HORMONAL FACTORS IN OBESITY AND BREAST CANCER

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Breast Cancer

5 year survival

- Obese: 55%
- Non-Obese: 79.9% (recent study: 30% higher)

(Abe et al, 1976)

Obesity and Cancer

Estrogen Dependent Cancers

- **Breast cancer**
- **Endometrial cancer**

- **Tumors express ER/PR**
- **Stimulated by estrogen**

Breast Cancer

- 70% patients menopausal
- Incidence increases with age
- ER levels increase in tumors
- Ovarian steroids decrease

Estrogen Synthesis/Production

- Postmenopause
- Ovarian cessation
- Conversion of adrenal androgens to estrogen
- Adipose tissue (abdomen and breast)
- Increase aromatase activity

Source of Estrogens

1. Ovaries
2. Peripheral aromatization
   - Adipose
   - Muscle
   - Liver
   - Breast tumors

Body Mass Index

- Endometrial Cancer
- Breast Cancer (ER+ & postmenopausal)

Steroid Biosynthesis

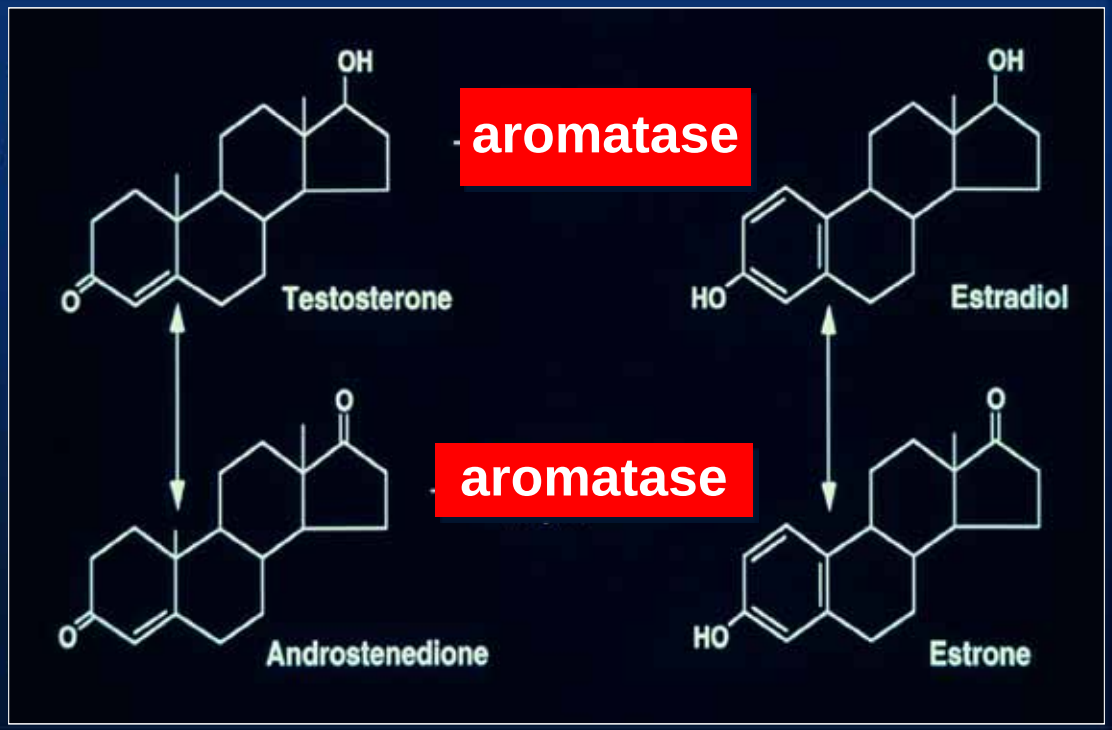
Cholesterol

Pregnenolone

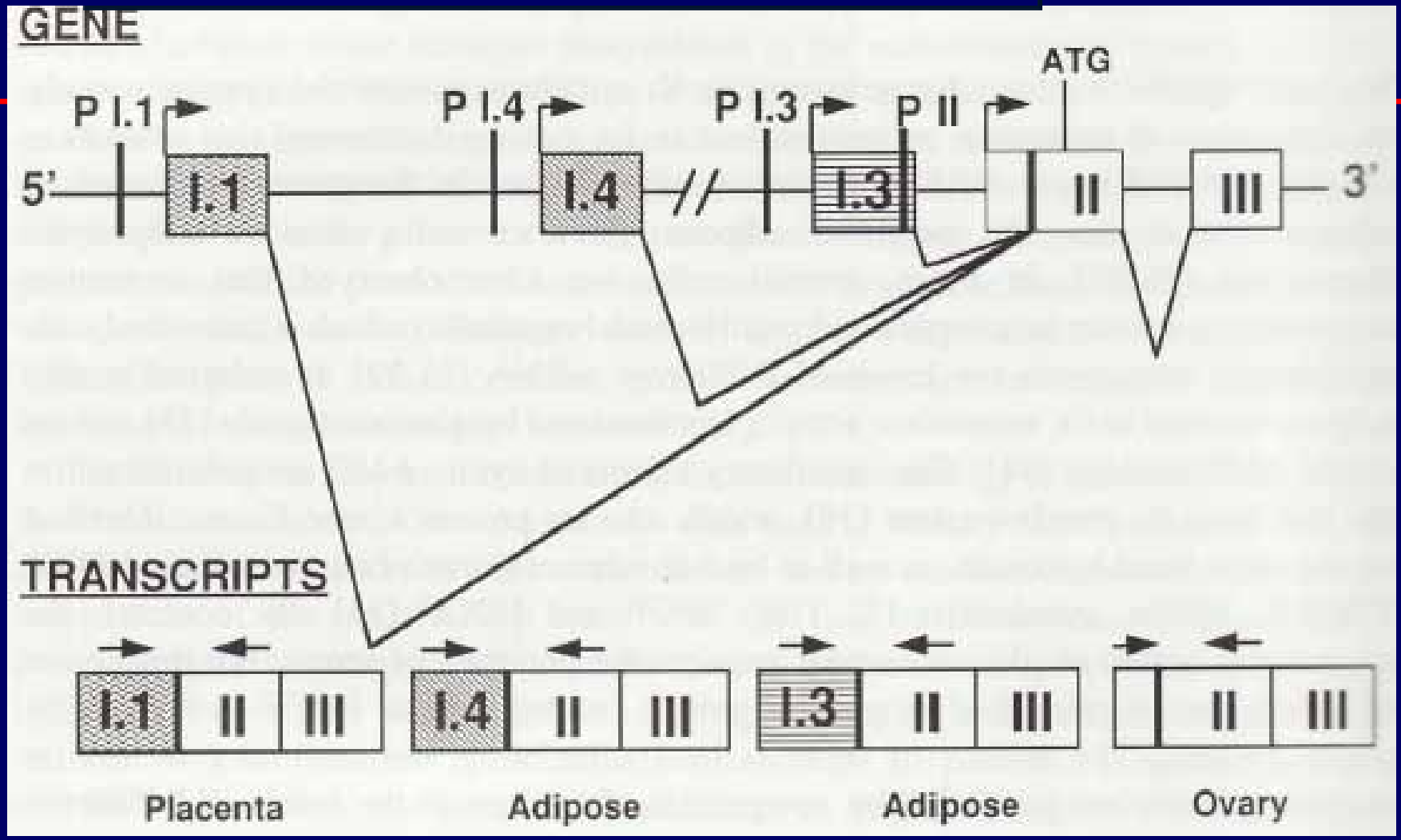
Progesterone

Aldosterone

Cortisol



Aromatase is regulated by multiple tissue specific promoters



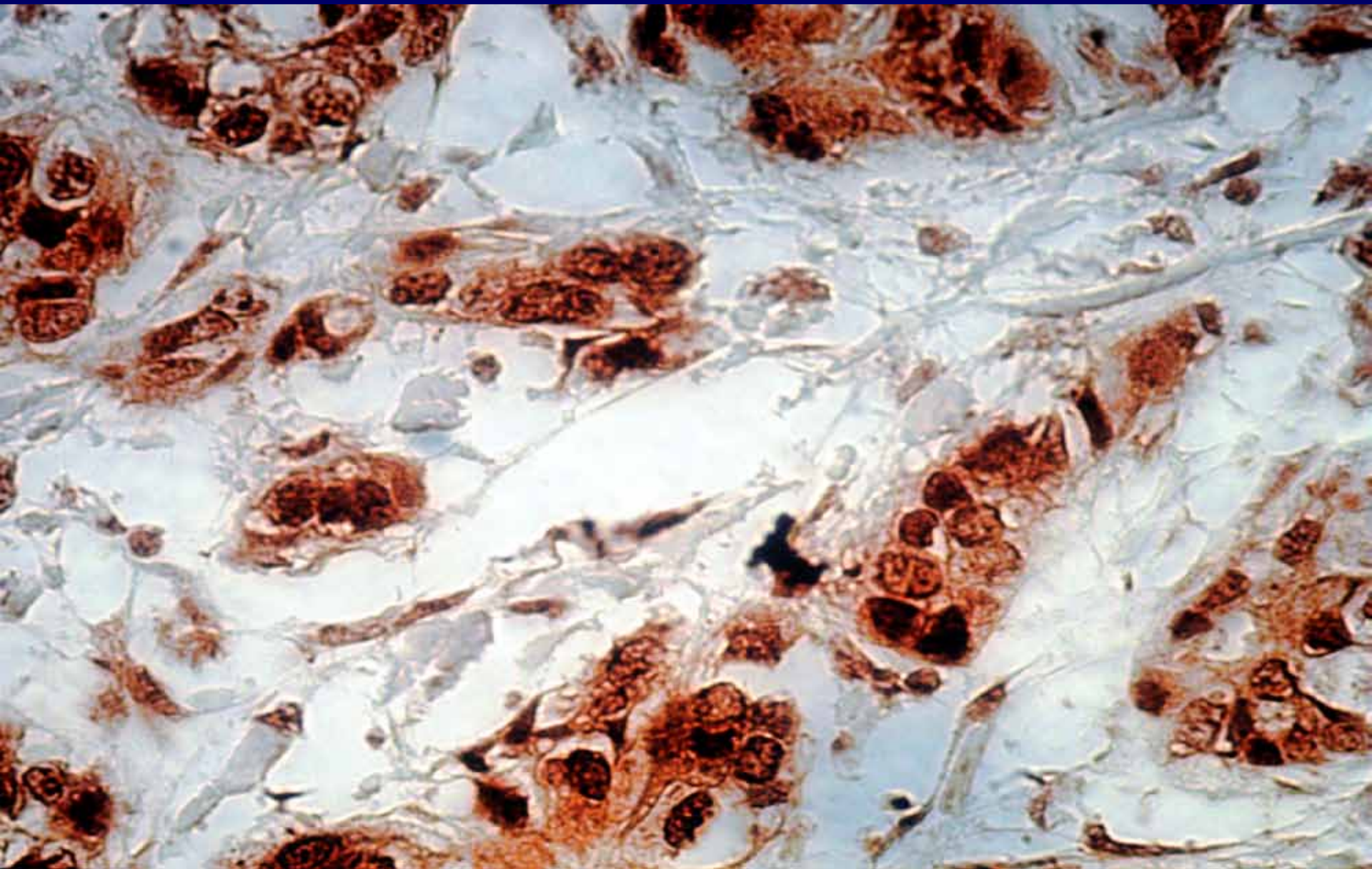
Simpson ER et al., 1981

Factors regulating aromatase

- FSH and LH gonadotropins
- Glucocorticoids
- Cytokines, IL-6
- PGE2
- cAMP

Simpson et al., 1981

Aromatase in Breast Tissue (Brodie et al., 2001)

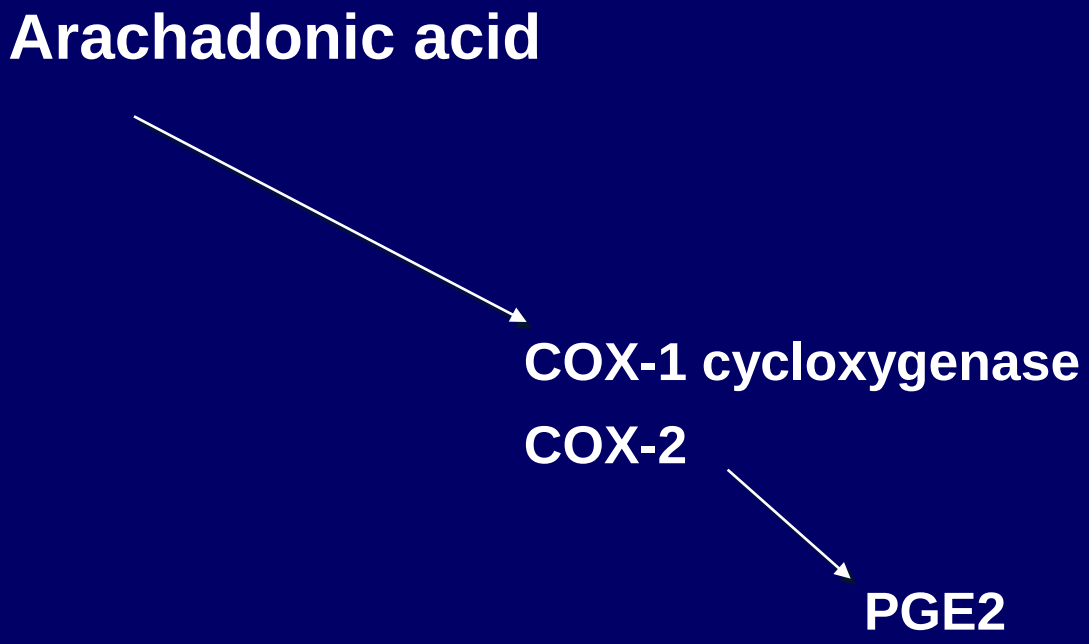


Aromatase Expression

Cell types:

- **Adipocytes**
- **Macrophages**
- **Endothelial cells**
- **Tumor cells**

Prostaglandin Biosynthesis



Relationship of Aromatase & COX-2 Expression in Tumors of Breast Cancer Patients (n=102)

COX-2	Aromatase
Positive	28.9 ± 1.3%
Negative	9.4 ± 1.6%

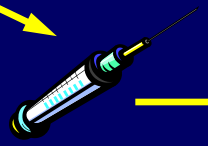
($p<0.001$)

Brodie et al., 2001

A Xenograft Model for Hormone Dependent Breast Cancer in Postmenopausal Patients

Aromatase-transfected ER+ MCF-7Ca (2.5×10^6 cells/site), s.c.

D4A (100 mg/day), s.c. Duration of the experiment



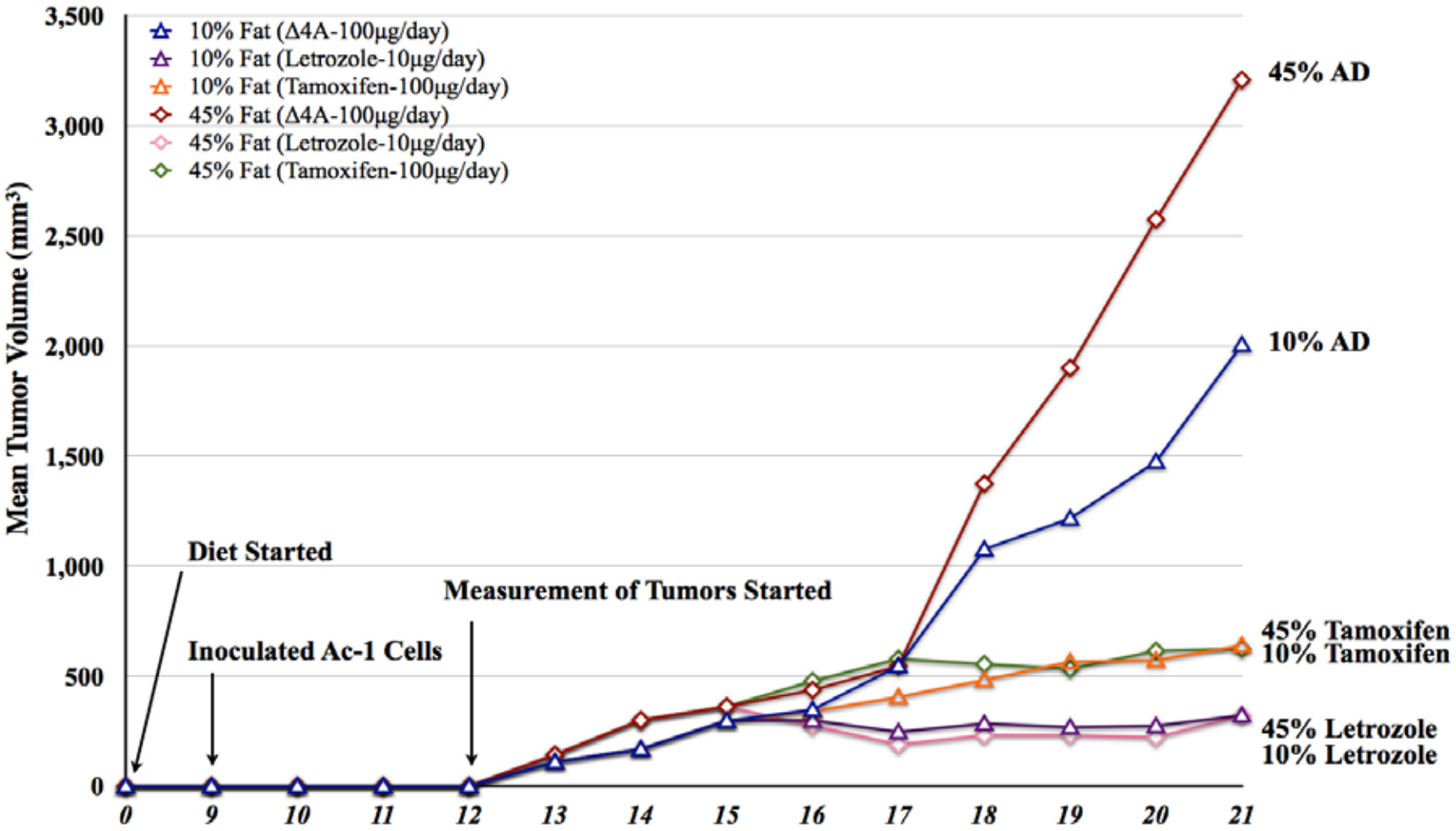
Ovariectomized

Estrogens are produced locally by the aromatization of D4A

TUMORS ARE SENSITIVE TO BOTH ANTIESTROGENS AND AROMATASE INHIBITORS

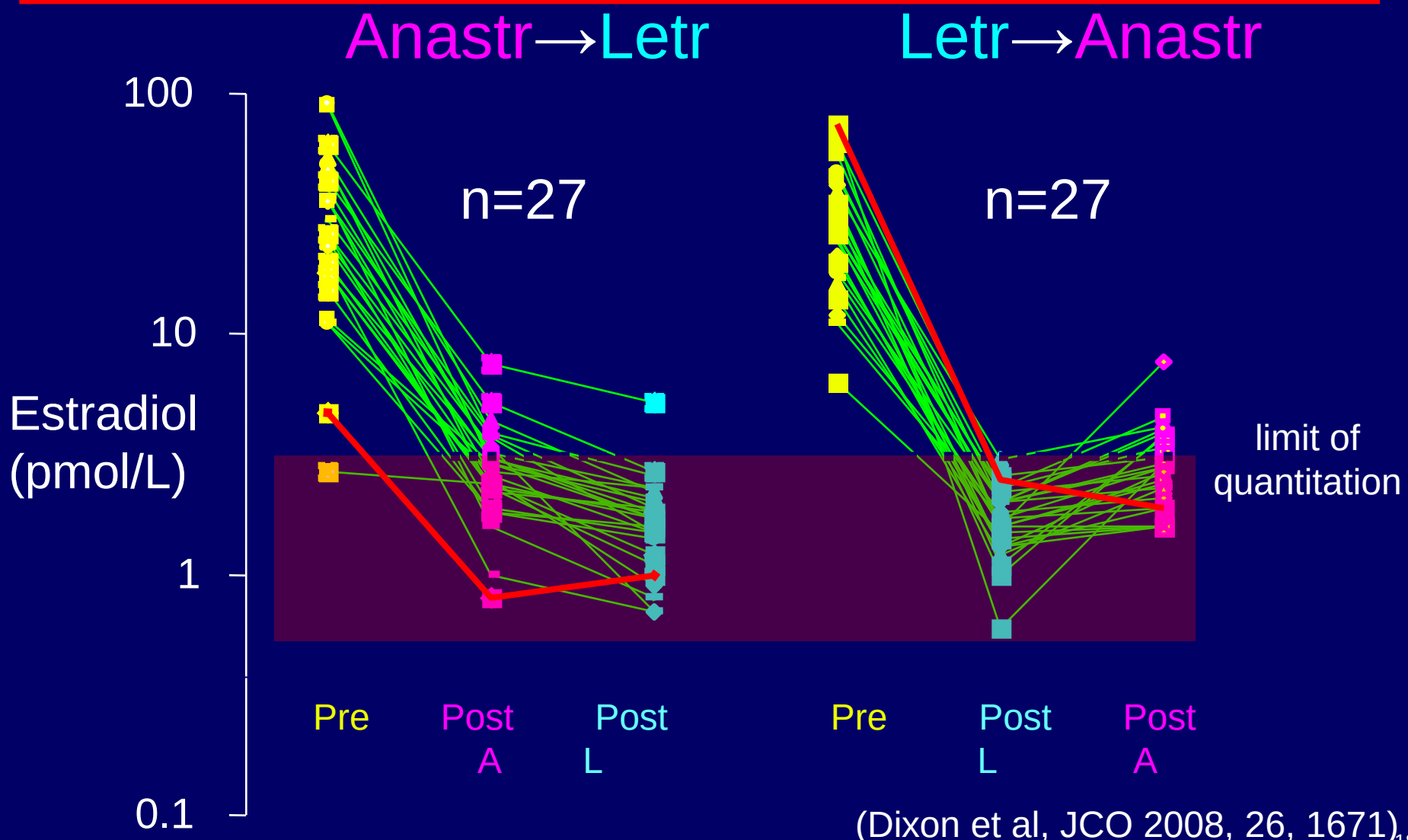
The Effect of Diet on Mouse Body Weight

The Effect of Diet on Growth of Tumors in Mouse Xenografts



Sabnis et al.

Estradiol suppression by anastrozole and letrozole



(Dixon et al, JCO 2008, 26, 1671)

Estradiol suppression by anastrozole and letrozole: subgroup analysis by BMI

	BMI				Spearman Rank Correlation	P-Value
	<25	26-30	31-35	>35	(95% Confidence Interval)	
Estradiol pmol/l						
Mean pre treatment (SEM)	20 (3.2)	26 (3.2)	39 (6.4)	55 (4.0)	0.57 (0.35 to 0.73)	<0.001
Mean post Anastrozole (SEM)	2.8 (0.33)	2.5 (0.22)	3.2 (0.43)	4.2 (0.95)	0.21 (0.07 to 0.46)	0.14
Mean post Letrozole (SEM)	1.4 (0.16)	1.4 (0.11)	2.0 (0.15)	2.4 (0.78)	0.35 (0.08 to 0.57)	0.011
Mean Anastrozole/Letrozole	2.4	1.8	1.6	2.3		

Dowsett et al, unpublished)

ATAC (Anastrozole)

Recurrences:

Pre and postmenopausal obese women:

AI Dose/Weight:

Not adjusted	**Adjusted**
increased	no change

Breast Cancer

Risk Recurrence: 1502 premenopausal patients

ER+ Node +

Obese vs. Normal

- 40% higher risk recurrence
- 50% increased risk of death

ER- Node +

Obese vs. Normal

- No difference.

Breast Cancer

Risk reduction in 4560 women

Aromatase inhibitor for 35 months

	Invasive cancers
Placebo	32
Exemestane	11

Goss et al., 2011

Summary

Obesity:

- **Breast and endometrial cancer**
- **Reduced survival**
- **Estrogen levels correlate with BMI**
- **Increased cancer recurrence**
- **Requires dose/BMI adjustment in AI treatment.**

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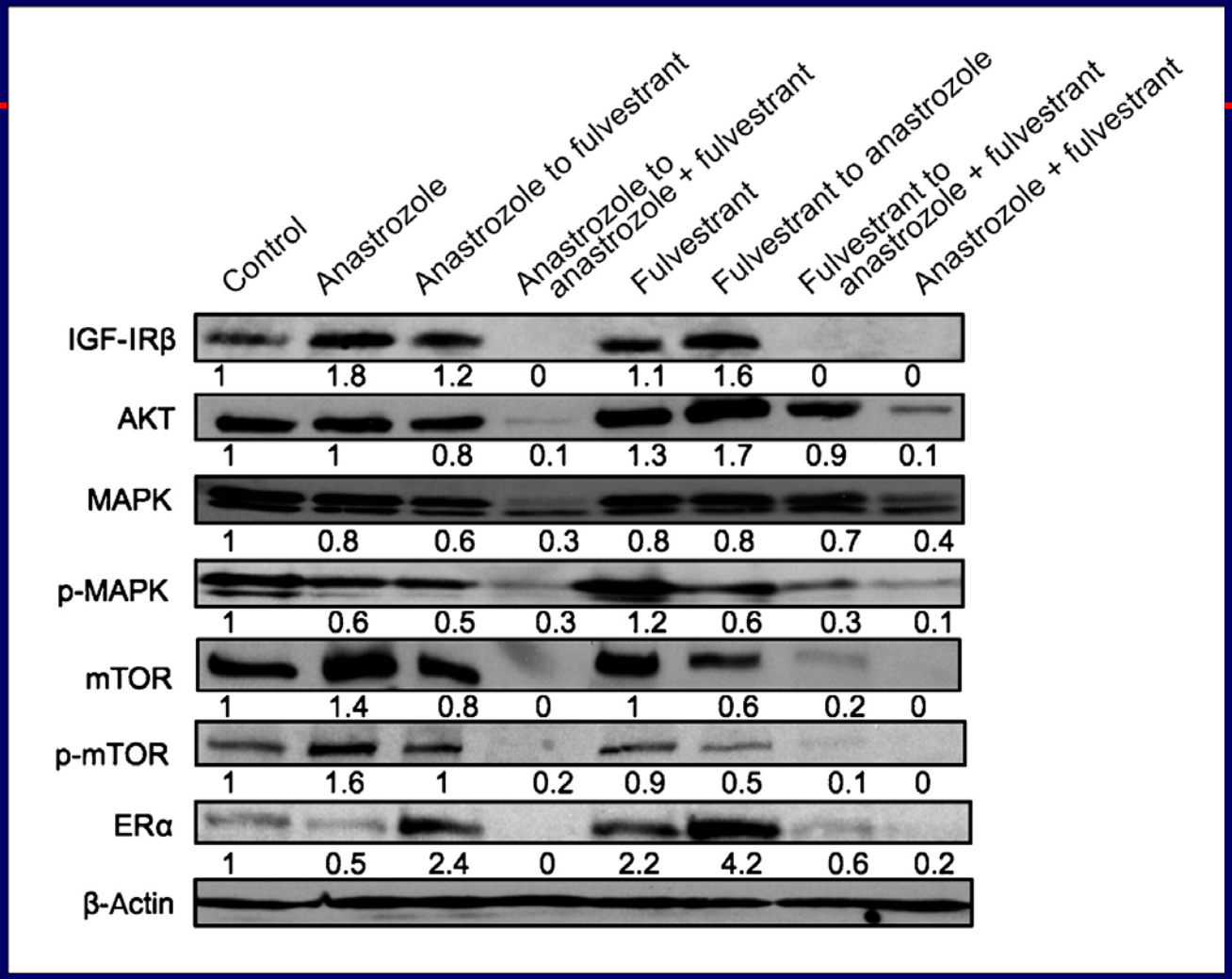
ÿ Mitch Dowsett

Effect of anastrozole and fulvestrant alone, in sequence, or in combination on tumoral signaling transduction proteins.

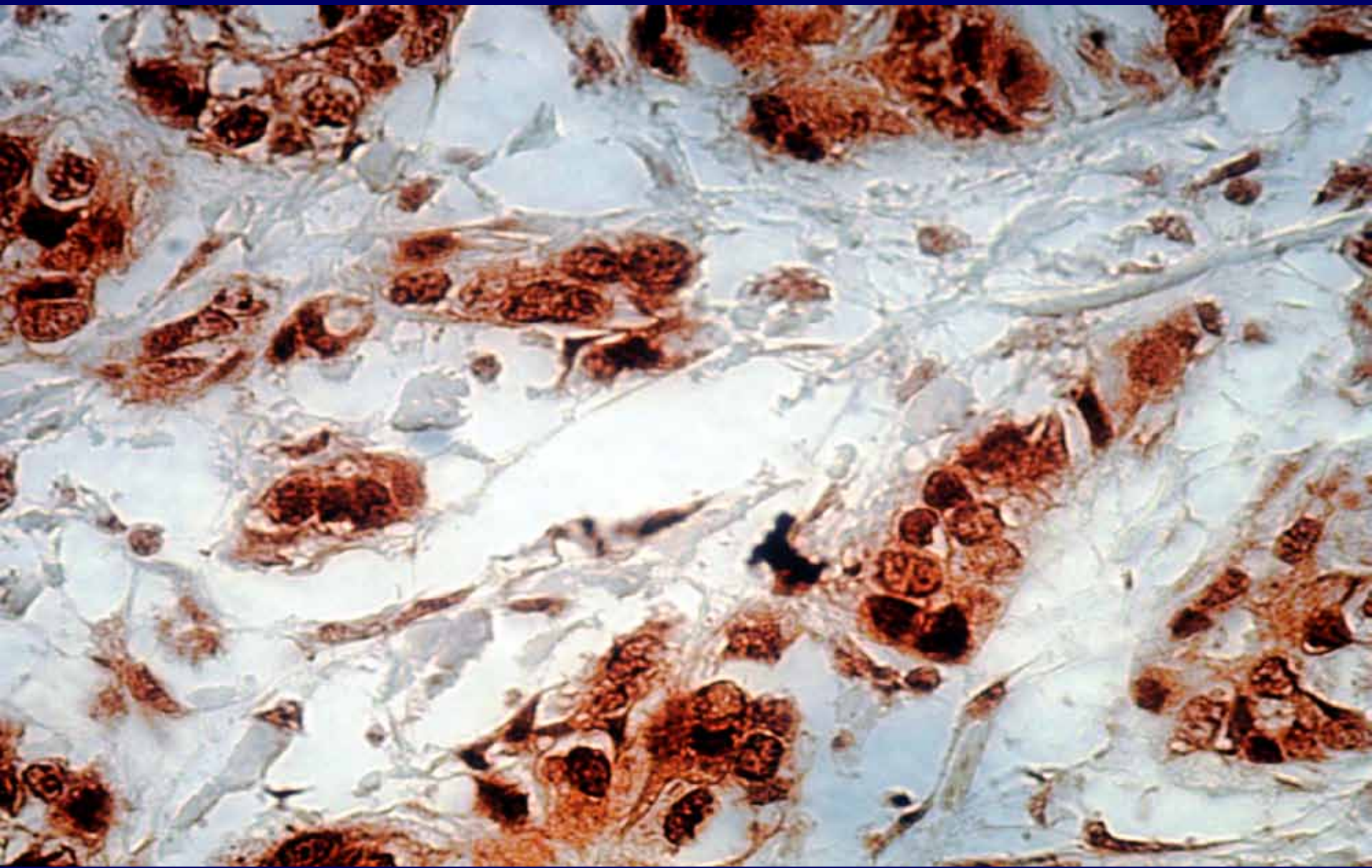


Macedo L F et al. Cancer Res 2008;68:3516-3522

Body Mass Index

- Endometrial Cancer
- Breast Cancer (ER+ & postmenopausal)

Aromatase in Breast Tissue



MAPK-signaling pathway is activated in LTLT-Ca cells