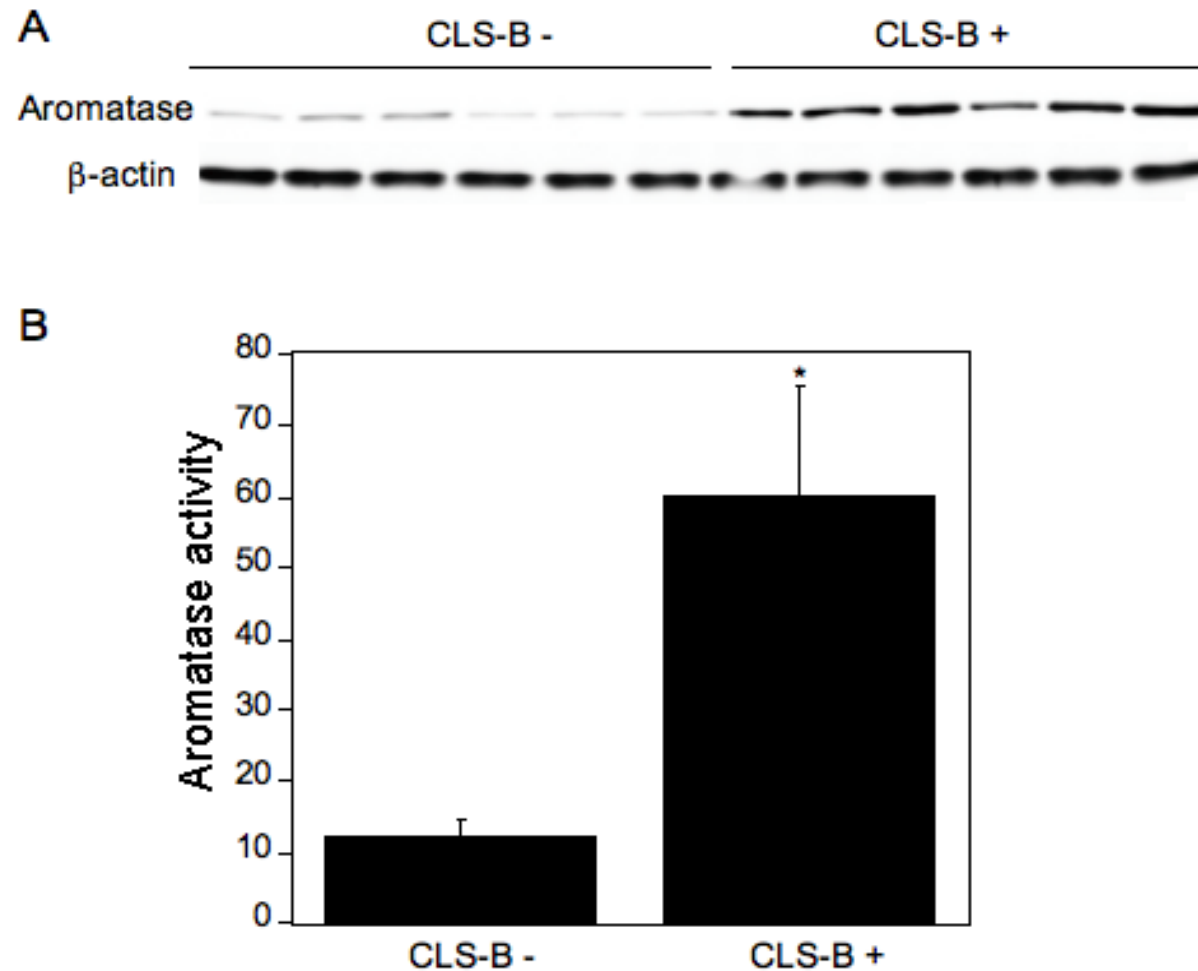
Aromatase and the Local Production of Estrogens

From Kristy Brown

Aromatase Protein Levels and Activity are Increased in the Inflamed Breast Tissue of Normal Sized Women

Iyengar NM et al. Cancer Prev Res 2017

RESEARCH ARTICLE

Open Access

Relationship between crown-like structures and sex-steroid hormones in breast adipose tissue and serum among postmenopausal breast cancer patients

Maeve Mullooly[1,2*], Hannah P. Yang[1], Roni T. Falk[1], Sarah J. Nyante[3], Renata Cora[4], Ruth M. Pfeiffer[1], Derek C. Radisky[5], Daniel W. Visscher[6], Lynn C. Hartmann[6], Jodi M. Carter[6], Amy C. Degnim[6], Frank Z. Stanczyk[7], Jonine D. Figueroa[8], Montserrat Garcia-Closas[1], Jolanta Lissowska[9], Melissa A. Troester[10], Stephen M. Hewitt[11], Louise A. Brinton[1], Mark E. Sherman[12†] and Gretchen L. Gierach[1†]

Blood Variables Stratified by Inflammation

Variables	CLS-B - (n=44)	CLS-B + (n=28)	p-value*
hsCRP (ng/mL)			
Median (range)	0.5 (0.02,7.06)	0.67 (0.07,7.5)	**0.05†**
IL-6 (pg/mL)			
Median (range)	0.83 (0.22,48.79)	1.03 (0.24,15)	0.26†
Leptin (pg/mL)			
Median (range)	6.29 (0.72,21.08)	9.56 (3.43,25.32)	**0.01†**
Adiponectin (µg/mL)			
Median (range)	13.37 (1.99,23.05)	10.45 (3.02,23.85)	0.33†
Glucose (mg/dL)			
Median (range)	69.5 (54,95.15)	80.67 (33.7,105.6)	0.19†
Insulin (mU/L)			
Median (range)	3.74 (1.26,10.19)	4.99 (1.38,9.18)	**0.02†**
HOMA2 IR			
Median (range)	0.4 (0.14,1.1)	0.55 (0.12,1)	**0.004**
Total Cholesterol (mg/dL)			
Median (range)	192 (129,284)	195 (152,285)	0.54
LDL Cholesterol (mg/mL)			
Median (range)	103 (38,183)	108.2 (66.2,184.8)	0.41
HDL Cholesterol (mg/dL)			
Median (range)	74 (48,120)	68 (41,101)	0.15
Triglycerides (mg/dL)			
Median (range)	61.5 (29,136)	68.5 (39,225)	**0.002**

* P-values were obtained using linear regression adjusted for potential cohort differences.
† Log-transformed data were used to ensure the underlying model assumptions were met.

Iyengar NM et al. Cancer Prev Res 2017

Elevated Insulin Levels Are a/w Increased Breast Cancer Risk in Normal Weight Women

Table 2. The associations of incident postmenopausal breast cancer risk with metabolic health defined by HOMA-IR or insulin levels, stratified by BMI category

BMI category	N (cases/ subcohort)	Age-adjusted HR (95% CI)	P	Multivariate HR[a] (95% CI)	P
HOMA-IR–based definition of metabolic health					
Normal weight (<25 kg/m^2)					
Metabolically healthy[b]	113/356	1.00 (Referent)		1.00 (Referent)	
Metabolically unhealthy[c]	18/182	1.68 (0.85–3.33)	0.13	1.80 (0.88–3.70)	0.11
Overweight (≥25 kg/m^2)					
Metabolically healthy[b]	87/339	0.93 (0.64–1.34)	0.68	0.96 (0.64–1.42)	0.83
Metabolically unhealthy[c]	169/1238	1.60 (1.12–2.28)	0.01	1.76 (1.19–2.60)	0.005
Insulin-based definition of metabolic health					
Normal weight (<25 kg/m^2)					
Metabolically healthy[d]	108/352	1.00 (Referent)		1.00 (Referent)	
Metabolically unhealthy[e]	19/180	1.86 (0.95–3.65)	0.07	2.06 (1.01–4.22)	0.048
Overweight (≥25 kg/m^2)					
Metabolically healthy[d]	86/329	0.93 (0.64–1.35)	0.71	0.96 (0.64–1.42)	0.82
Metabolically unhealthy[e]	175/1250	1.86 (1.30–2.66)	0.001	2.01 (1.35–2.99)	0.001

Gunter MJ et al. Cancer Res. 2015

Conclusions

- WATi is a/w numerous changes in gene expression in the breast.
- WATi is a/w systemic changes that occur in the metabolic syndrome.
- WATi and its associated pathophysiology occur in a significant subset of normal BMI women.
- WATi is a potentially targetable process linking obesity to breast cancer.

CONTRIBUTORS

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