Breast Cancer 101: The New Basics

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1/29/2010

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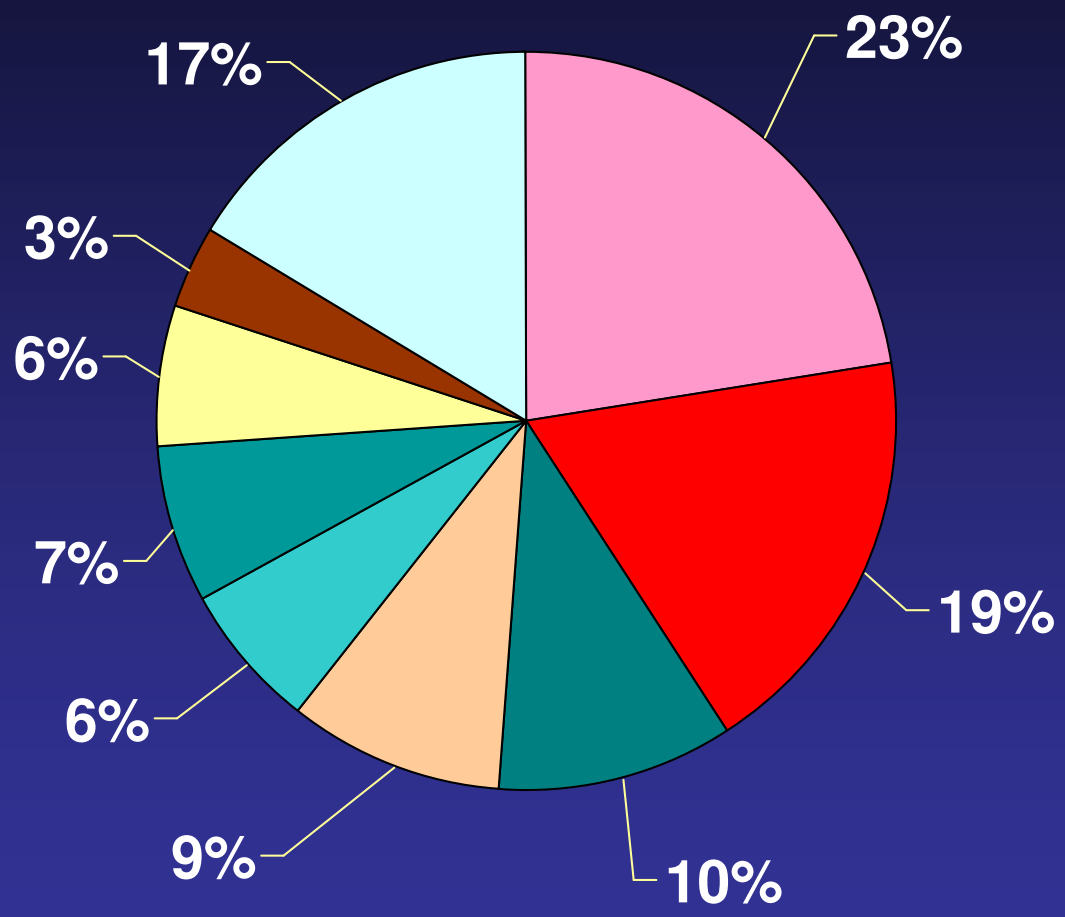
10.5 million people with cancer in the U.S.



- Female Breast
- Prostate
- Colorectal
- Gynecologic
- Other GU (Bladder & Testis)
- Hematologic (HD, NHL, Leukemia)
- Melanoma
- Lung
- Other

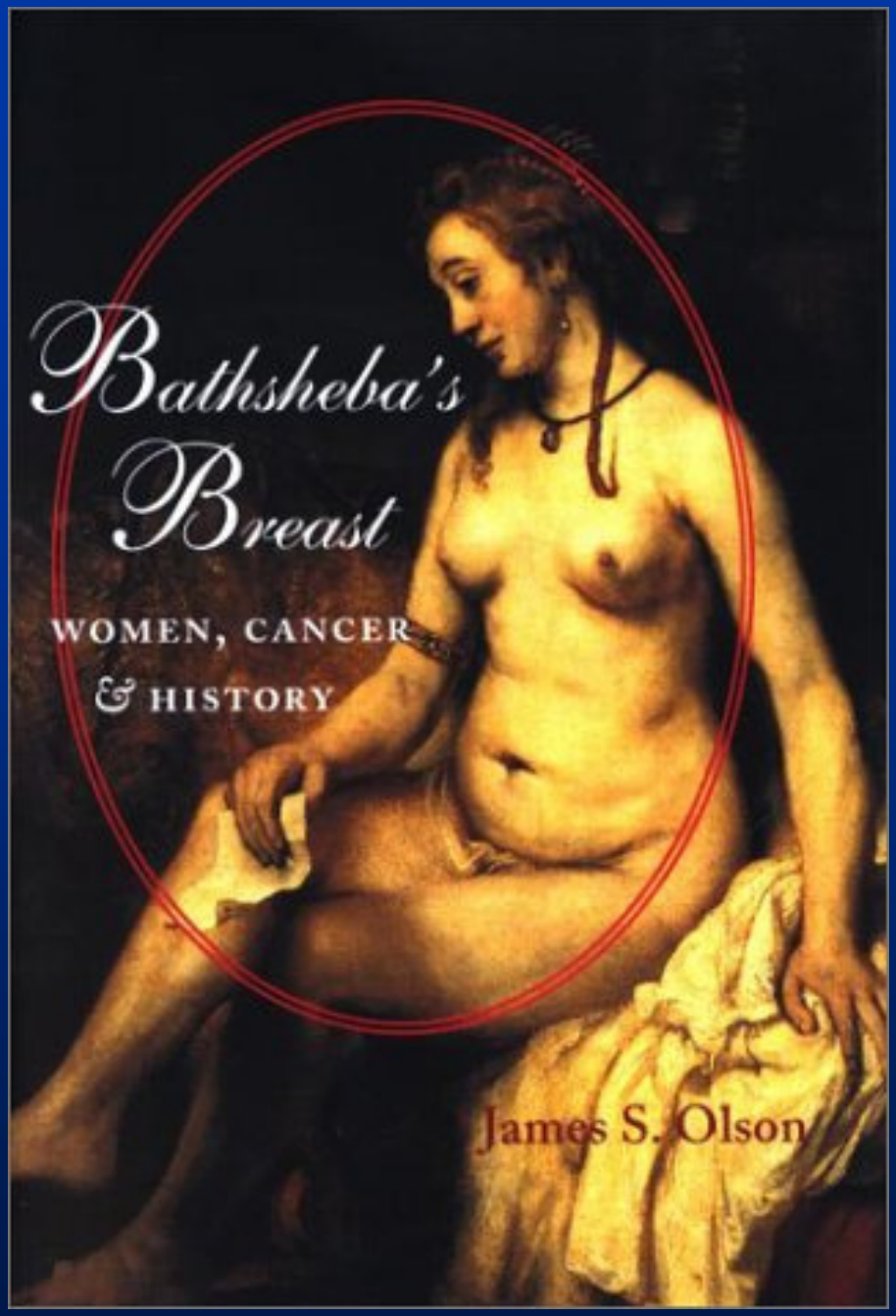
•Data source: 2005 Submission. U.S. Estimated Prevalence counts were estimated by applying U.S. populations to SEER 9 and historical Connecticut Limited Duration Prevalence proportions and adjusted to represent complete prevalence. Populations from January 2003 were based on the average of the July 2002 and July 2003 population estimates from the U.S. Bureau of Census.

Overview

- History
- Causes
- Pathophysiology
- Types and Subtypes
- Treatment Overview
- Systemic Therapy
- On the Horizon

Ancient breast cancer

- 3000-1500 BC "**Edwin Smith**" Papyrus, describes 8 cases of tumors or ulcers of the breast. The document said there is no treatment and recommended cauterization (the fire drill) as a palliative measure.

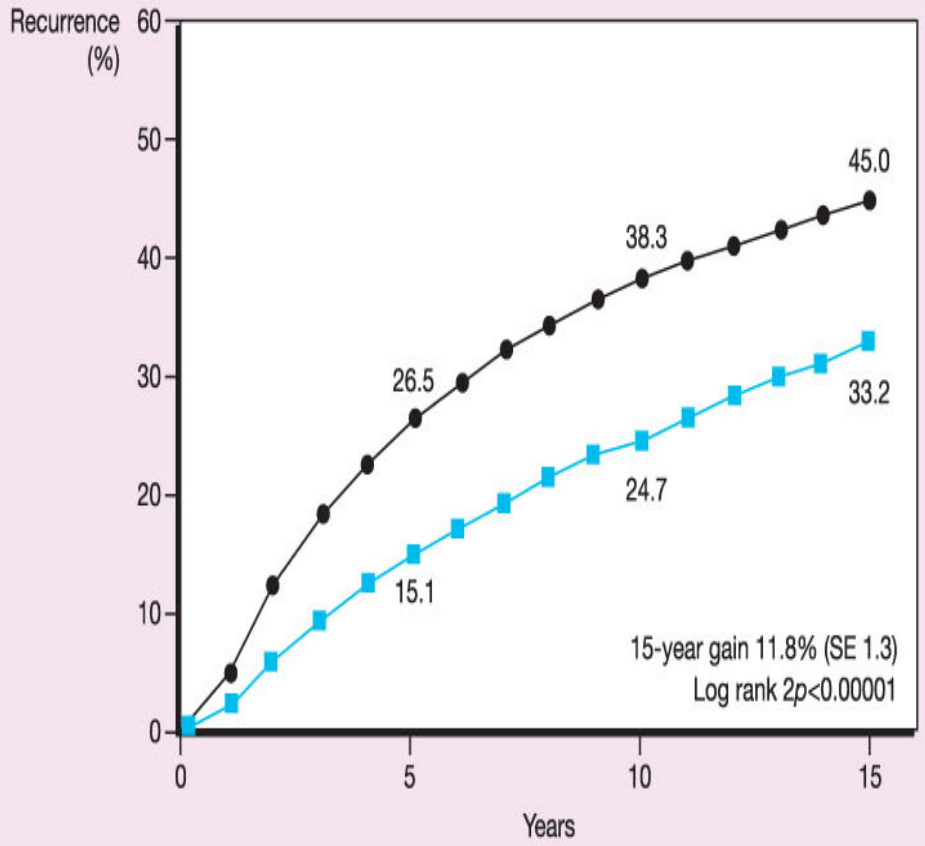


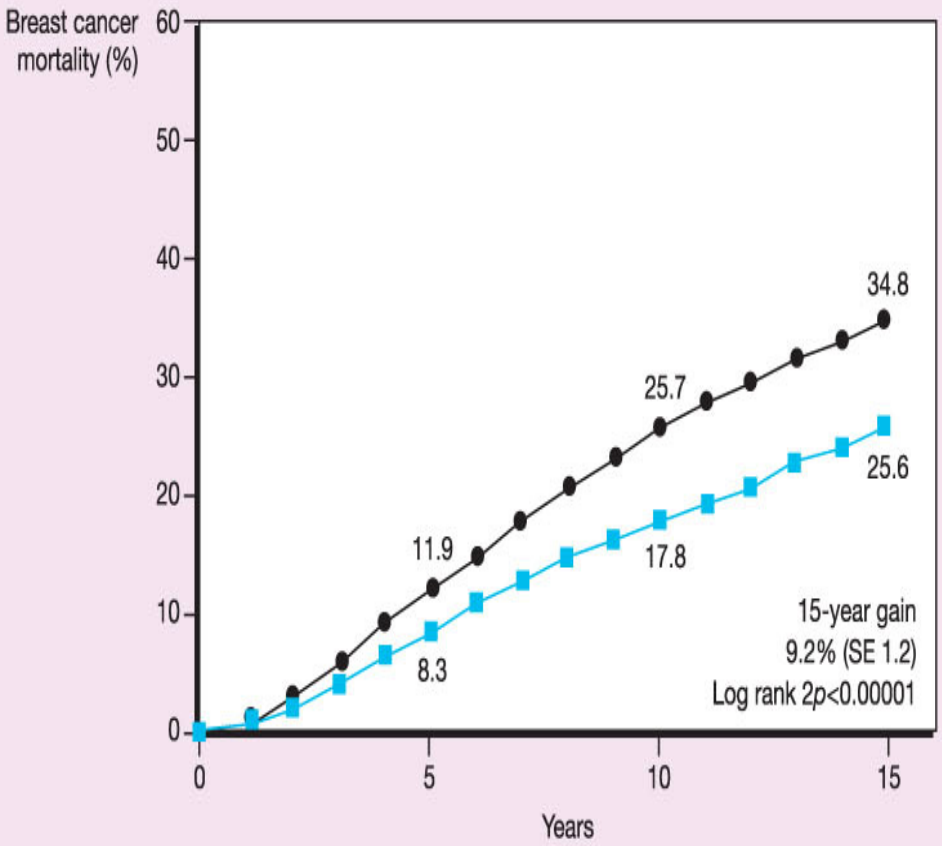
Rembrandt 1654

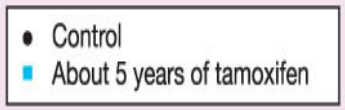
The Nun Link

- **1700s** Bernardino Ramazzini, the Italian founder of occupational medicine, recognized one female occupation whose members were far more likely to die from breast cancer than any other - nuns.

About 5 years of tamoxifen treatment versus no tamoxifen treatment: 15-year probabilities of recurrence and breast cancer mortality







•Participants (n=10,386) had either oestrogen receptor (ER)-positive or ER-unknown disease: 20% ER-unknown, 30% node-positive. Error bars are ±1SE.

•Reproduced with permission from the EBCTCG (2005).

5 year survival (%) in 2000

	•1974-1976	•1983-1985	•1995-2000
• All sites	50	53	64
• Breast (female)	75	78	88
• Colon	50	58	63
• Leukemia	34	41	46
• Lung and bronchus	13	14	15
• Ovary	37	41	44†
• Pancreas	3	3	4
• Prostate	67	75	99

•*5-year relative survival rates based on follow up of patients through 2001.
•†Recent changes in classification of ovarian cancer have affected 1995-2000 survival rates
•Source: Surveillance, Epidemiology, and End Results Program, 1975-2001, Division of Cancer Control and
•Population Sciences, National Cancer Institute, 2004.

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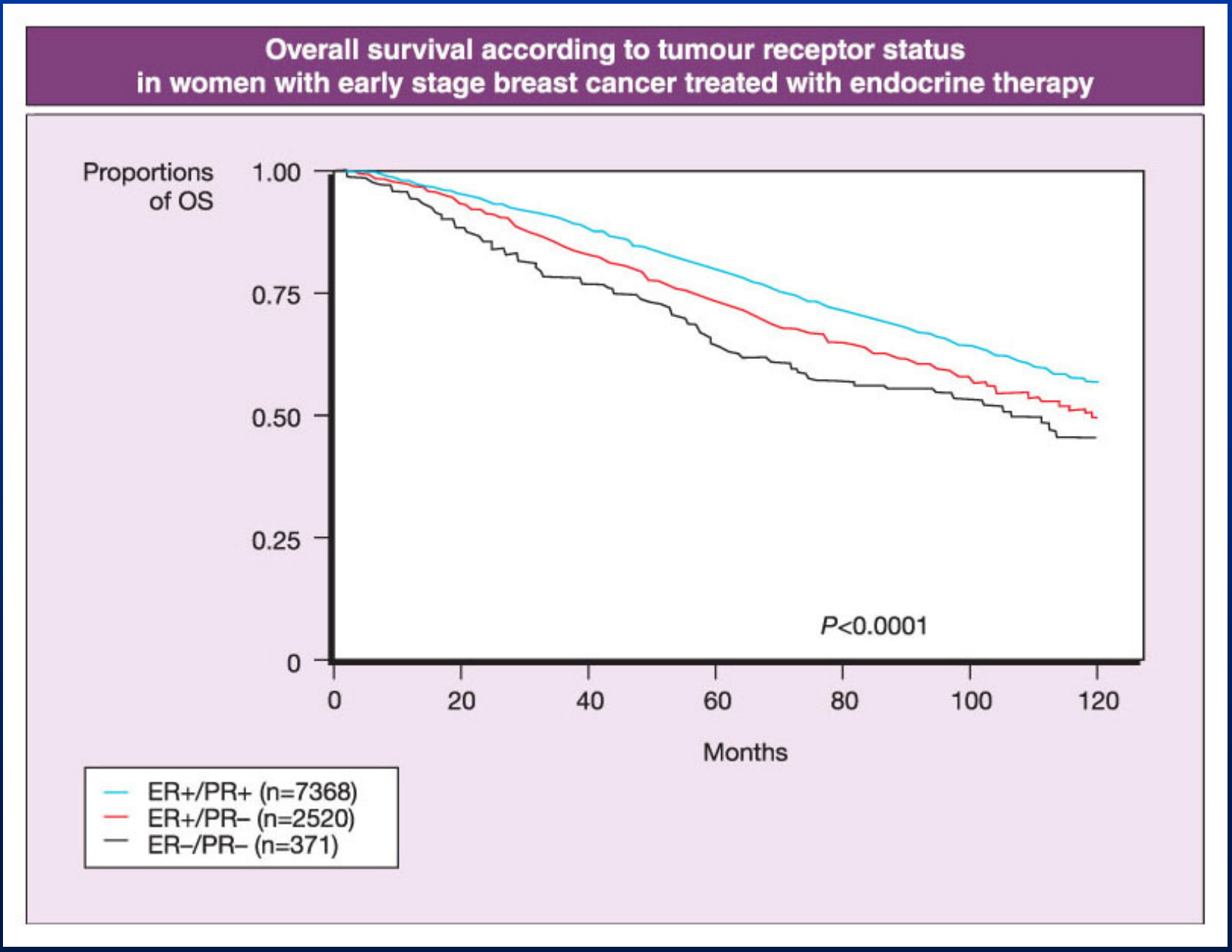
But what about 10-yr survival?



•Cui *et al.* (2005).

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Non-Modifiable Risk Factors for BC

- Gender
- Aging
- Genetics
- Family Hx of BC
- Personal History of BC
- Race
- Abnormal Breast Biopsy
- Previous Chest Radiation for Hodgkin's Lymphoma
- Family history of Ovarian cancer
- Personal history of ovarian cancer
- Use of Diethylstilbestrol

Modifiable Risk Factors for BC

Factors With Controversial, and Unproven Risk

- **Nulliparous**
- **Oral Contraceptive Use**
- **Hormone Replacement Therapy**
- **Breast Feeding**
- **Alcohol intake**
- **Obesity / High Fat Diet**
- **Physical Activity**
- **High breast density**
- **Radiation exposure**

- Antiperspirants
- Underwire Bra
- Breast Implants
- Tobacco Smoke
- Environmental Pollutants
- Night Work / Melatonin

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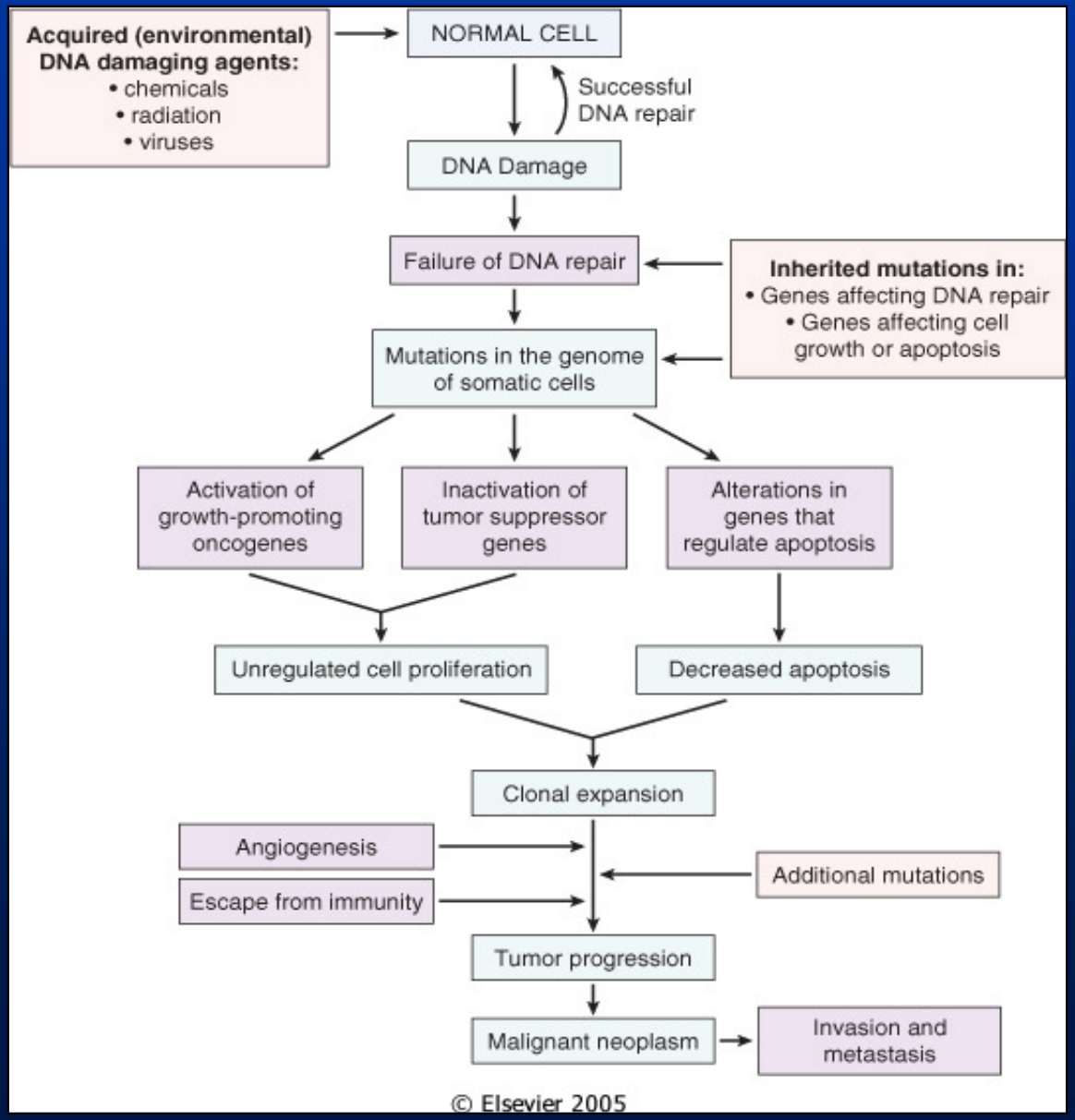
If we look in a textbook…



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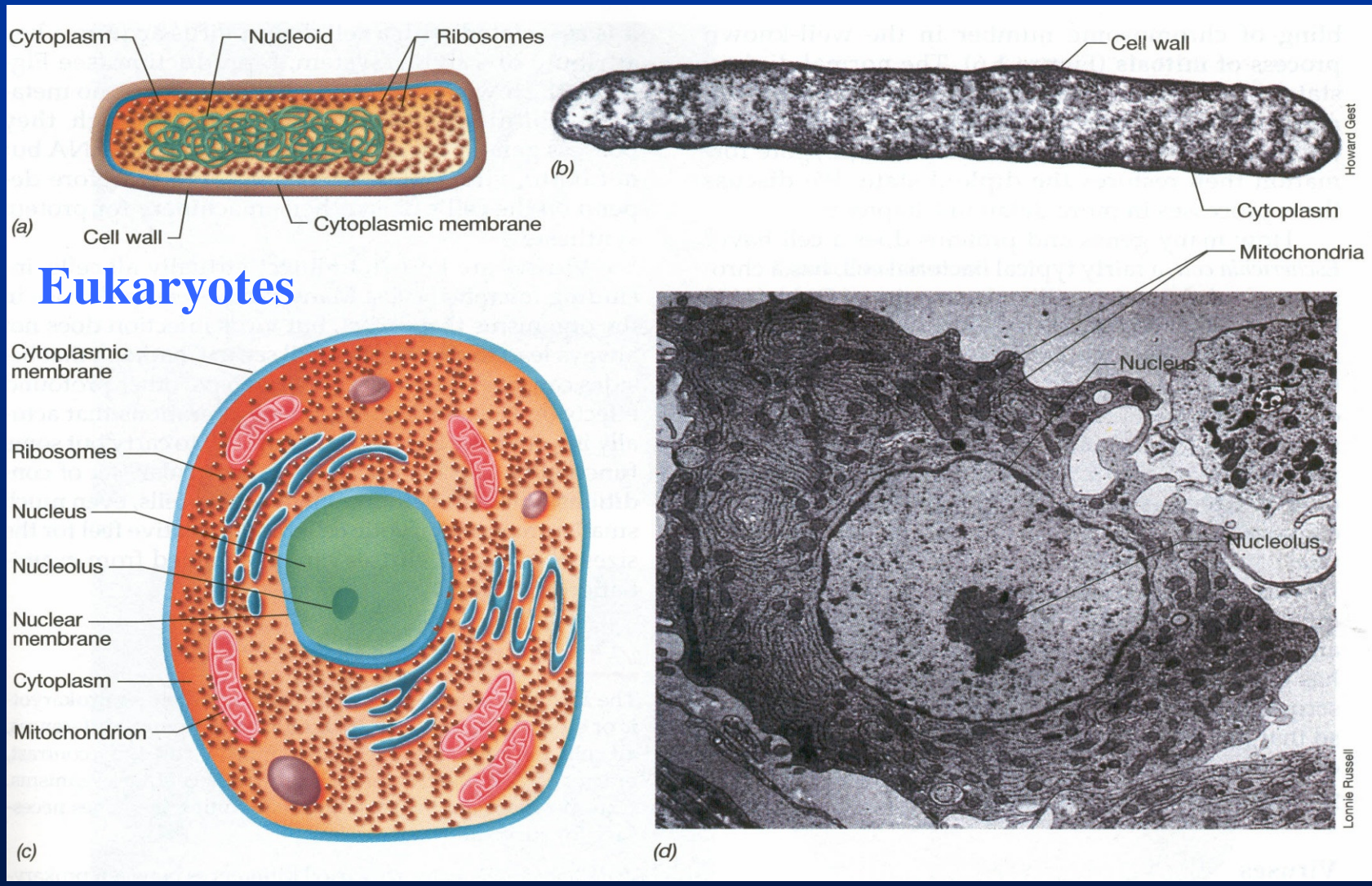
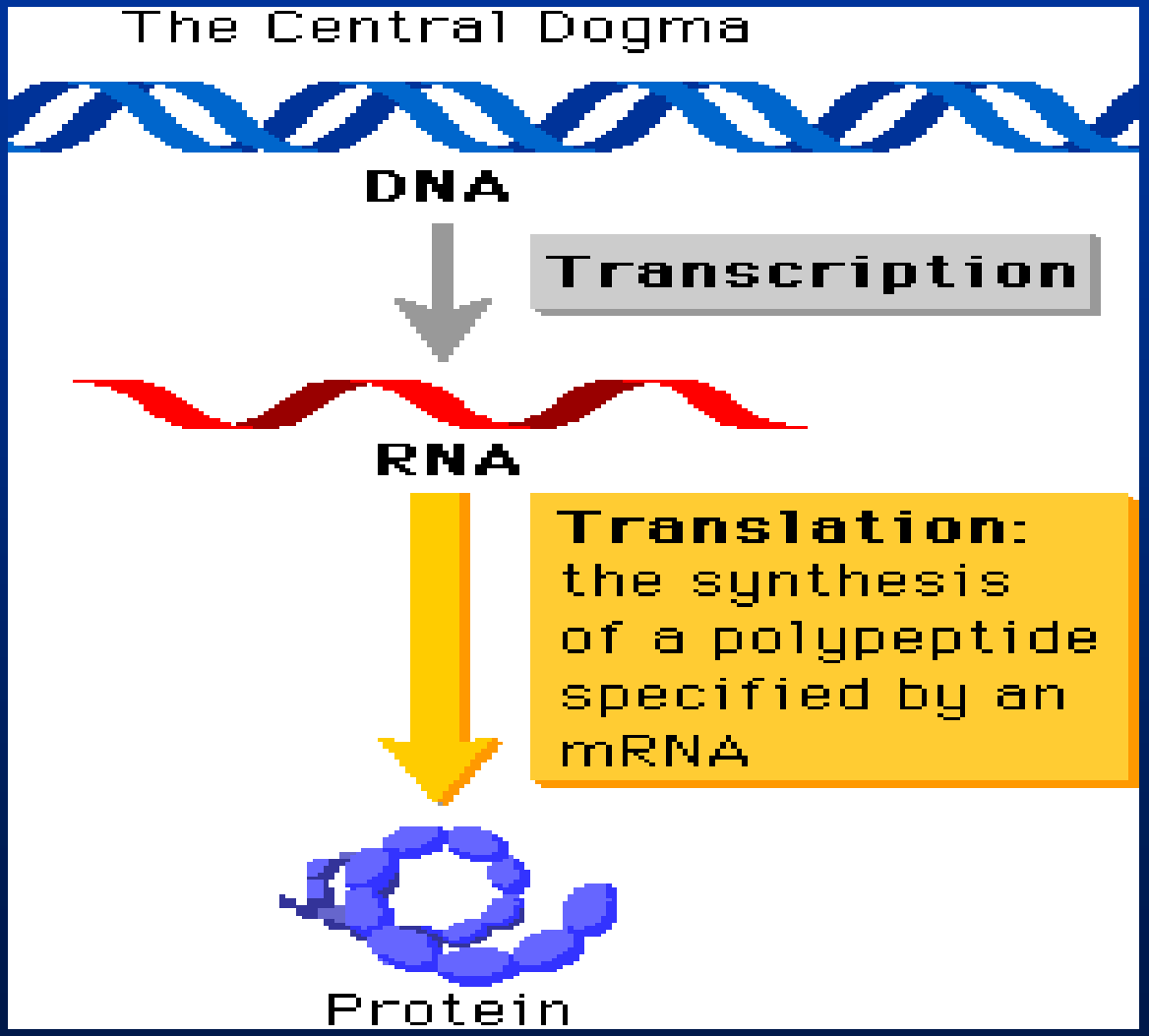
The Basics: Cell Organization

Prokaryotes



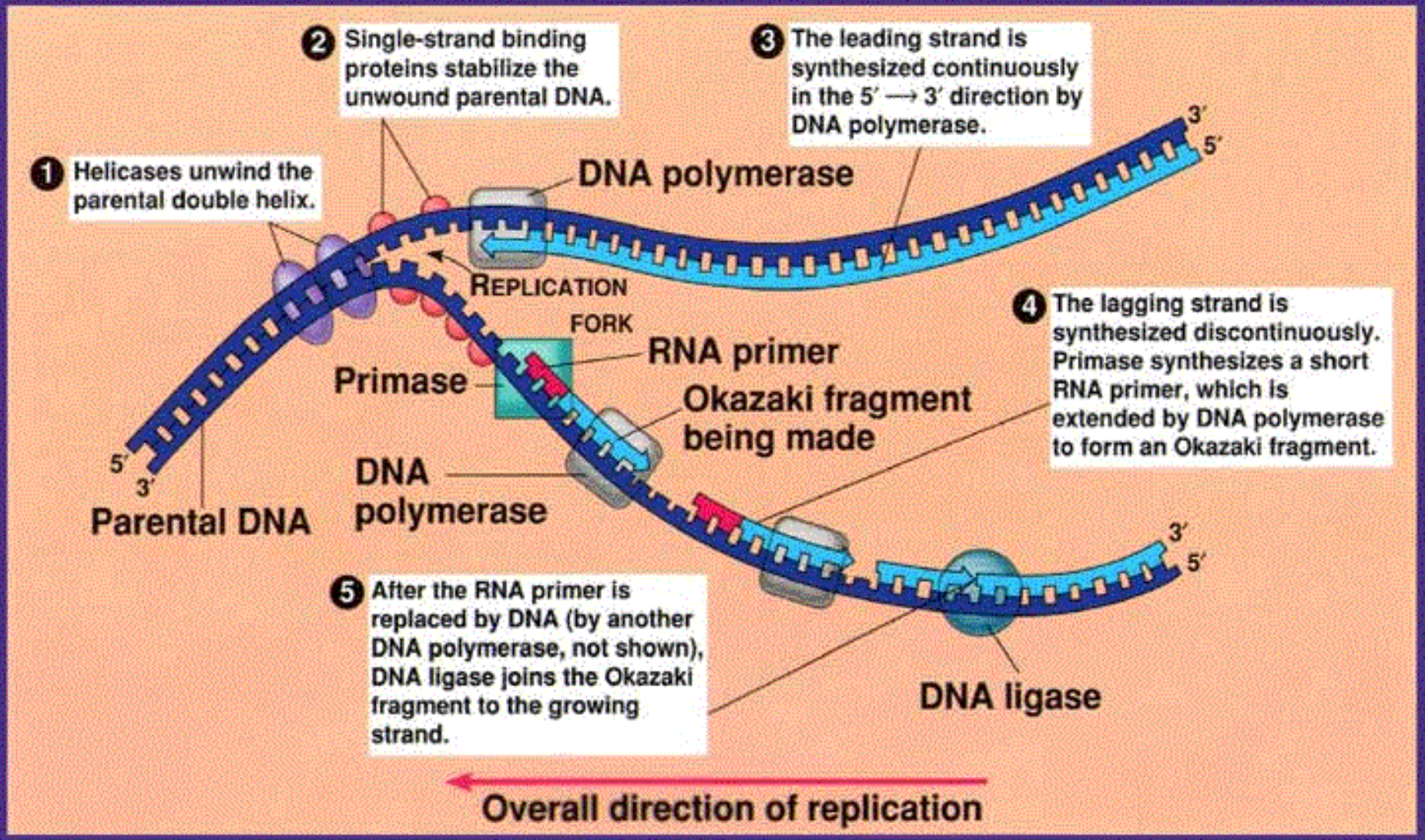
Eukaryotes

The Central Dogma

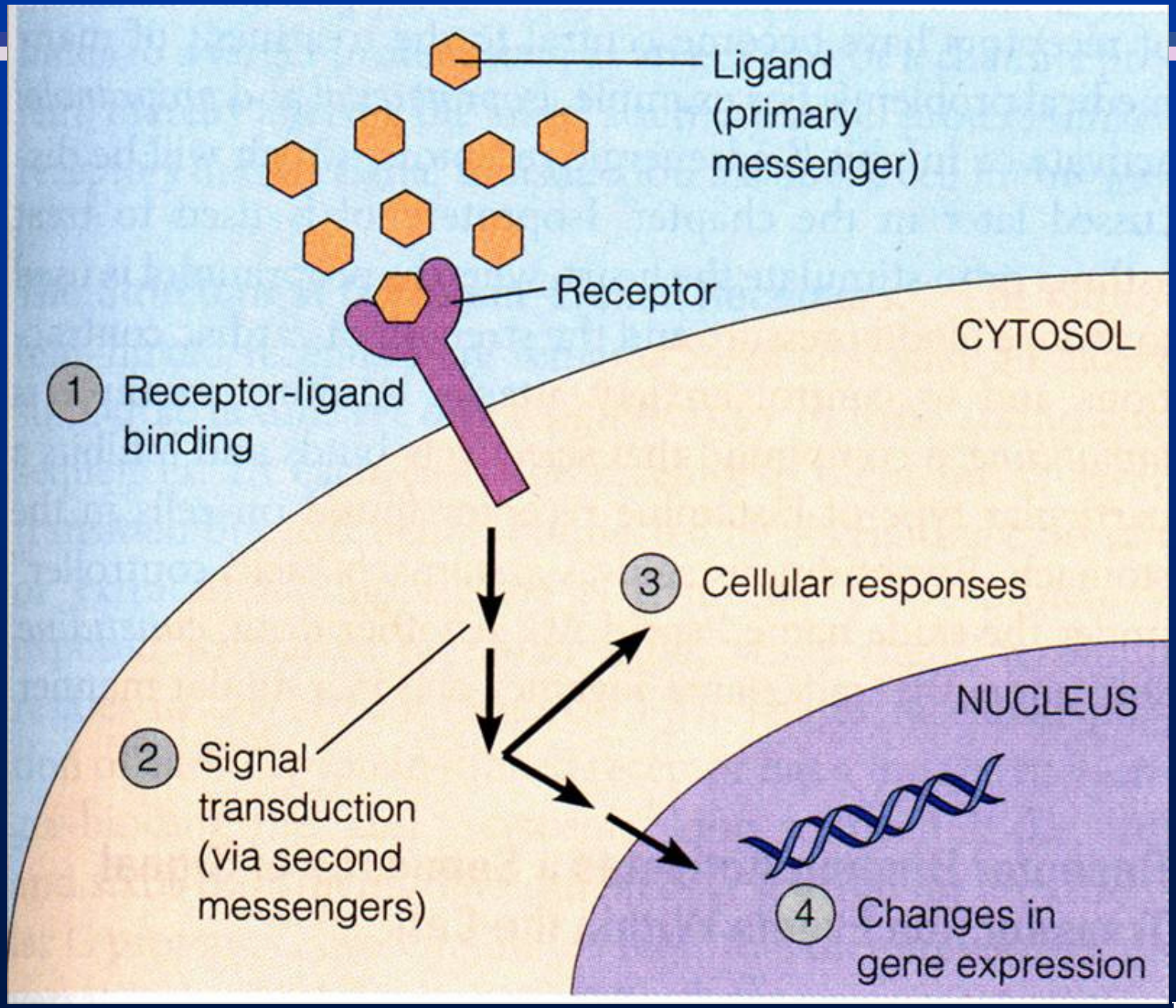


- DNA directs formation of RNA which directs formation of proteins by the cell. This is a one-way process!

A SUMMARY OF DNA REPLICATION



Cell Signaling



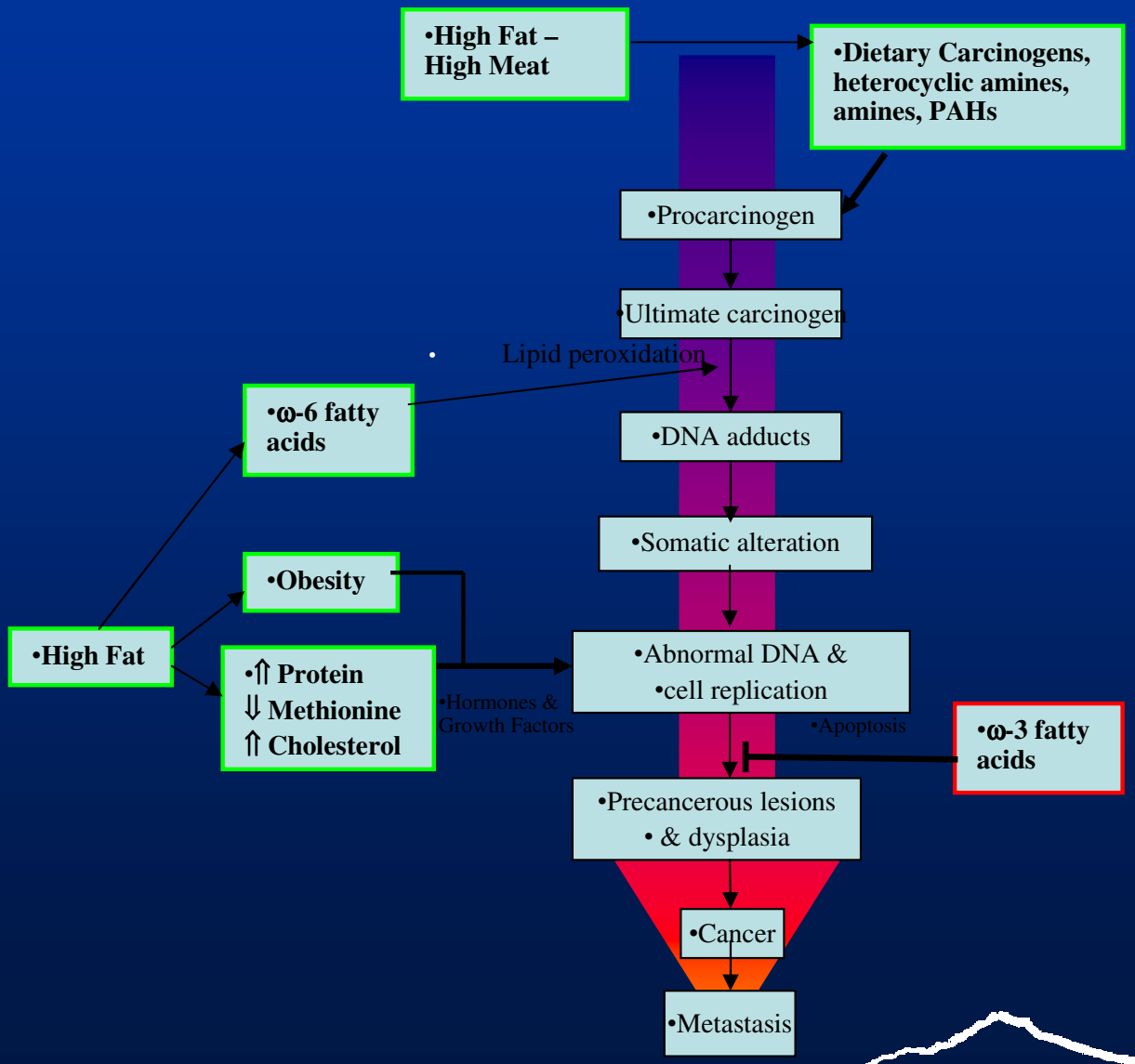
Fat in Breast Carcinogenesis

Animal evidence 1940's (Tannenbaum)

- Kcal restricted = ↓tumorss
- ↑ fat diet = ↑ mammary tumors.

1997 Fay & Freedman – Meta-analyses of animal studies.

- Similar findings, unclear if effect is due to fat, calories, type of fat etc…



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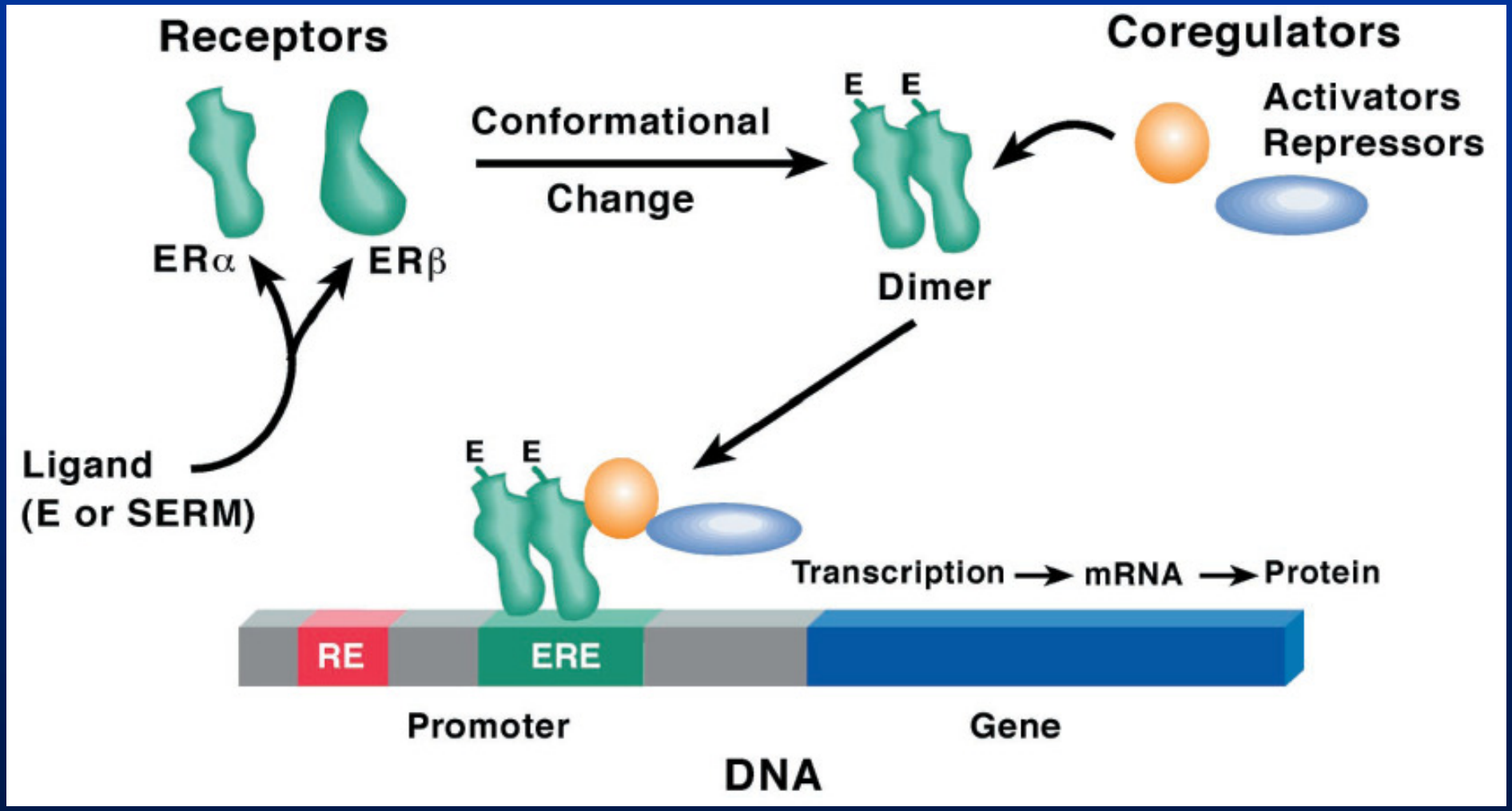
I-Classical Mechanism: *ERE* dependent Gene Transactivation Mechanism



•Osborne, C. K.; Zhao, H.; Fuqua, S. A. Selective estrogen receptor modulators: structure, function, and clinical use. *J Clin Oncol* 2000, *18*, 3172-3186.

To Summarize So Far…

- Breast cancer has been around a long time
- Exposure to hormones plays a role
- We have identified risk factors but we don't know what causes it
- Whatever the cause, it leads to DNA changes which leads to changes in cell behavior, ie cancer

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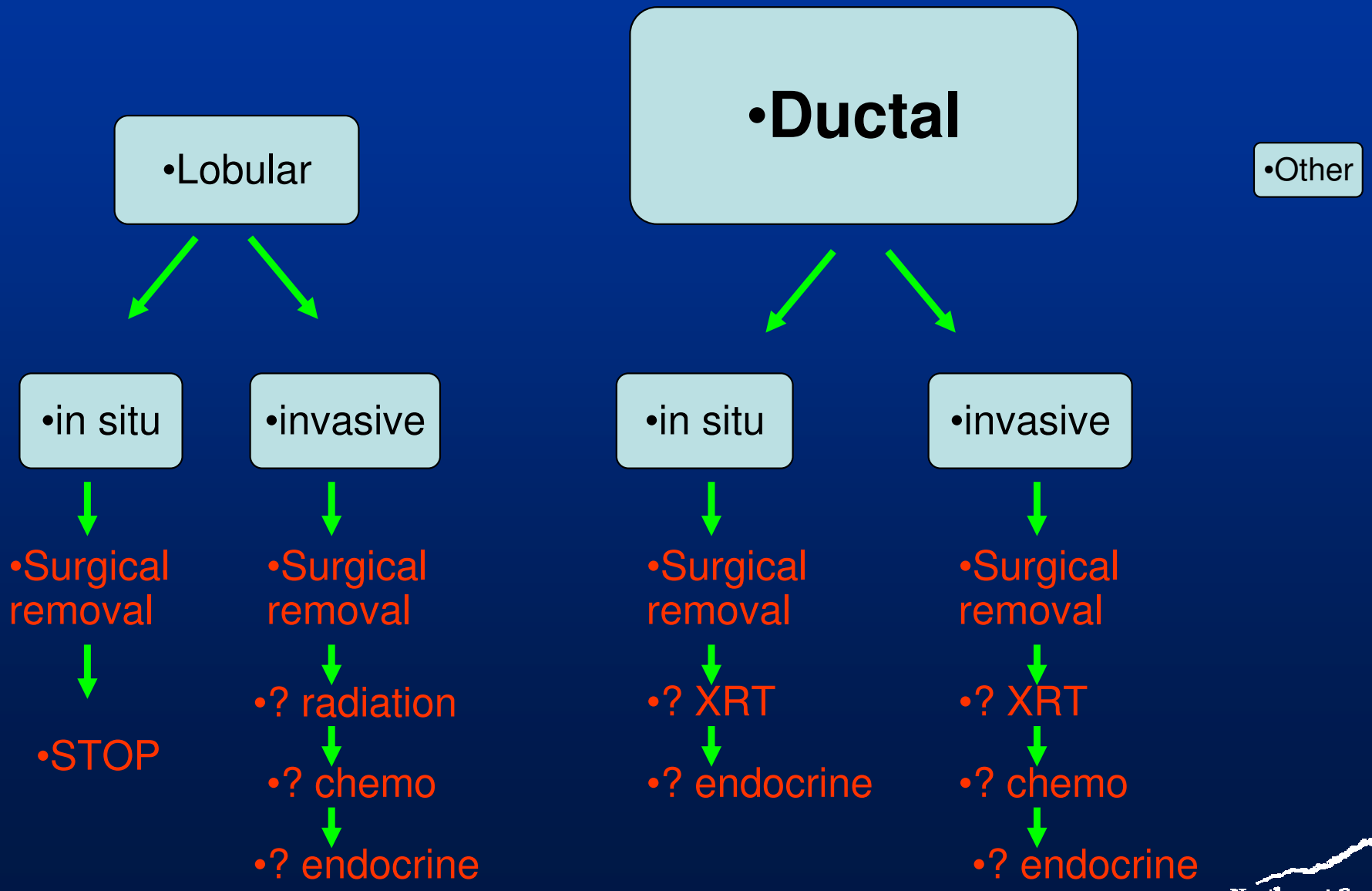
Breast Cancer Breakdown



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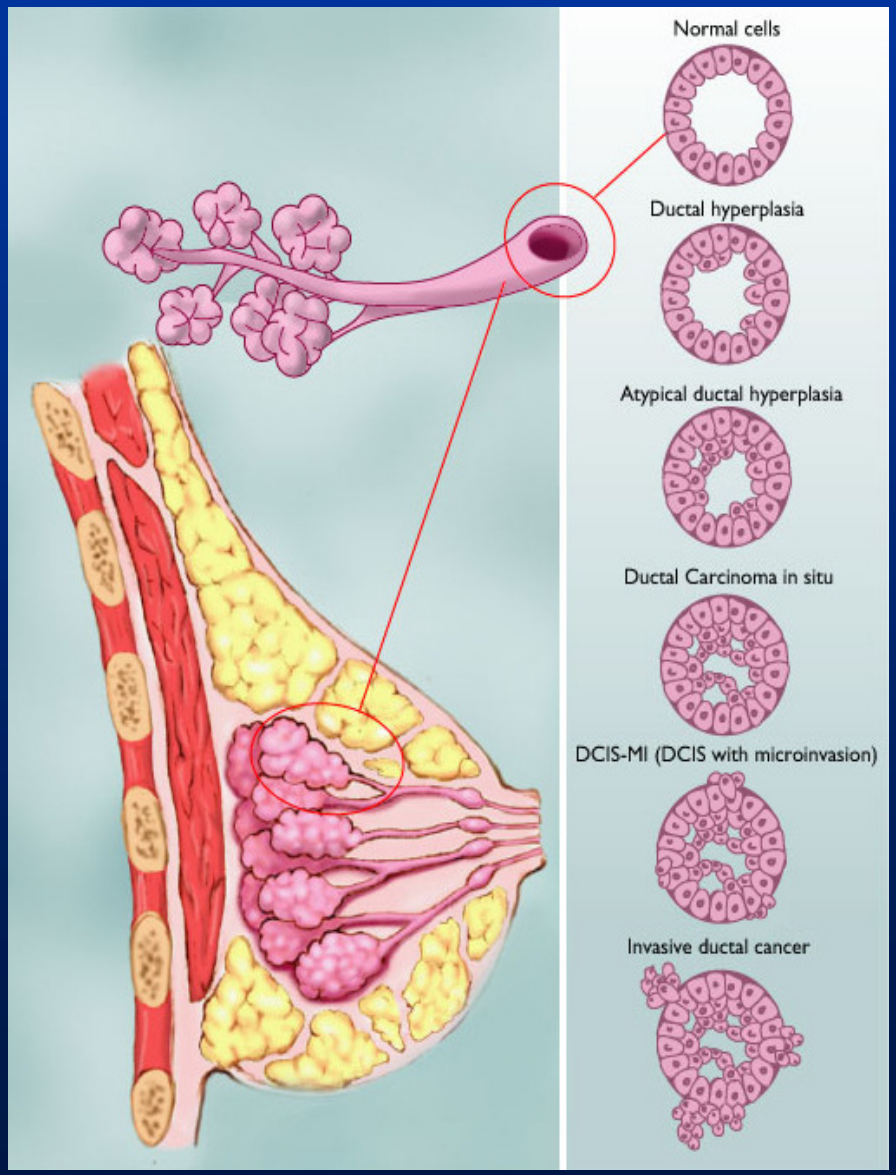
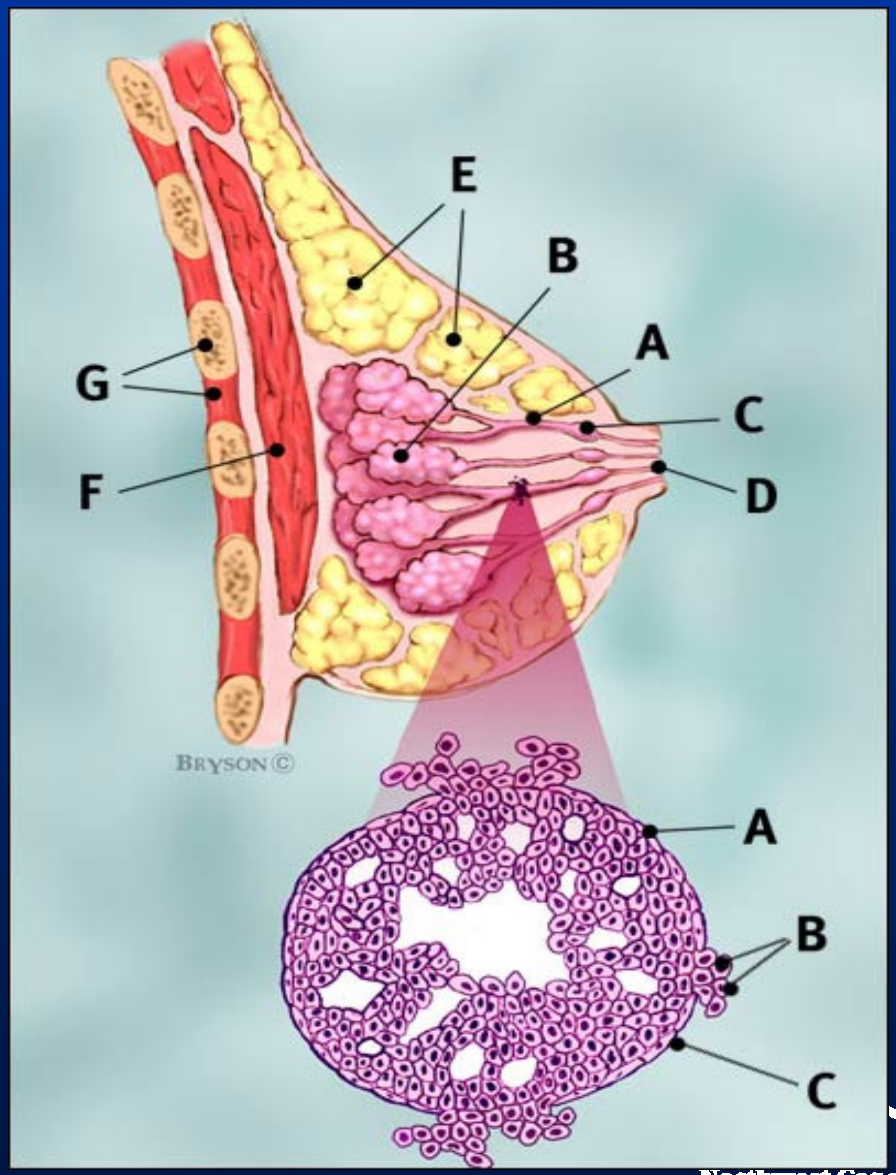
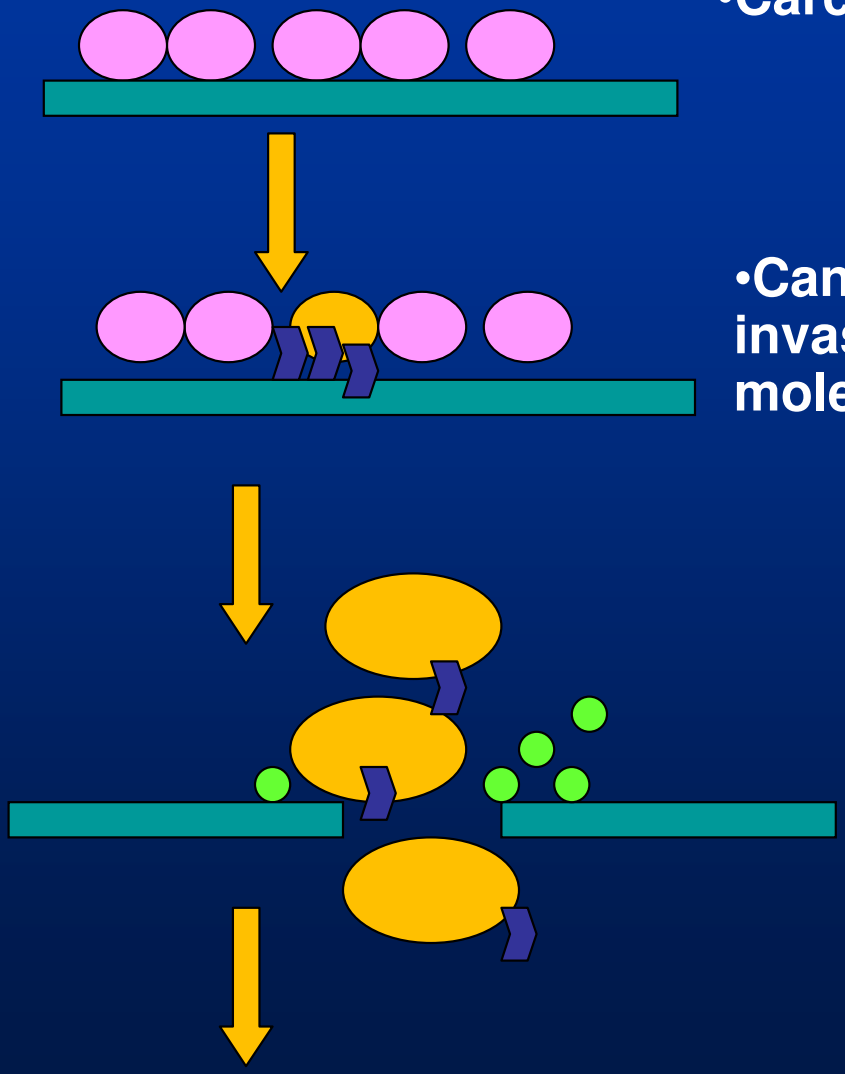
Types of breast carcinoma



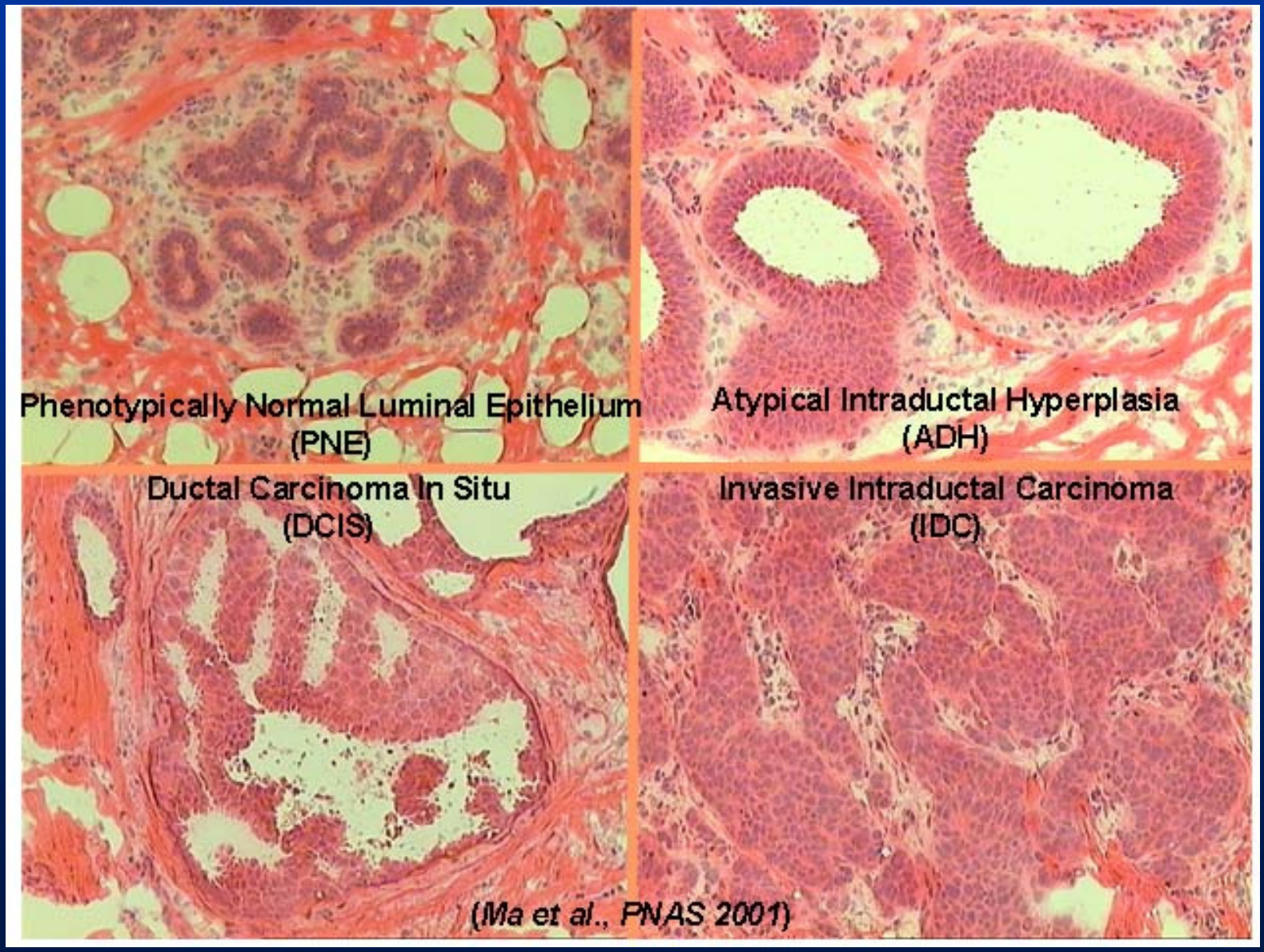


Another way to look at it…

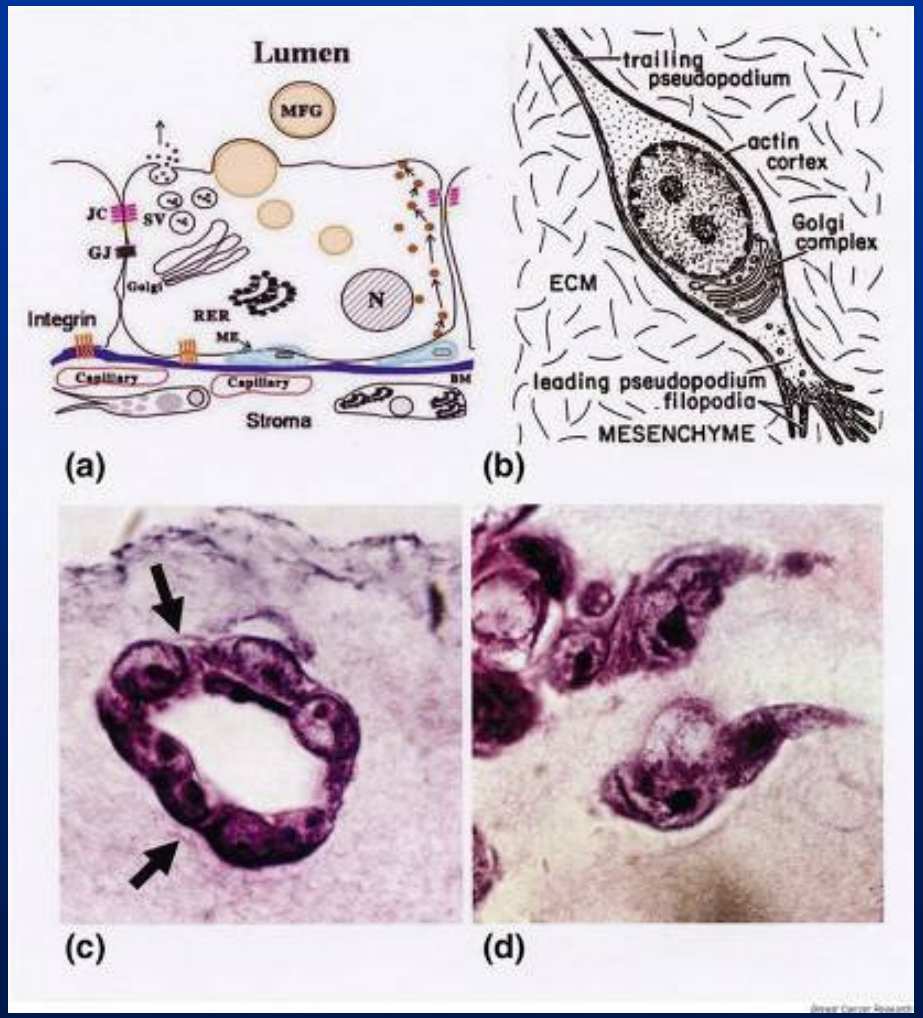


- Carcinoma in situ
- Cancer cell becomes capable of invasion (expresses surface adhesion molecules)
- Tumor cells release proteolytic enzymes, disruption of ECM
- Invade ECM

In situ to invasive progression



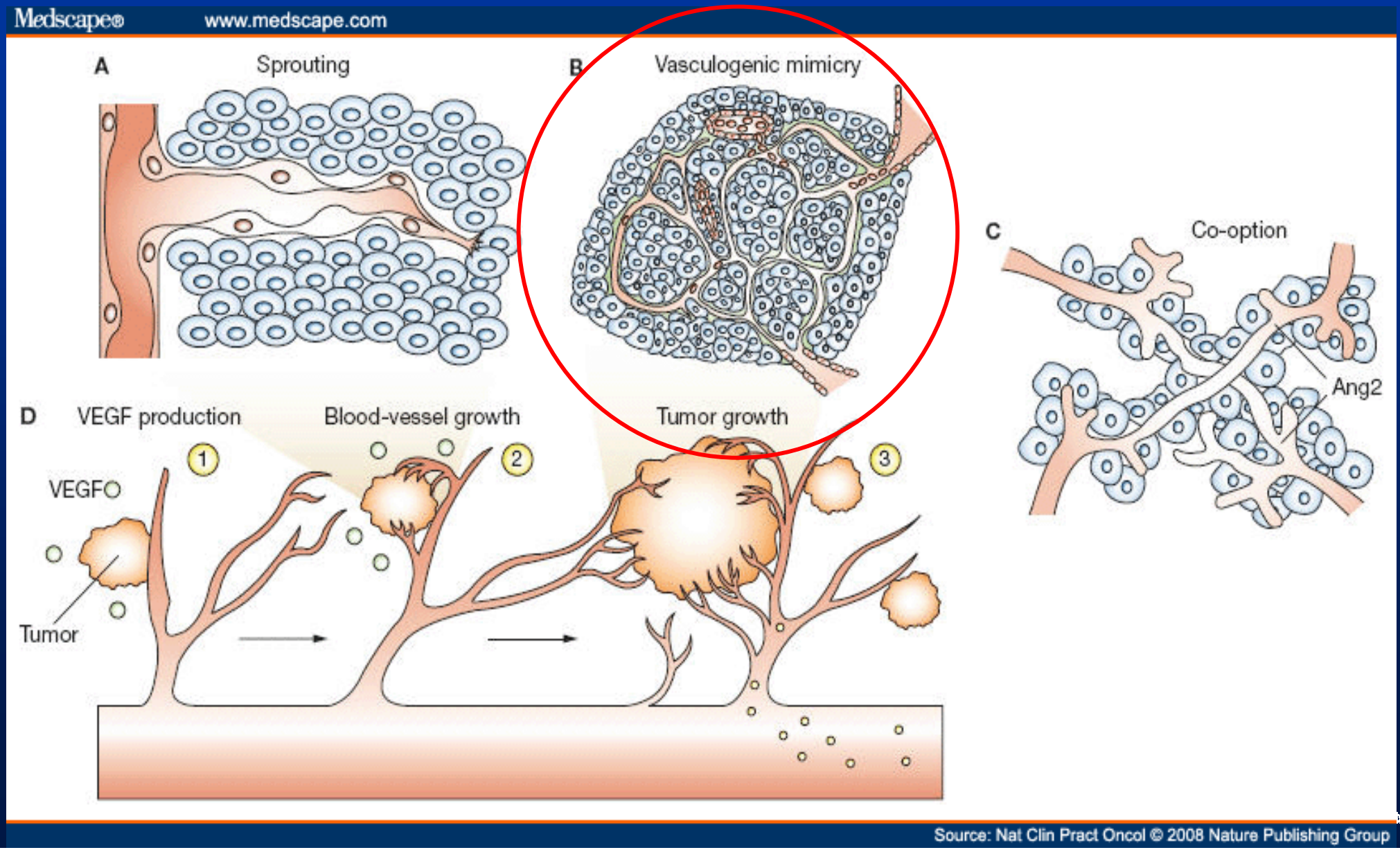
EMT



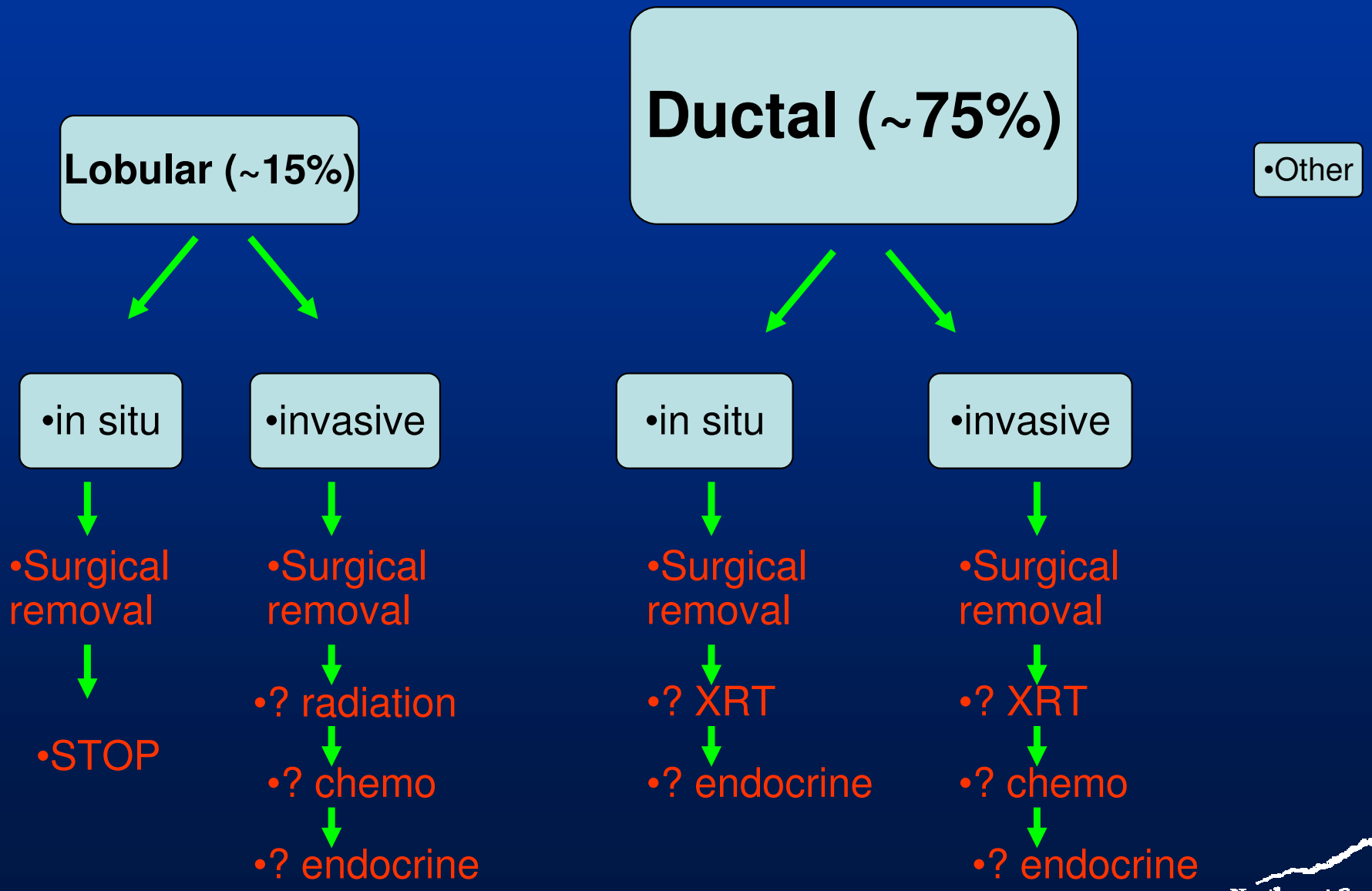
a) Normal epithelium
b) Mesenchymal-like cell
c) Duct-like structure with polarized cells
d) Loss of cell-cell interaction, loss of polarity

Breast Cancer Research volume 6 no 2 Schedin and Elias

Vasculogenic Mimicry



Breast Cancer Breakdown



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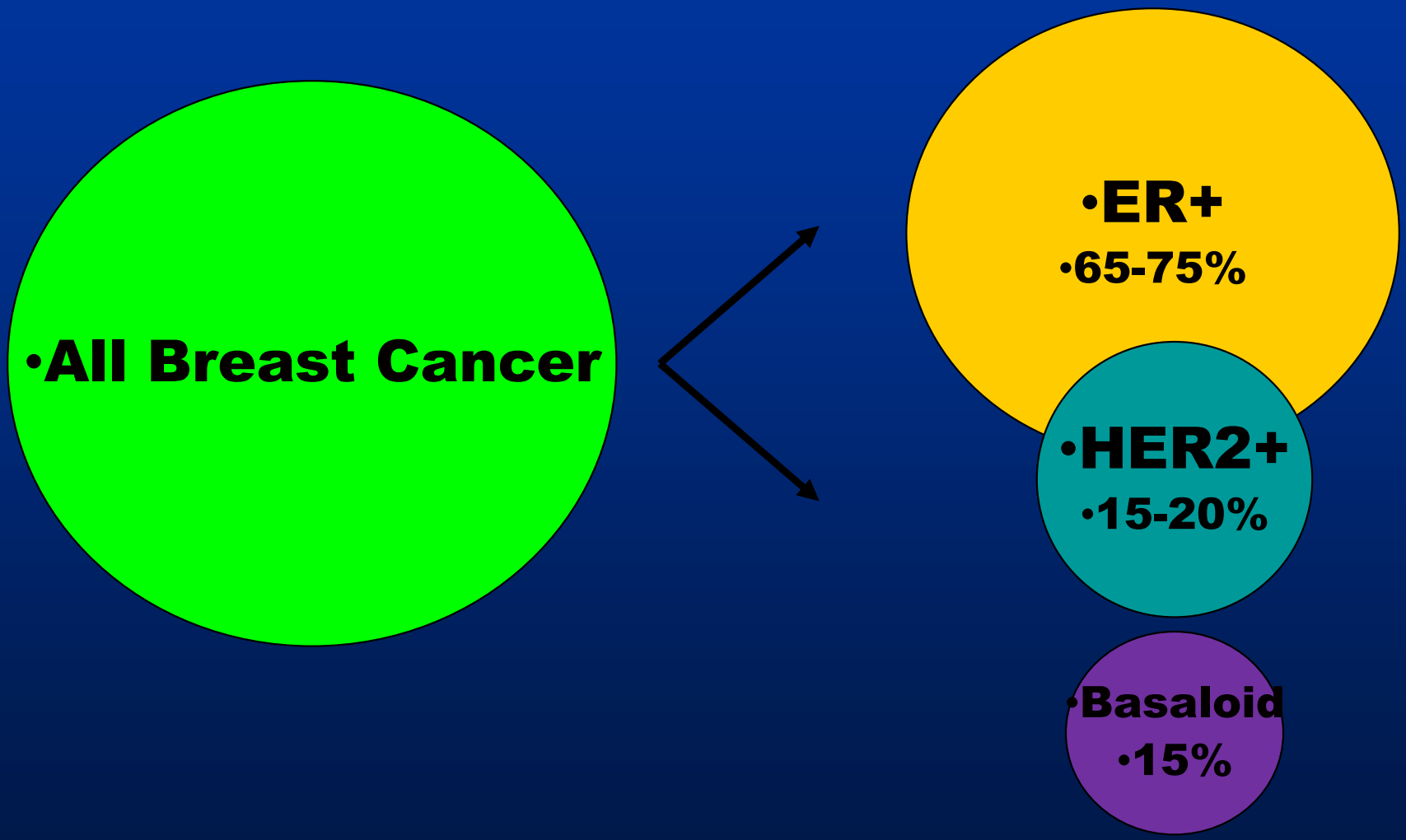
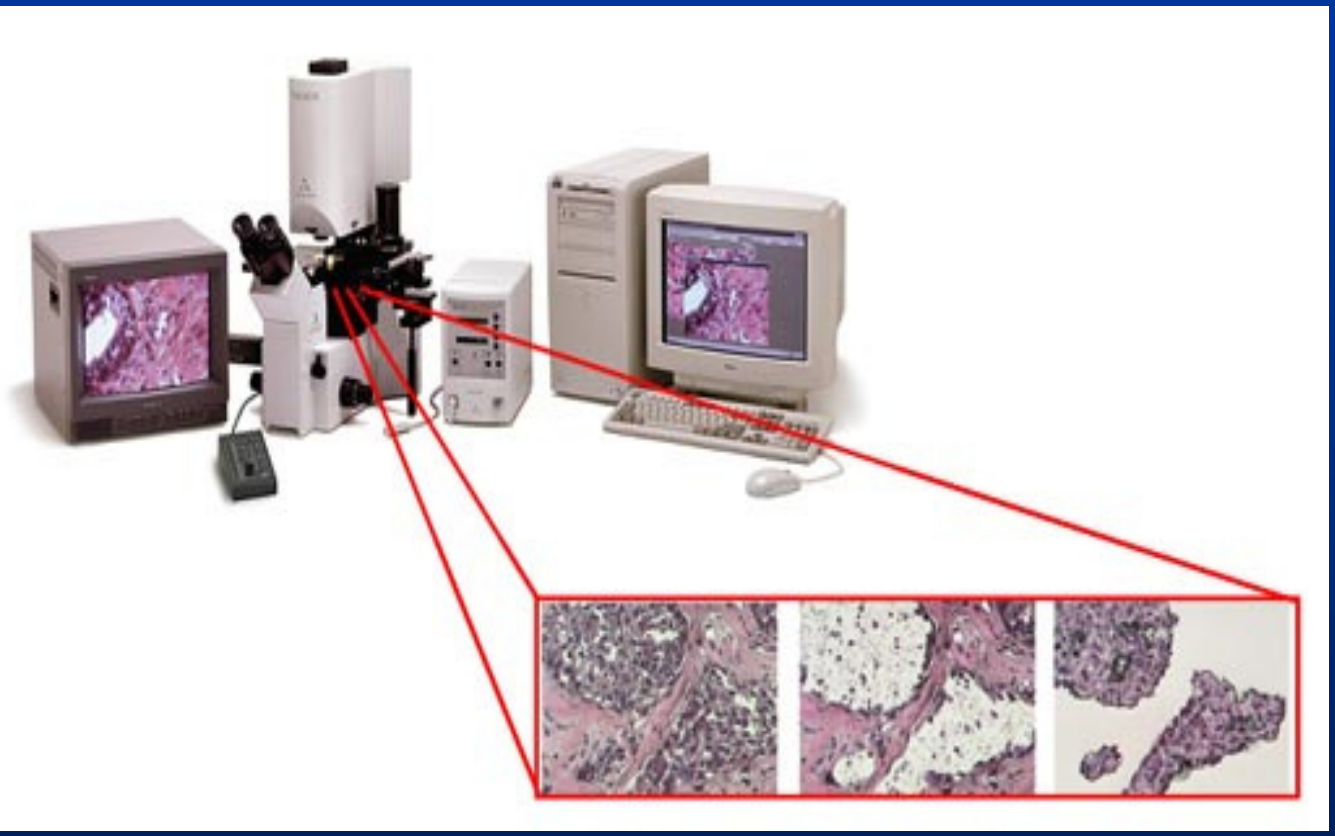
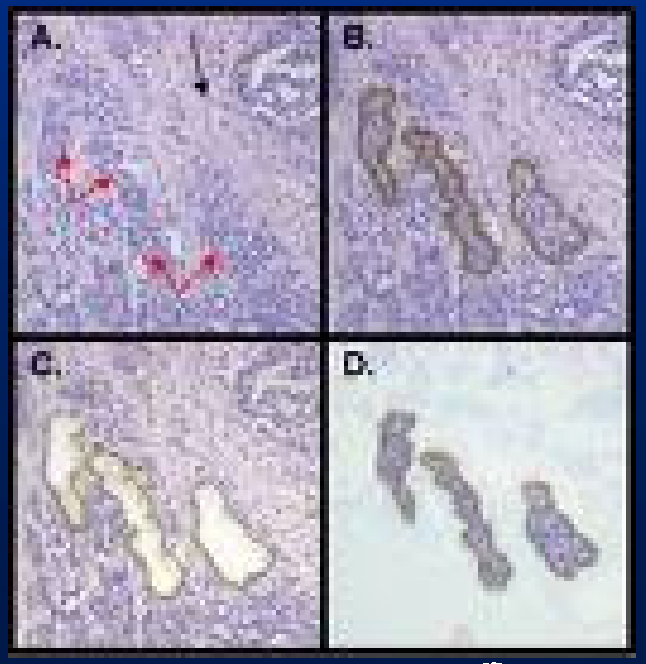
Another way to look at it…



Laser Capture Microdissection





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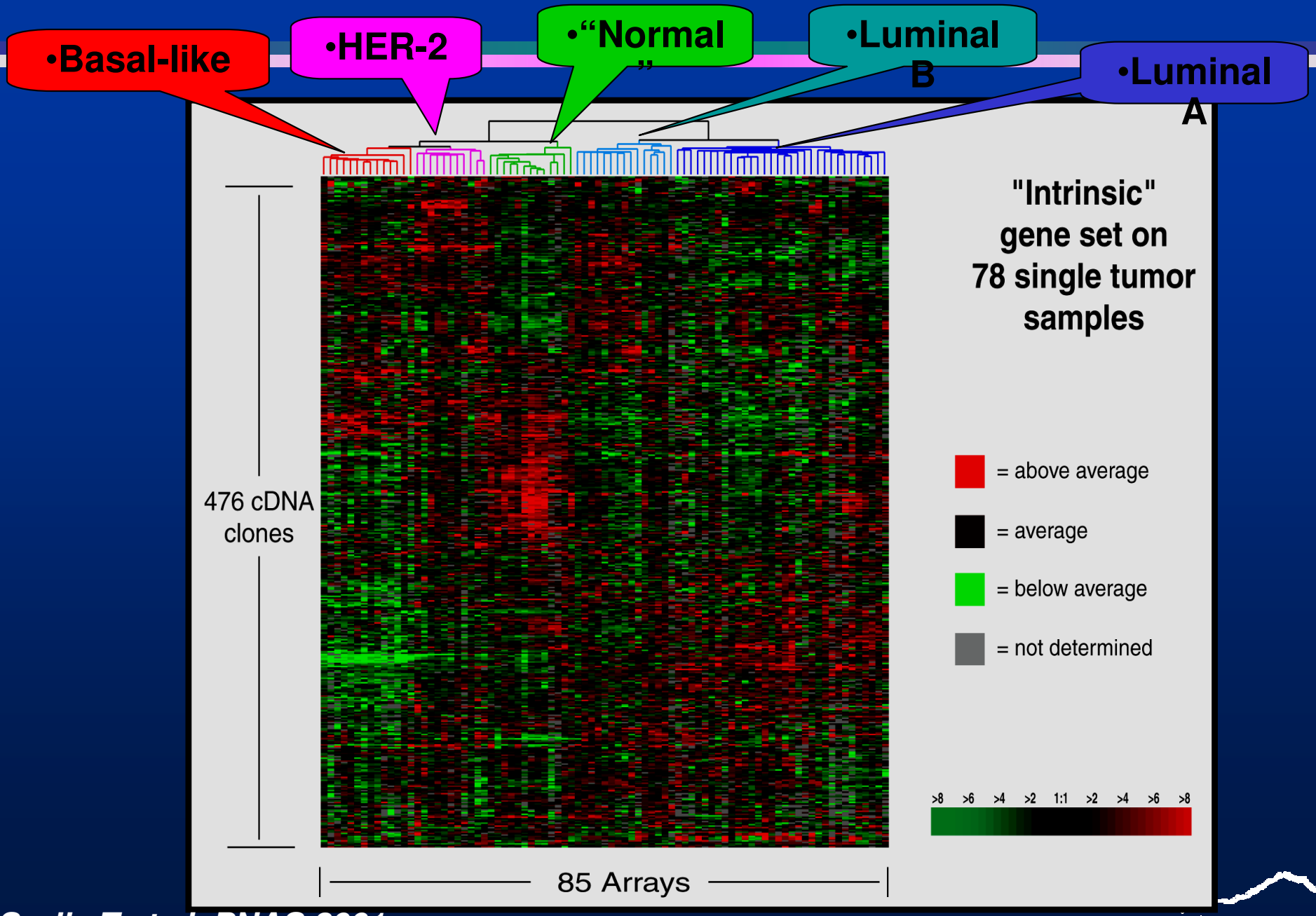
Molecular Portrait of Breast Cancer



•*Sorlie T et al, PNAS 2001*

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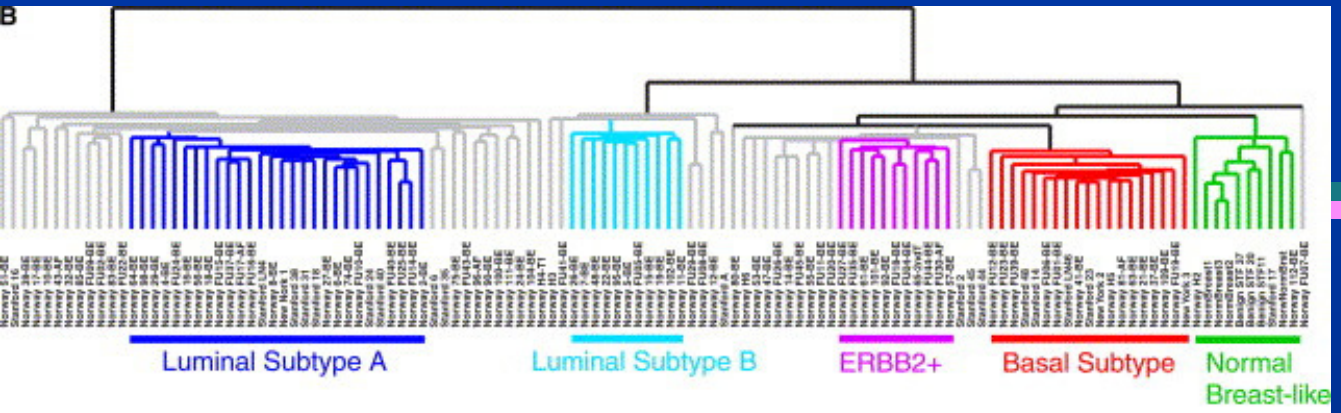
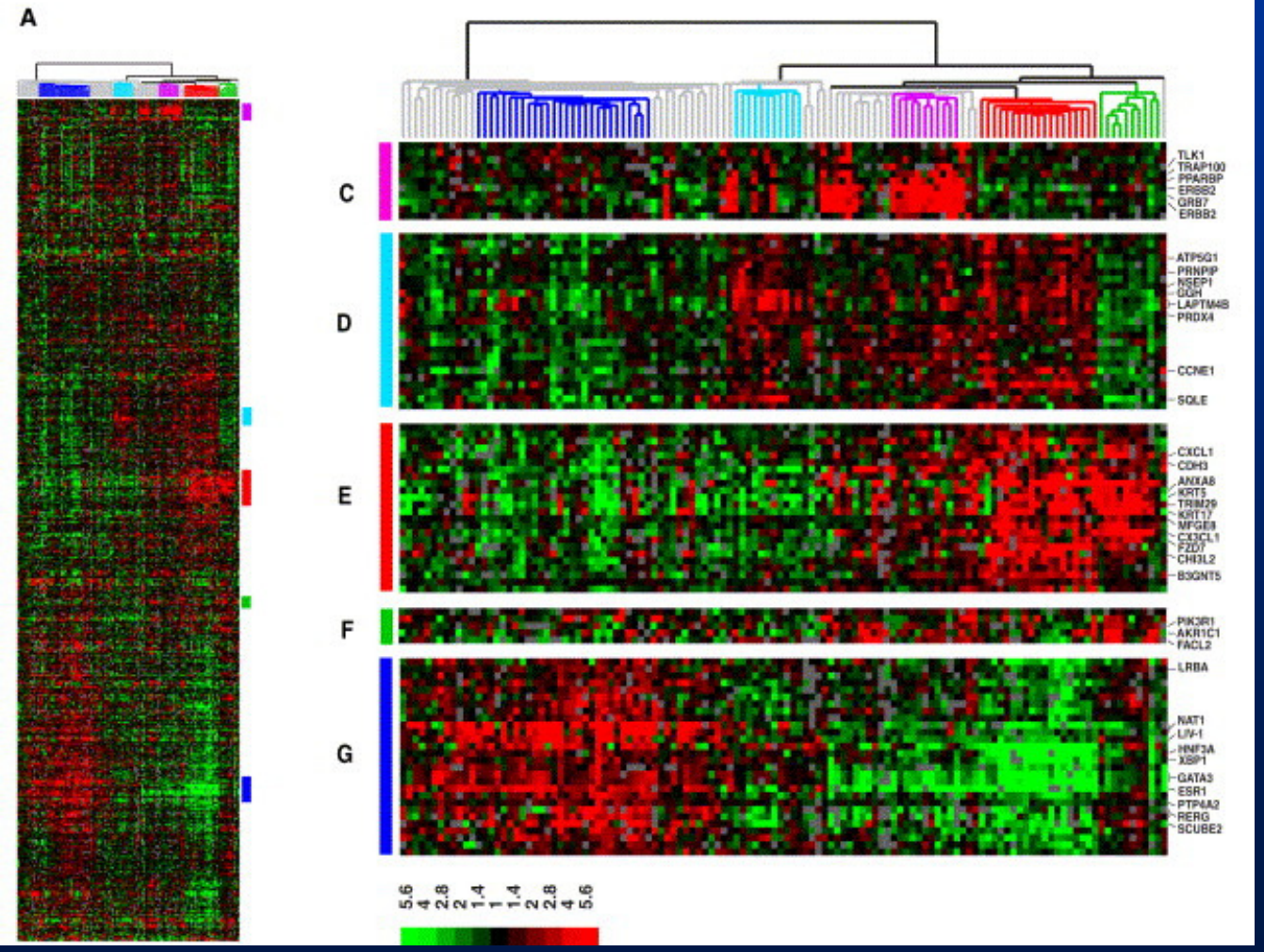
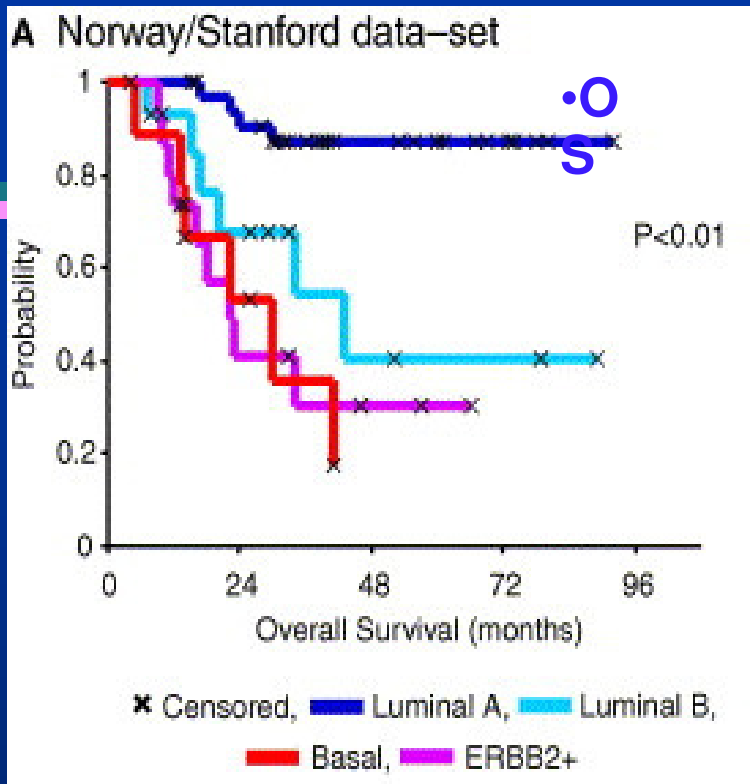
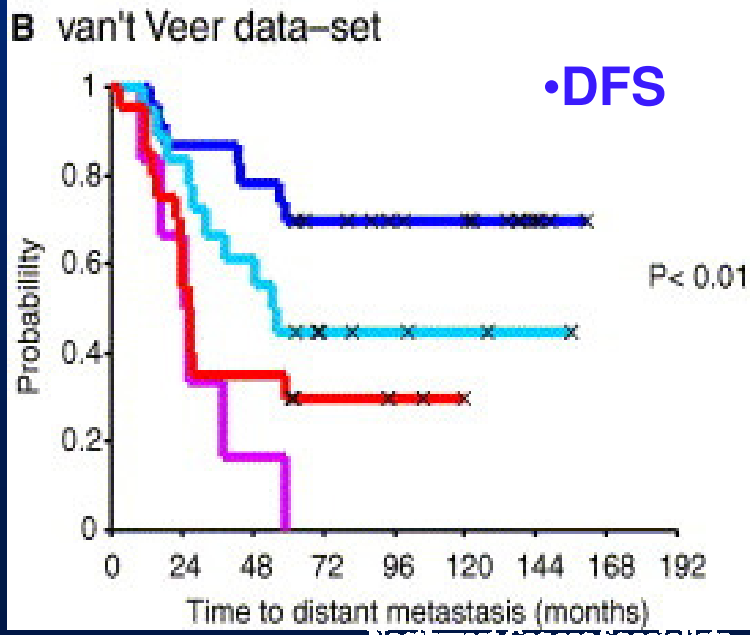
• Breast Cancer = MANY Diseases







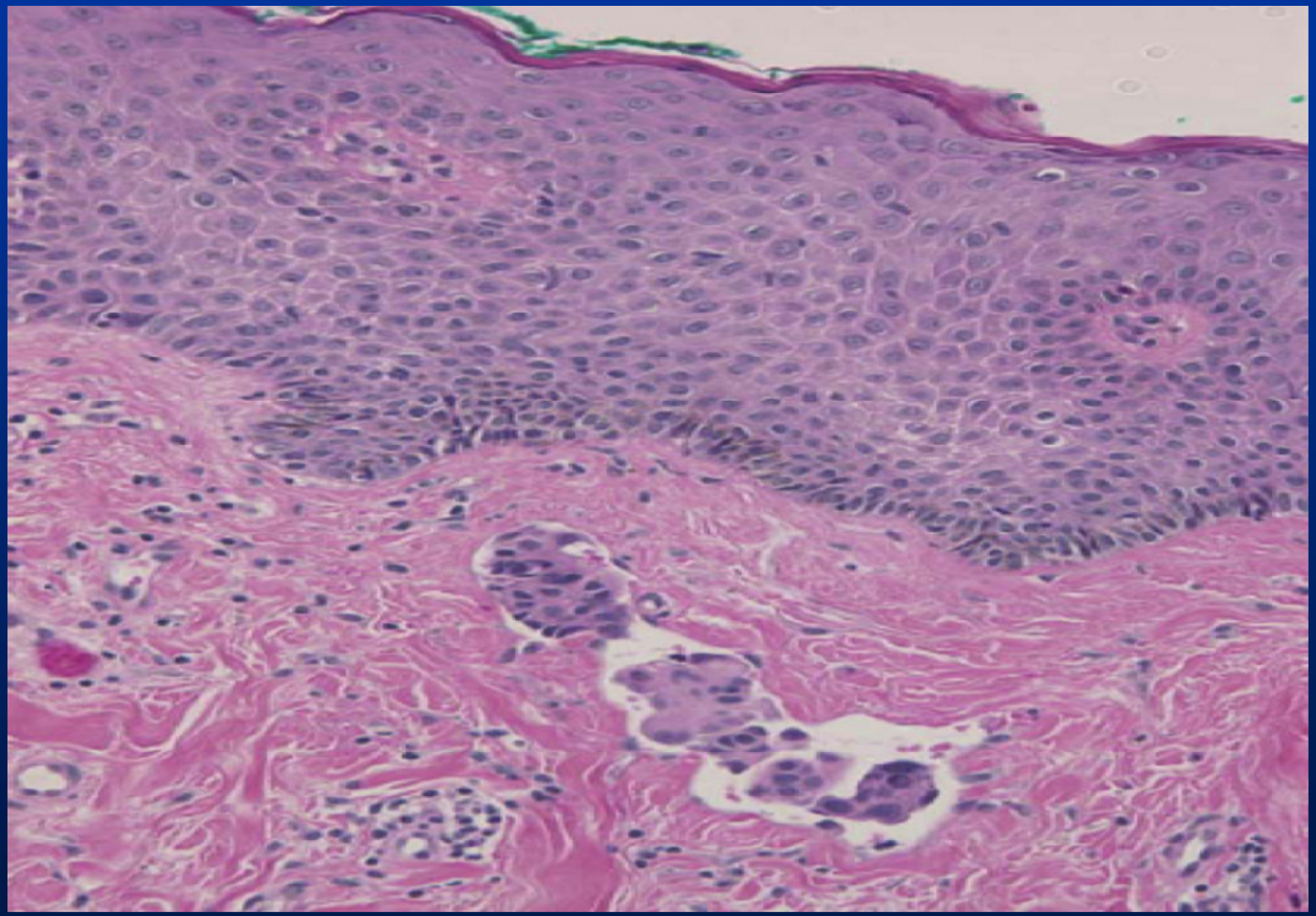


Inflammatory Breast Cancer

- **Clinical diagnosis:**
  - Diffuse erythema
  - Peau d'orange
  - Pain
  - Subjective heaviness
  - Rapid progression
  - Often no mass

Peau d’orange

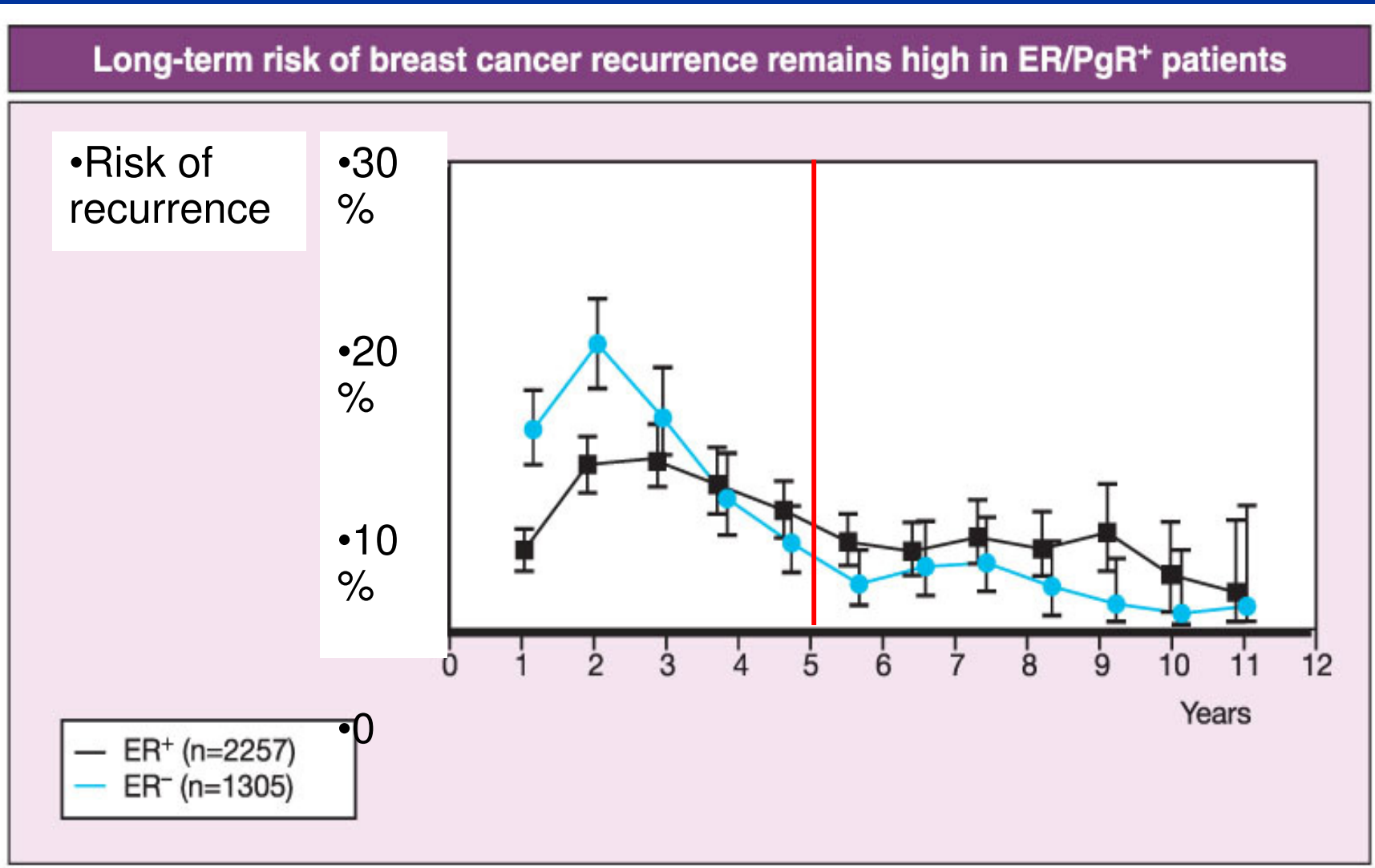
Tumor Microemboli



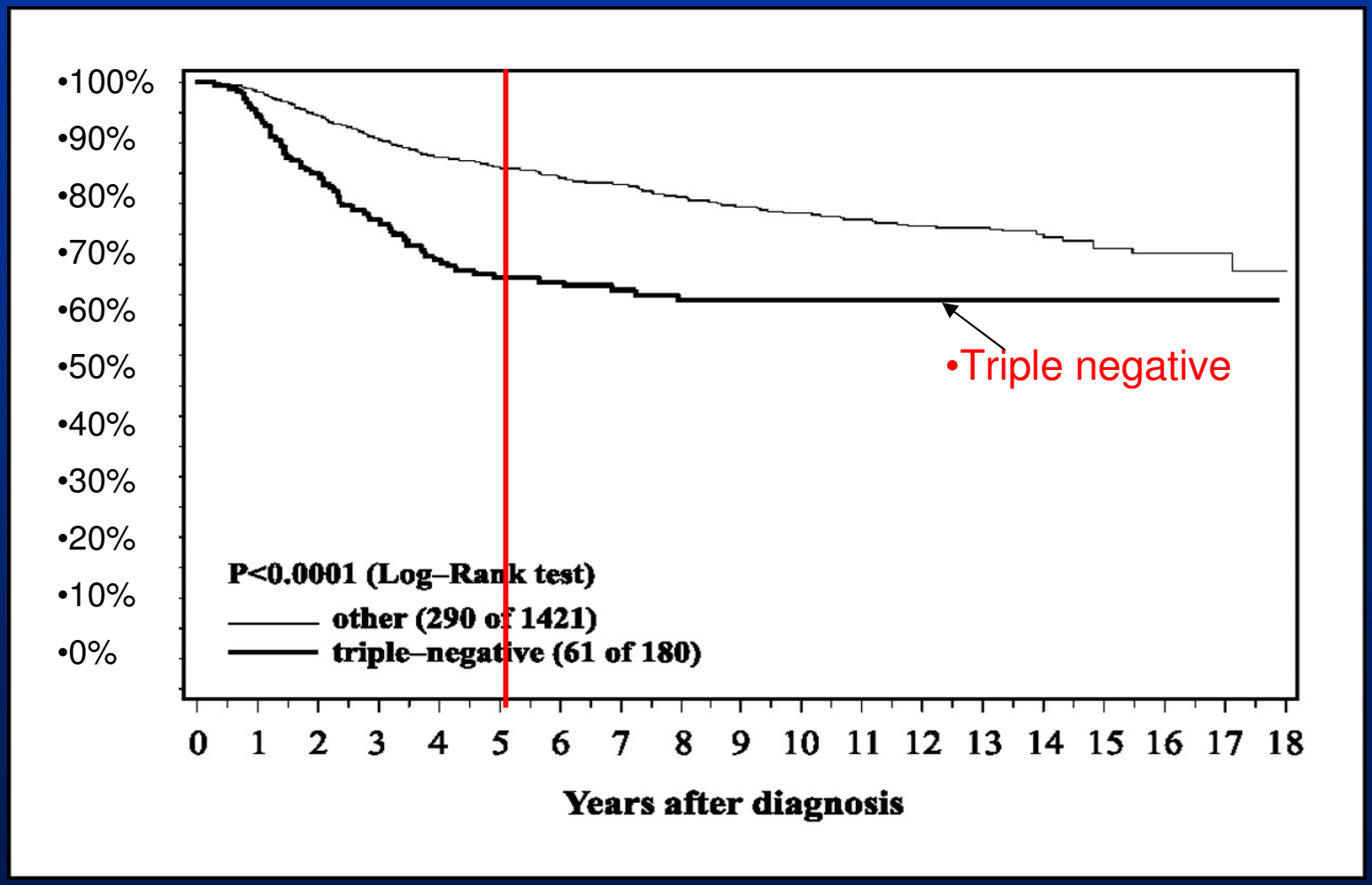
“I have the ER receptor. That’s good, right?”

	ER-	ER+
Can be treated with estrogen blockade		✓
More biologically aggressive	✓	
Lower response to chemo		✓
Higher risk for late relapse (>10yr)		✓
More common in premenopausal	✓	

Risk of Recurrence: ER+ vs ER-



•Risk of Recurrence: Triple Negative vs Everyone Else



Clinical Cancer Research

Dent, R. et al. Clin Cancer Res 2007;13:4429-4434

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"My breast cancer is ER/PR negative. I'm hoping to be HER2 positive, right?

A. YES. The HER2 receptor is associated with more aggressive breast cancers but we have a targeted biologic treatment.

B. Yes. The HER2 receptor is associated with less aggressive breast cancers.

C. No. The HER2 receptor means you won't respond to most chemotherapy agents.

C. Yes. The HER2 receptor is associated with better response to hormonal therapy.

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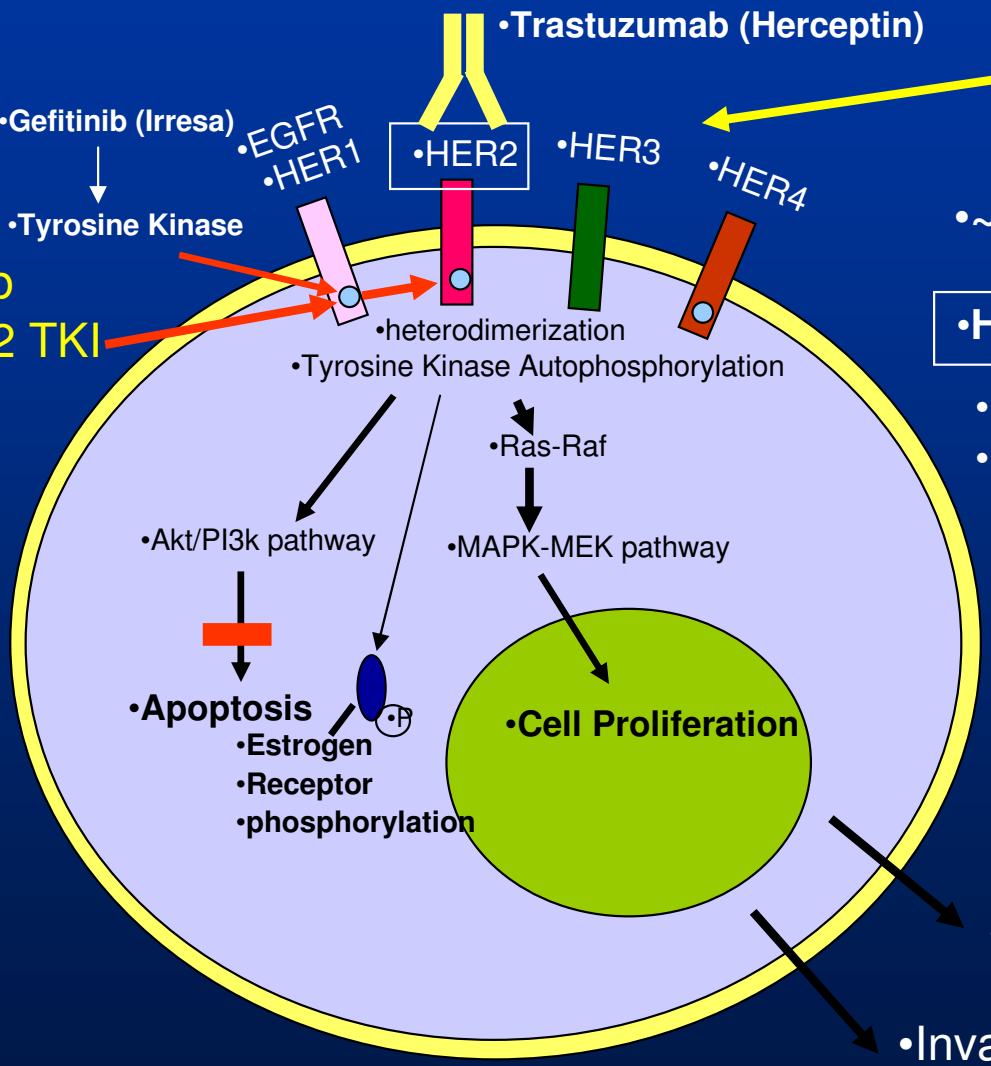
•What the HECK is Her2?



•Pan-Her Antibody
•Pertuzumab

•~ 25 % Breast Cancer

•Her2 Overexpression

•IHC Stain +++
•FISH Ratio > 2

•Aggressive Tumor

•Responsive to
•Trastuzumab

•Angiogenesis

•Invasiveness

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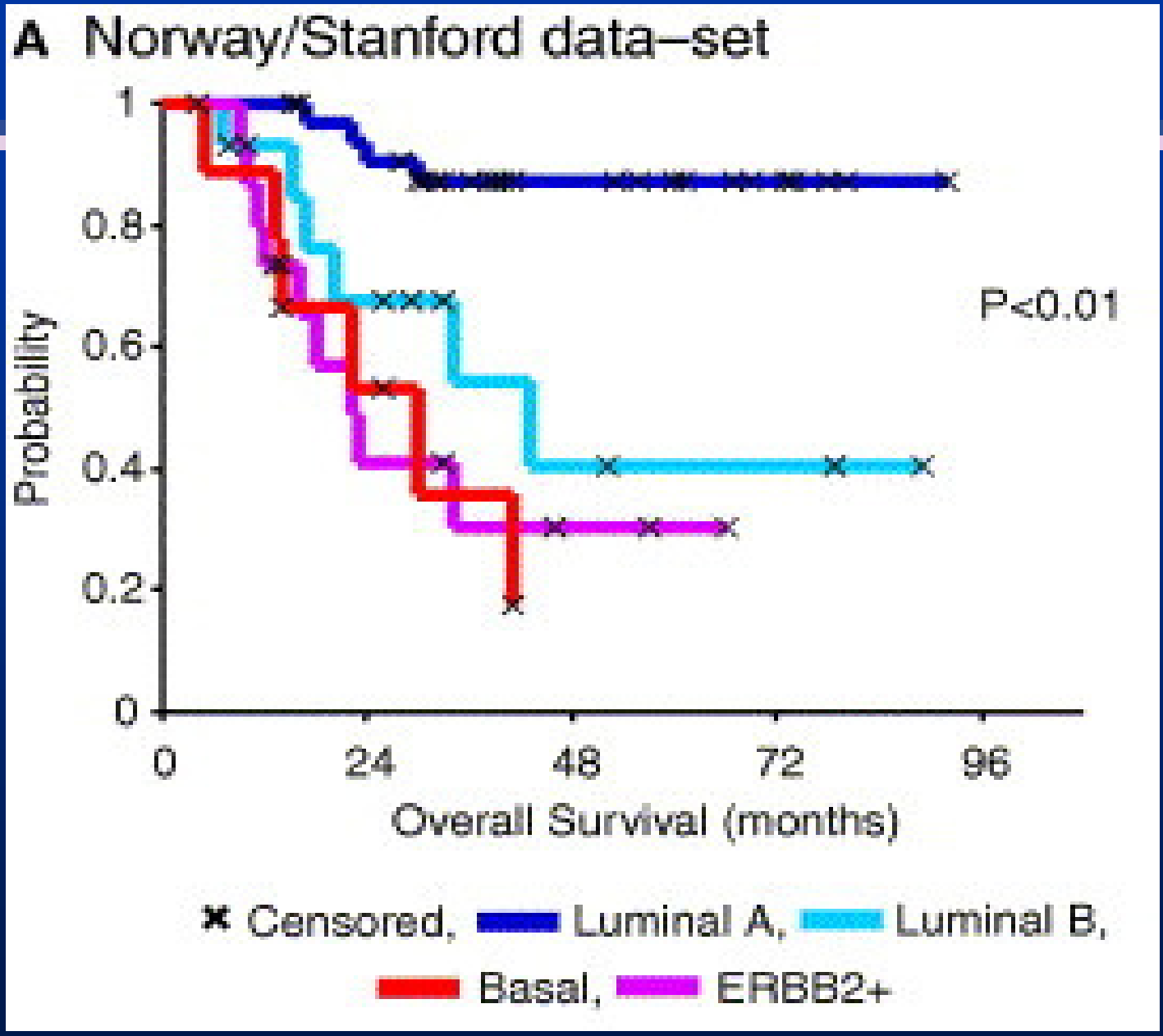
Bringing it all together…

Luminal A	ER + high	Prolif -	Mutant P53 16%
Luminal B	ER + low	+	71%
Basal -like	ER -	+	75%, BRCA1
ERBB2 +	ER-/+	-/+	86%
Normal-like	ER -	-	


A Norway/Stanford data–set
Probability
1
0.8
0.6
0.4
0.2
0
P<0.01
0
24
48
72
96
Overall Survival (months)
Censored,
Luminal A,
Luminal B,
Basal,
ERBB2+

To Summarize So Far…

- Most breast cancers are strongly ER+ and arise from the ducts (luminal A)
- The type of breast cancer determines its behavior
- Molecular profiling has determined distinct subtypes based on where the malignant cells arise (basal vs luminal)
- These molecular subtypes predict recurrence and response to treatment

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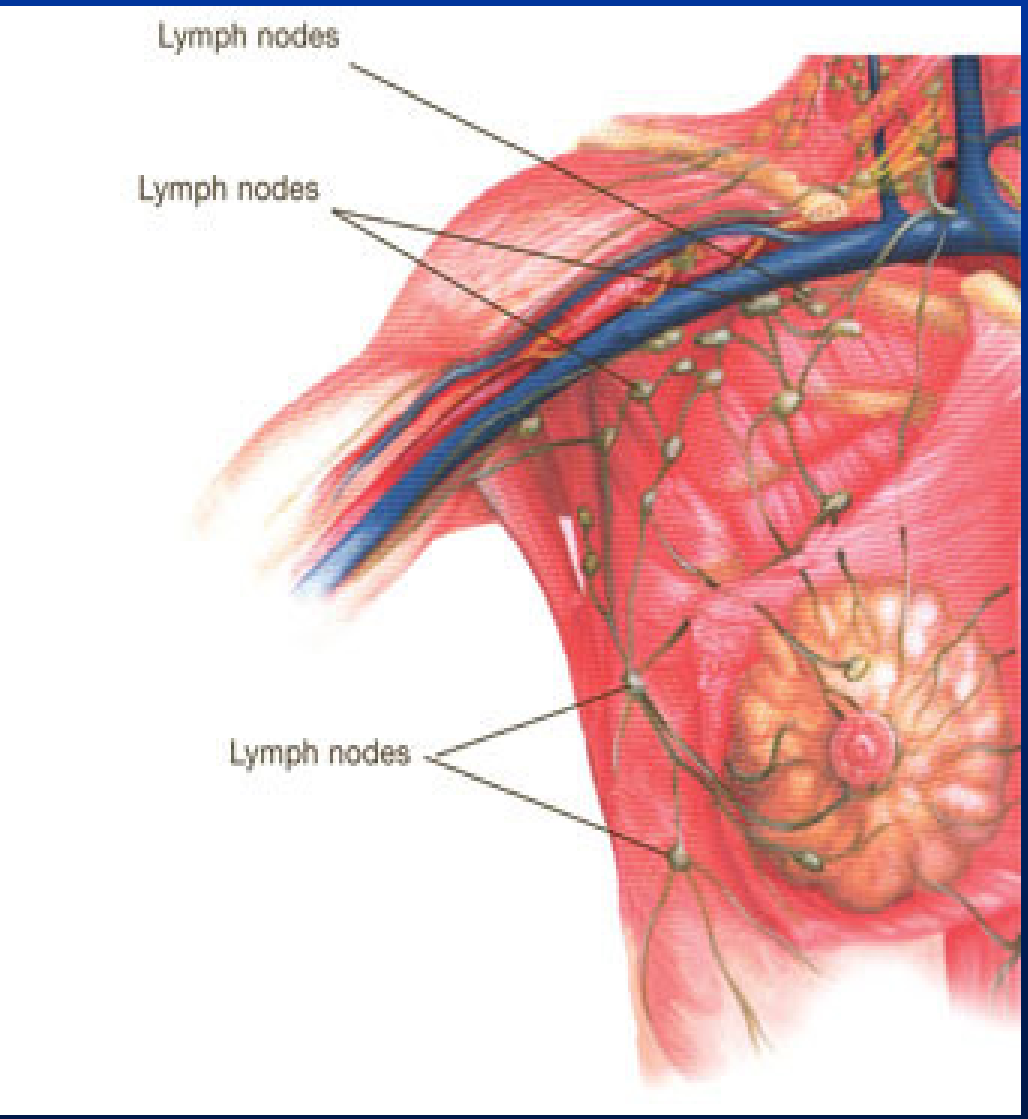
Before starting treatment:

- **Biopsy**
  - Determine breast cancer type
  - Test for ER, PR, HER2
  - Consider molecular testing (Oncotype DX or Mammaprint assay) based on results
- **Stage**
  - Determine extent of disease
    - If large tumor, aggressive biology or positive lymph nodes, CT or PET scan of chest/abd/pelvis

Breast Cancer Staging



• Stage 0	Tis	N0	M0
• Stage I	T1*	N0	M0
• Stage IIA	T0	N1	M0
•	T1*	N1	M0
•	T2	N0	M0
• Stage IIB	T2	N1	M0
•	T3	N0	M0
• Stage IIIA	T0	N2	M0
•	T1*	N2	M0
•	T2	N2	M0
•	T3	N1	M0
•	T3	N2	M0
• Stage IIIB	T4	N0	M0
•	T4	N1	M0
•	T4	N2	M0
• Stage IIIC	Any T	N3	M0
• Stage IV	Any T	Any N	M1

– *T1 includes T1mic

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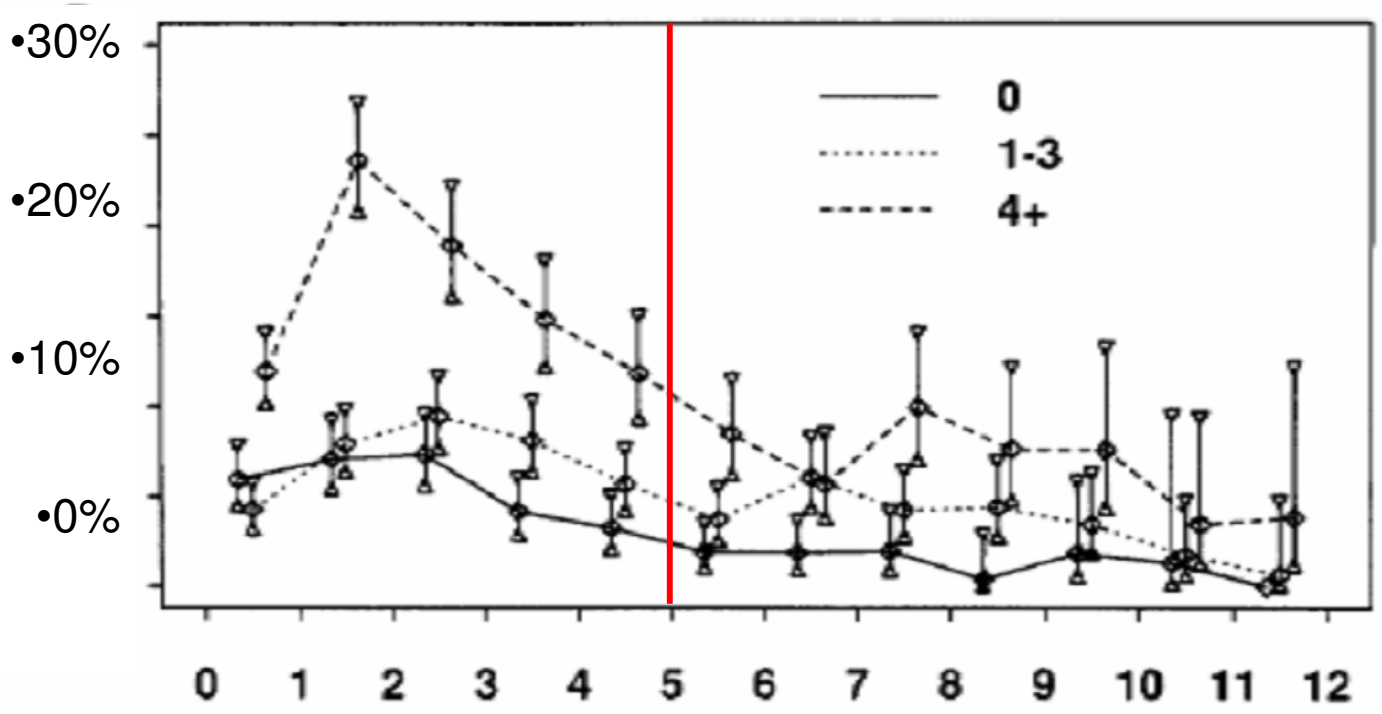
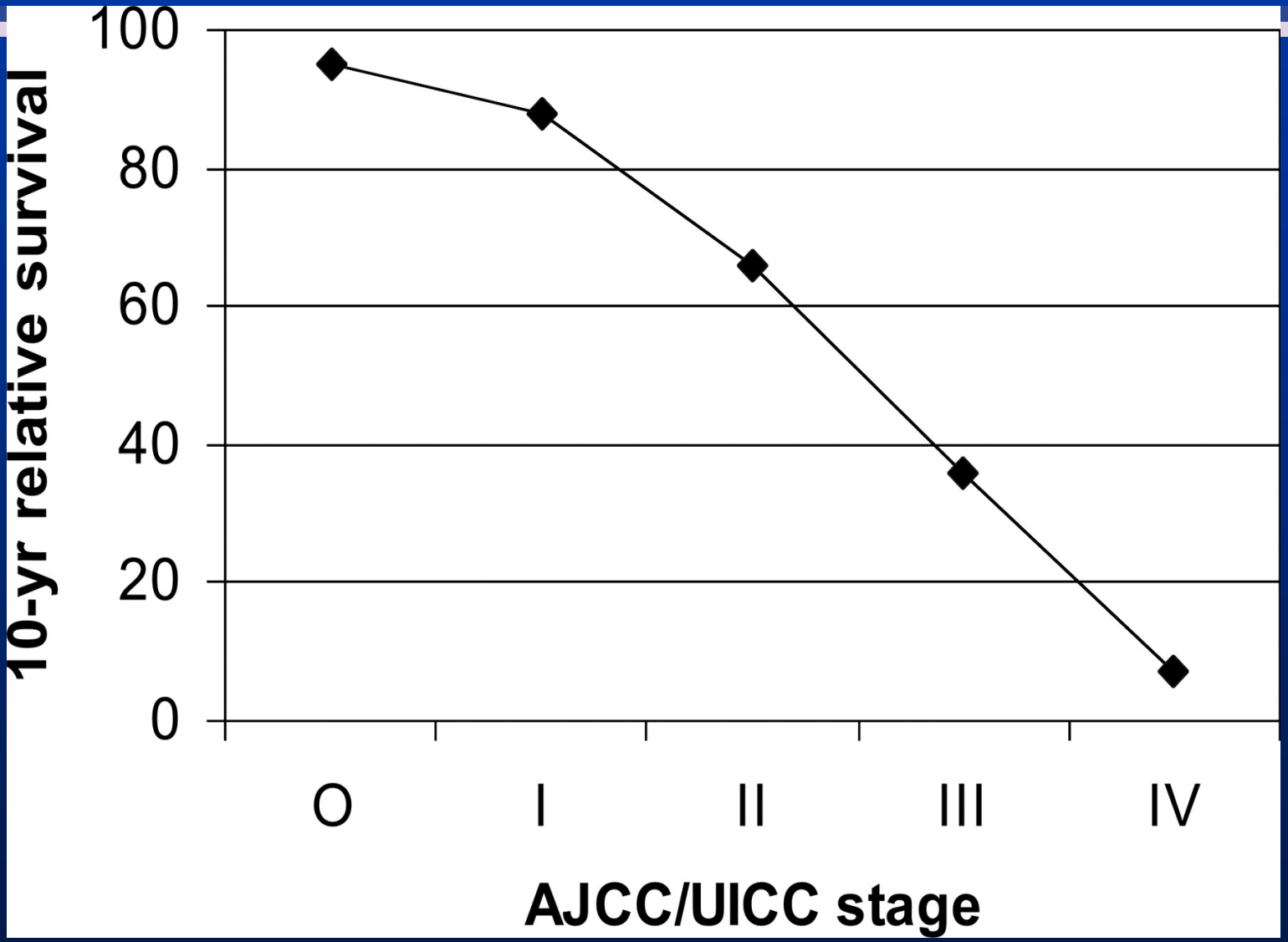
Recurrence by # Positive Lymph Nodes



•Saphner T, et al. J Clin Oncol 14: 2738, 1996

10 year survival by stage



From Singletary, S. E. et al.
CA Cancer J Clin 2006;56:37-47.

Types of Therapy

- **Local**
  - Surgery (usually including sentinel LN biopsy except in some DCIS or very non-aggressive tumors)
  - Radiation
- **Systemic Therapy**
  - Chemotherapy
  - Endocrine therapy
  - Biologic therapy

Local Therapy

- Surgery
- Radiation

Surgery

"A chance to cut is a chance to cure"

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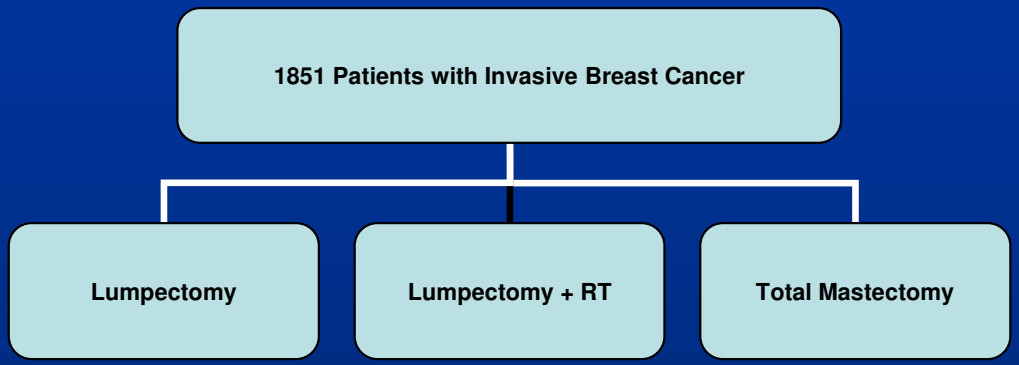
Radiation: NSABP B06 Trial



- Tumors 4cm or Less
- All Patients Had Axillary Node Removal
- No Radiotherapy Boost
- Limited Use of Adjuvant Chemotherapy

•Fisher,B. NEJM 2002;344(16);1233

NSABP B06: 20 Year Results

- No Difference in Overall Survival

Translation: People lived the same length of time

- No Difference in Cause Specific Mortality

Translation: People died from the same things

- Local Recurrence: 14.3% vs. 39.2% w/wo Radiotherapy

Translation: Radiation cut down risk of local recurrence

•Fisher,B. NEJM 2002;344(16);1233

Indications for Radiation

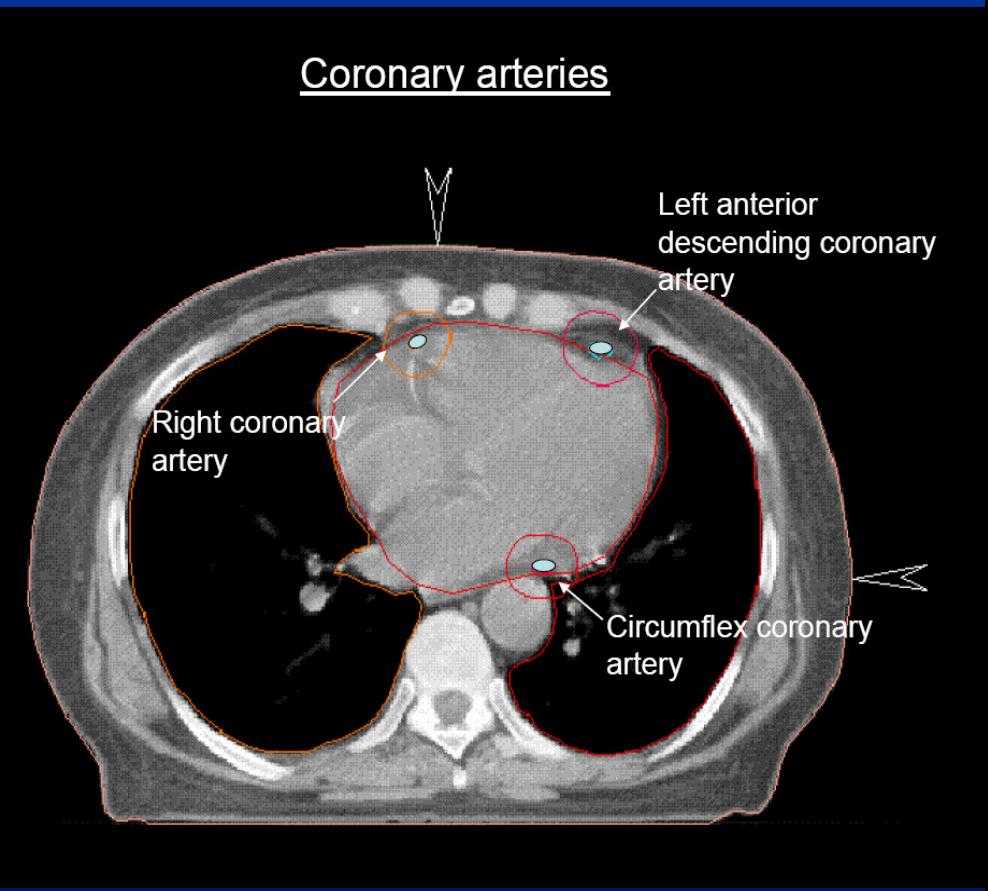
Whole breast:

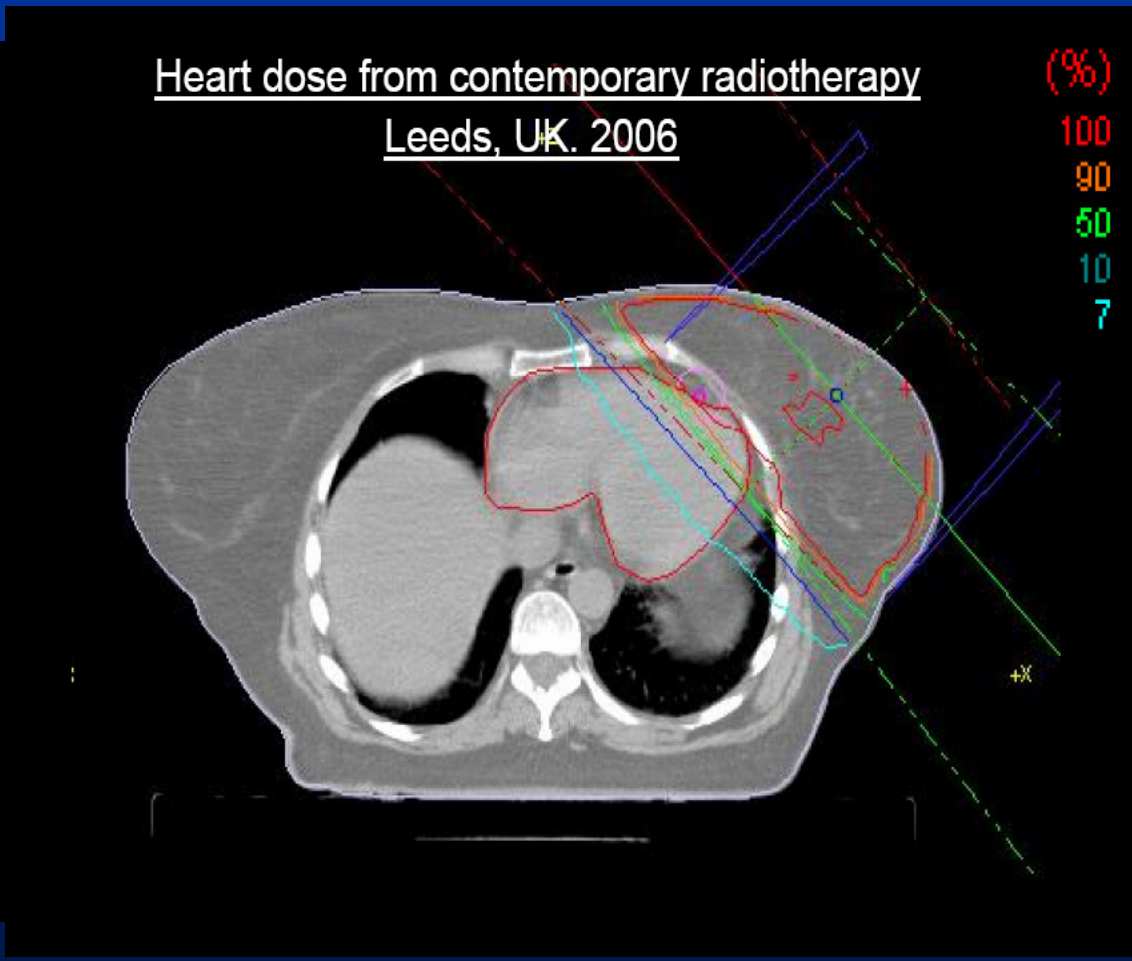
- Lumpectomy
- Mastectomy with large tumor (>5cm)
- Inflammatory breast cancer

Axillary lymph nodes:

- 4 or more positive nodes
- 1-3 positive nodes with aggressive biology
- Inflammatory breast cancer

Radiation and the heart





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Important Points

- More than ½ of breast cancer recurrences happen **AFTER 5 years**
- ER+ cancers are more likely to recur late (after 10 years)
- After 12 years, ~ 1 in 10 women who had a lumpectomy and radiation will have recurrence of cancer in the same breast
- **Local recurrence does not equal death**

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Cornered

by Mike Baldwin

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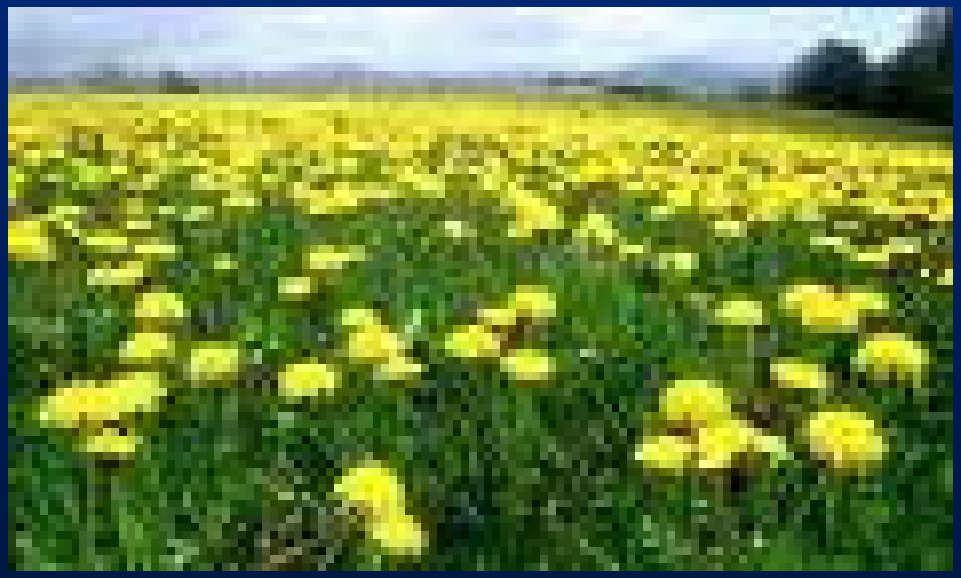
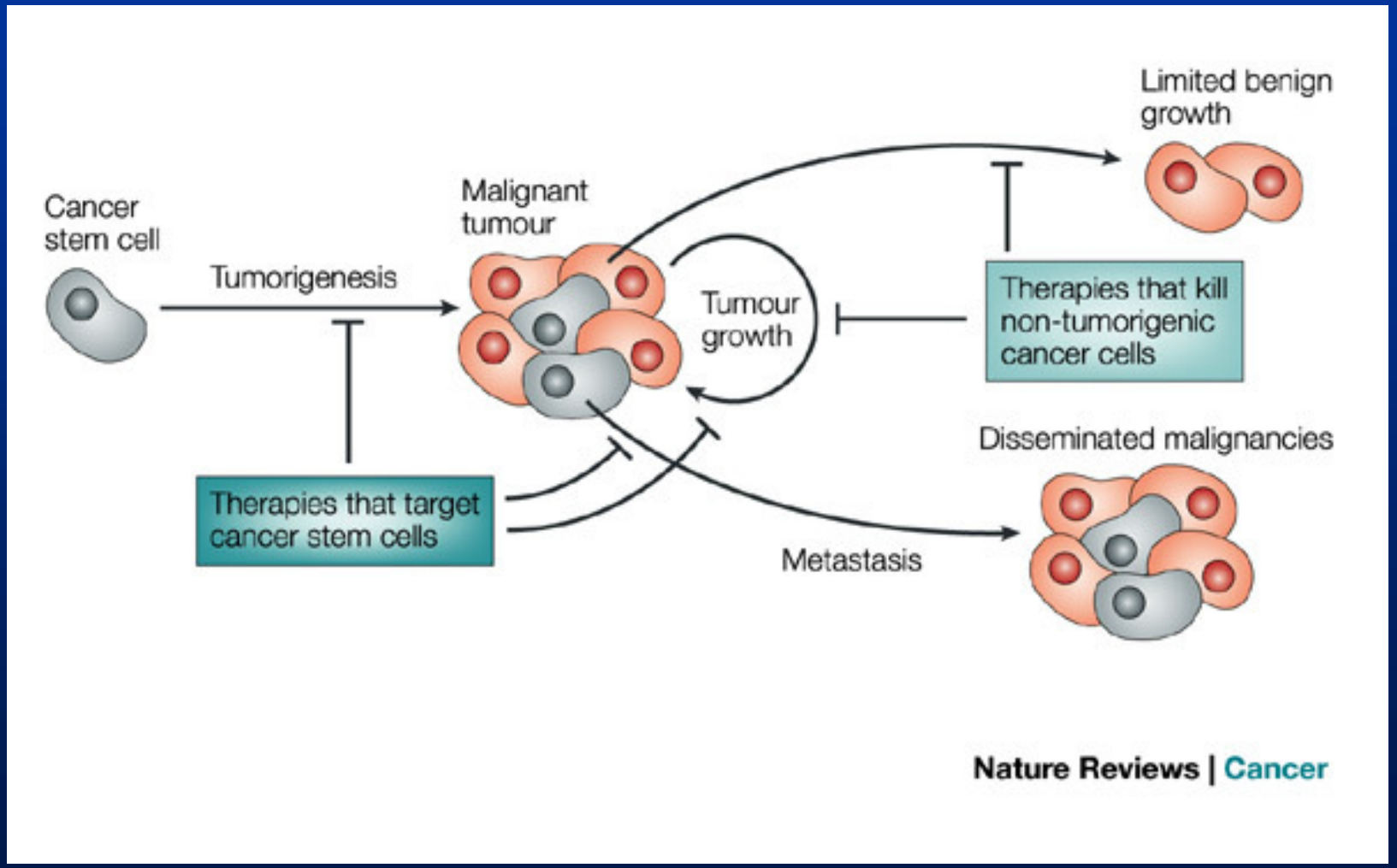
- Types and Subtypes
- Treatment Overview
- Systemic Therapy
- On the Horizon

Why Systemic Therapy?



Cancer Stem Cells

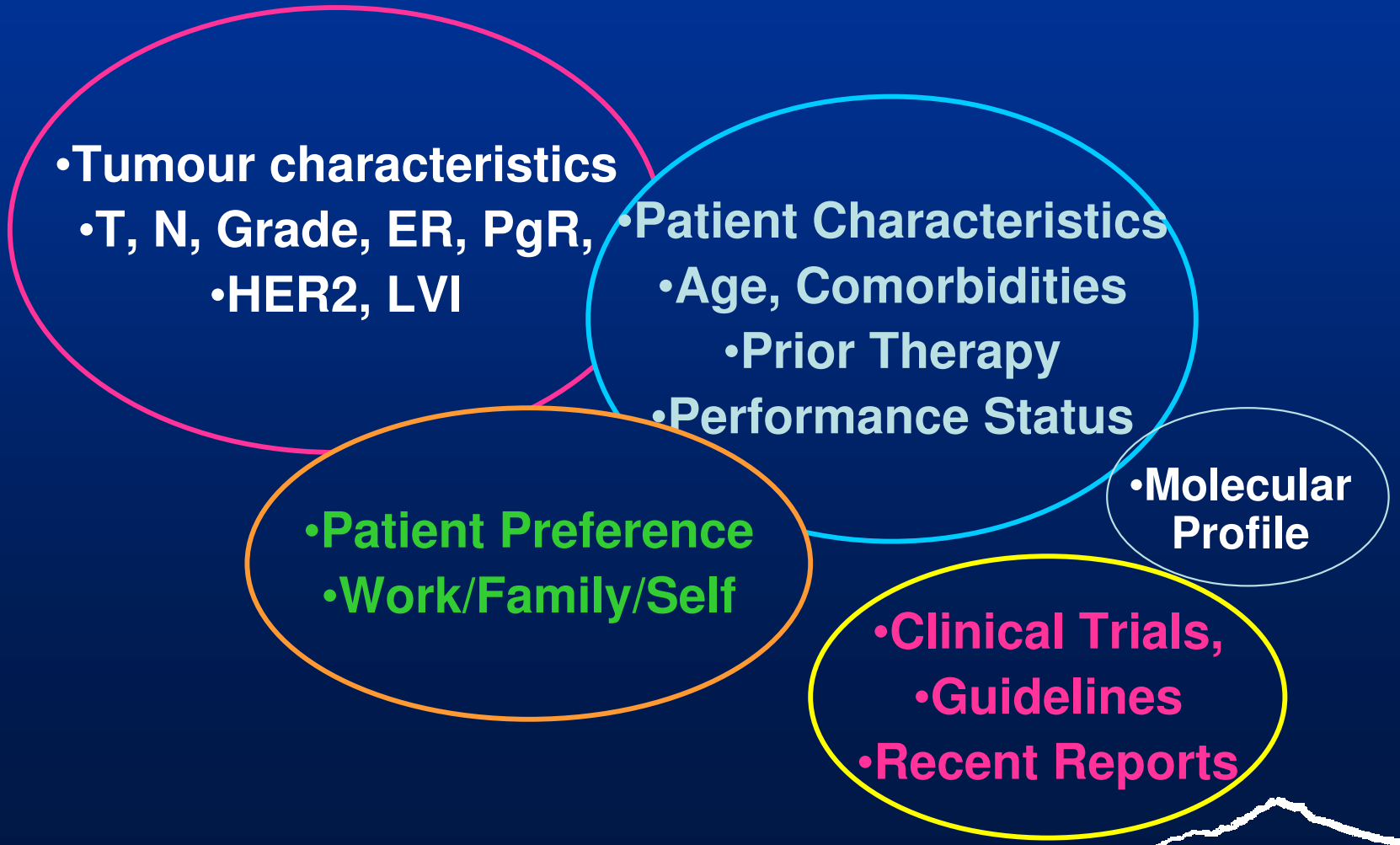


Before we move on…

- Adjuvant therapy: Systemic treatment given after local treatment is complete (surgery and/or) radiation

- Neoadjuvant therapy: Given BEFORE surgery for large tumors or inflammatory breast cancer

Adjuvant Therapy Decisions



Types of Systemic Therapy

- Hormonal therapy
- Chemotherapy
- Biologic Therapy

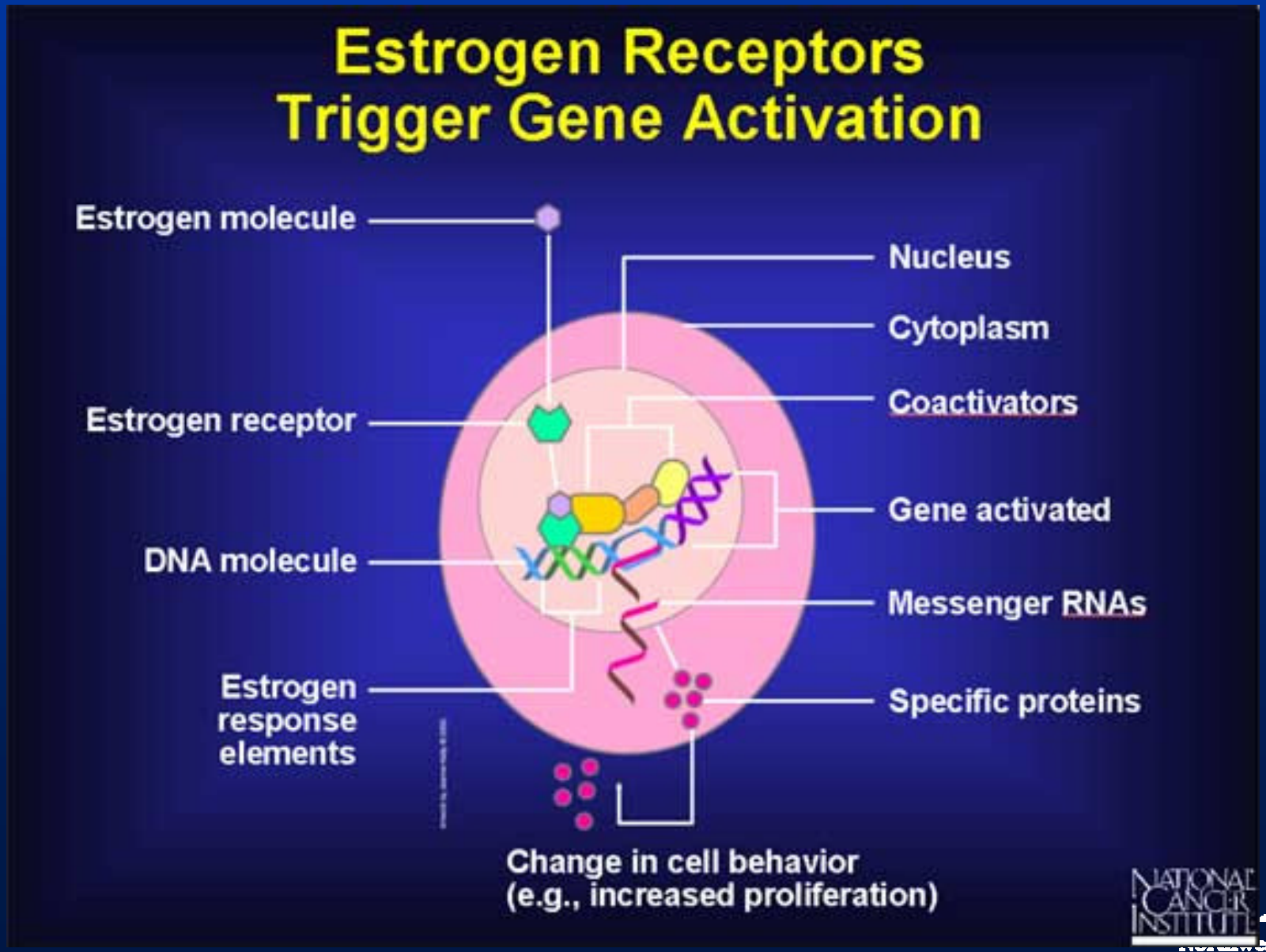
Hormonal Therapy

- Remove hormone-producing tissue
- Chemically suppress hormone-producing tissue
- Block hormones/receptors
- Give excess hormones

History

- 1896: Oopherectomy resulted in breast tumor regression
- Subsequent responses were seen after removal of pituitary and adrenal glands
- Tamoxifen developed 1966 to treat infertility

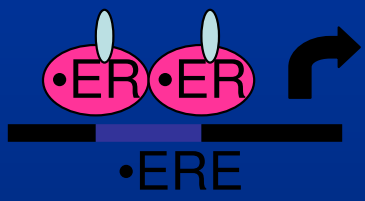
Relevance in Cancer



Estrogen Receptor-DNA Interactions

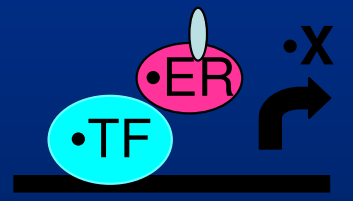
- **Classical Mechanism**

  E_2-*ER* complex binds directly to *ERE*s in target gene promoters.



- **Non-Direct DNA Binding Mechanism—*ERE* independent Genomic Action**

  Protein-protein interactions with other transcription factors.

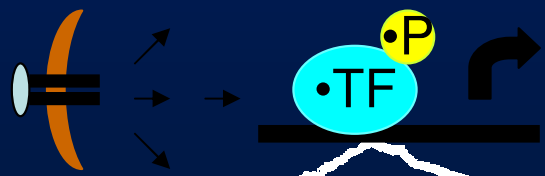


- **Ligand-Independent Genomic Action**

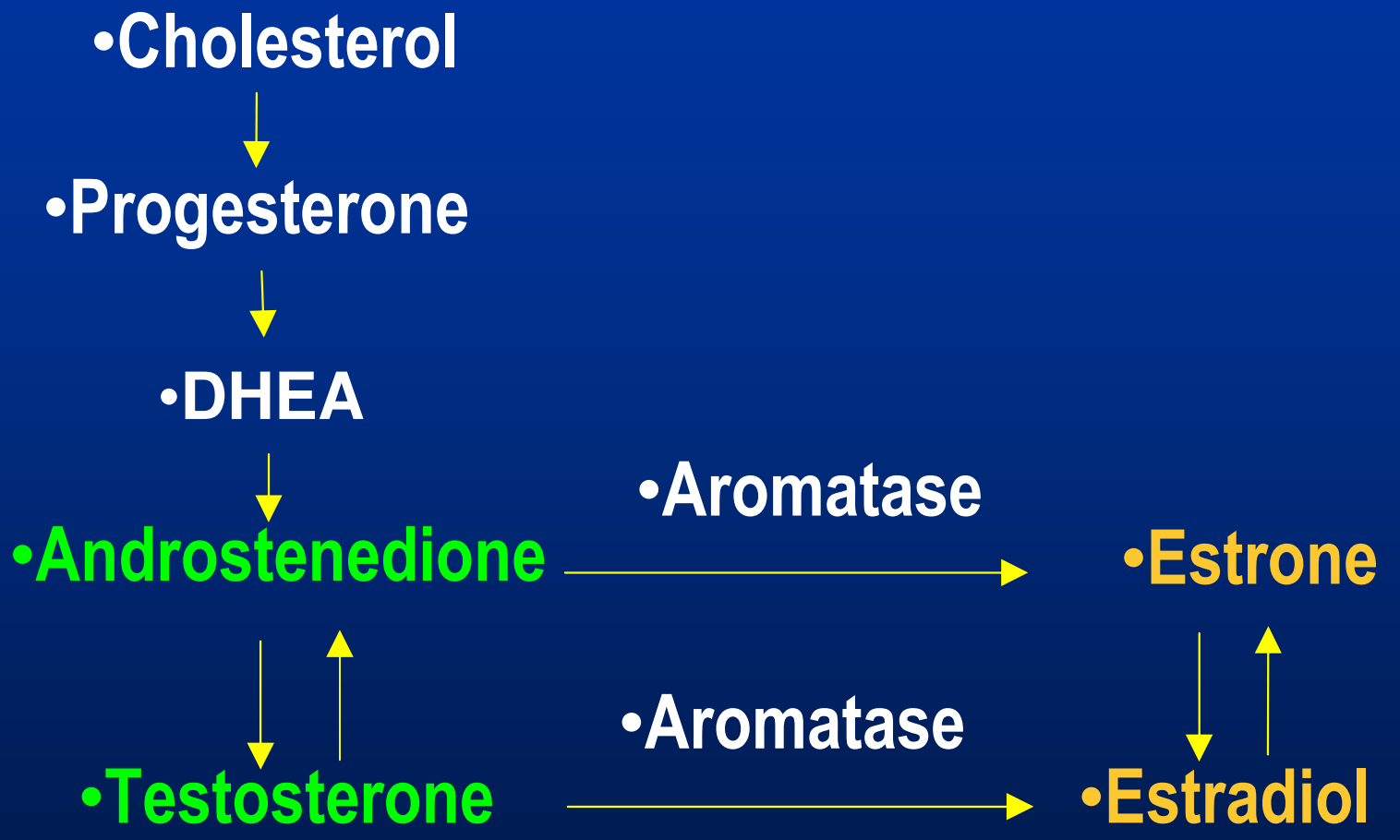
  Growth Factors activate Protein Kinase Cascades leading to phosphorylation (P) of *ER* at *ERE*s.

- **Non-Genomic Mechanism**

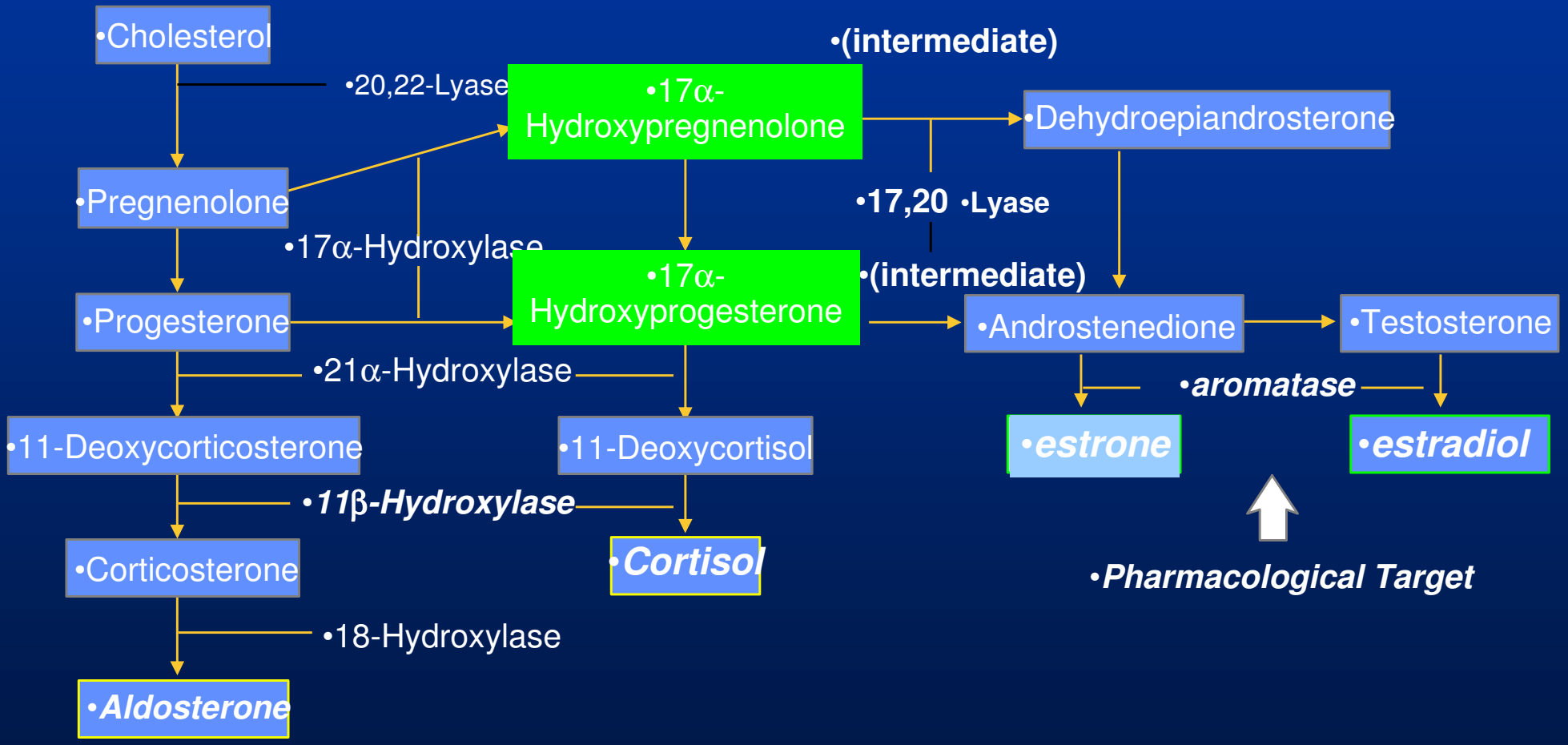
  Membrane-associated *ER*s mediate estrogen actions.



Estrogen Synthesis 101



Estrogen Synthesis 301



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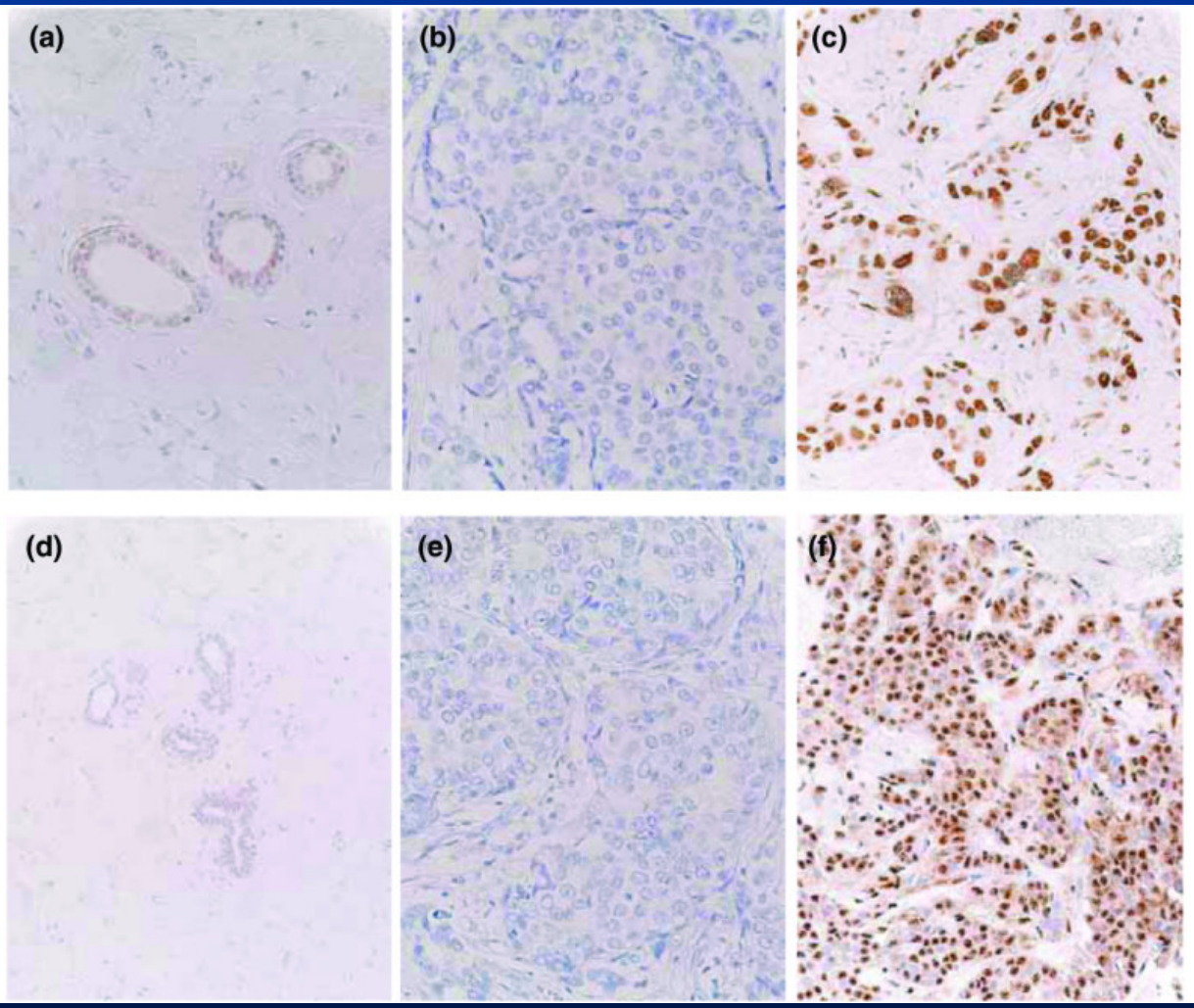
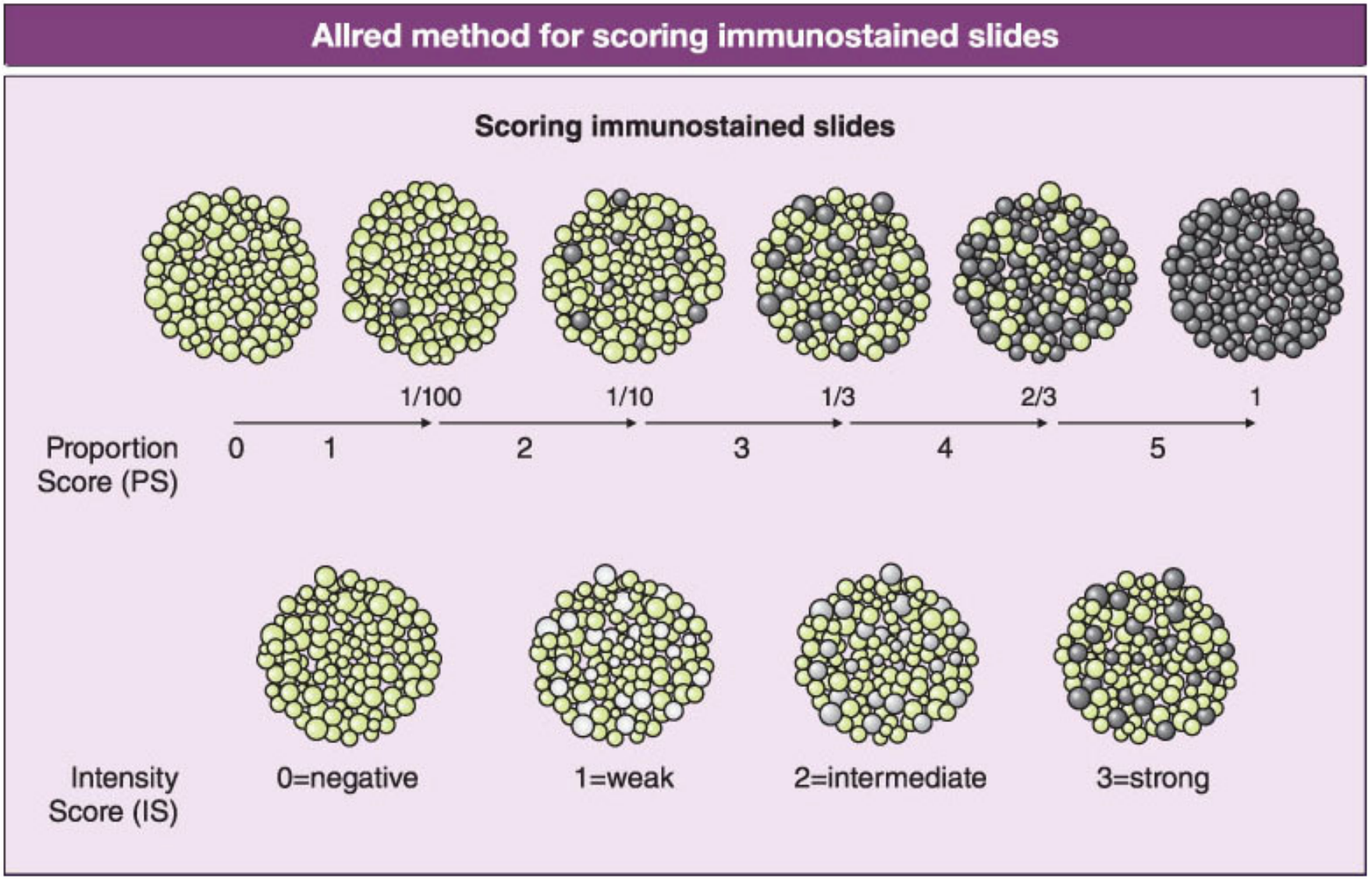
Normal vs Cancer: ER staining



How is ER level determined?



•Reproduced from *www.breastcenter.tmc.edu/research/cores/path/services/er.htm.*

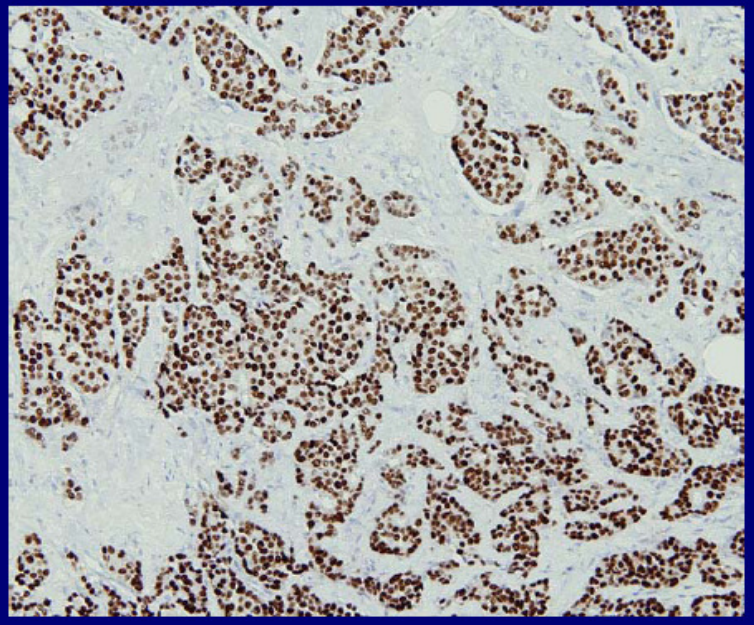
Caveat !

Initial Pathology Assessment Prior to Preoperative Therapy

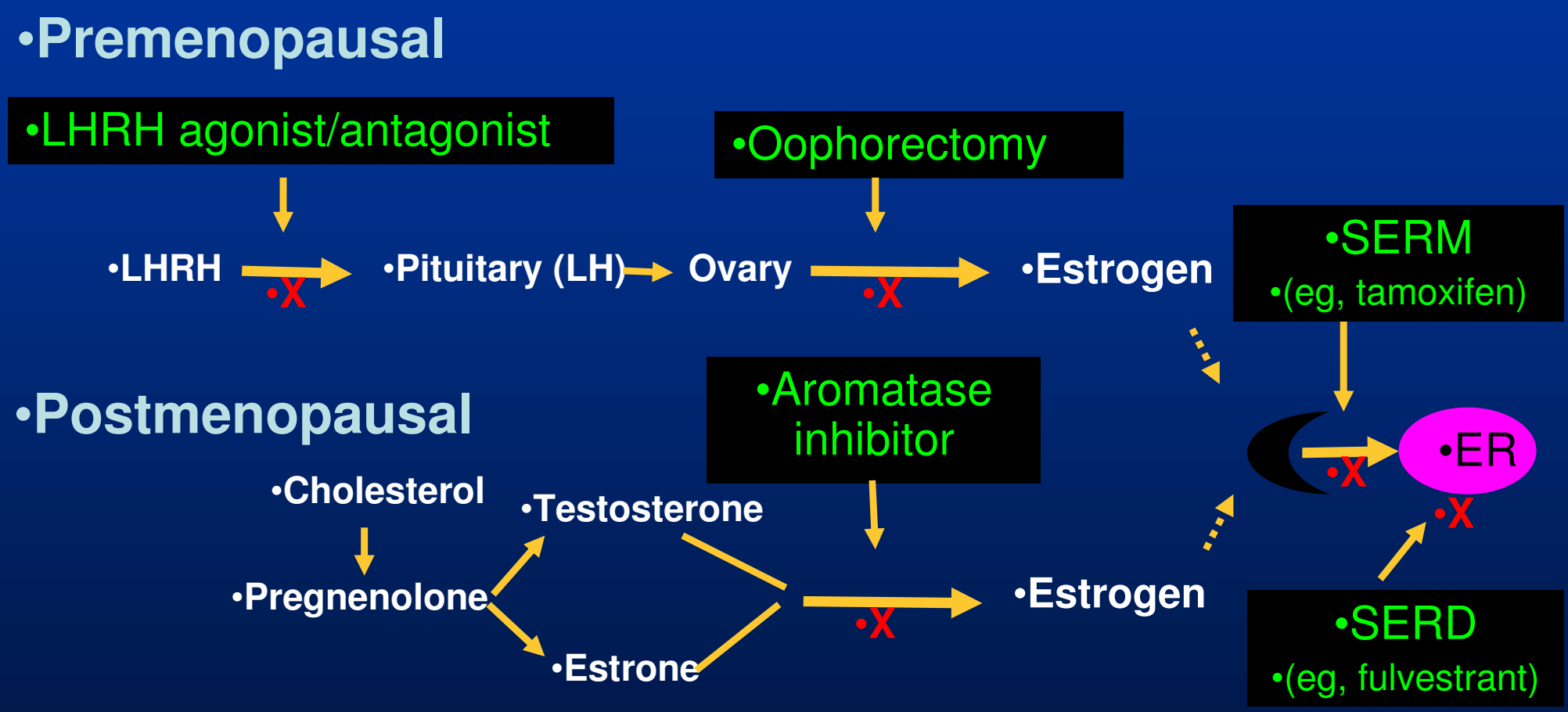
BIOMARKER ANALYSIS

Estrogen And Progesterone Receptor Status Assessment

By IHC Is Not a Standardized Test



Targets of Inhibition



•LH, luteinizing hormone; SERM, selective estrogen receptor modulator; SERD, selective estrogen receptor down-regulator.

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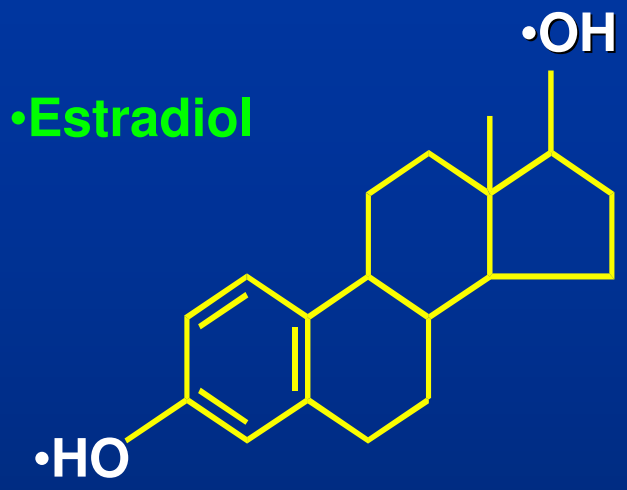
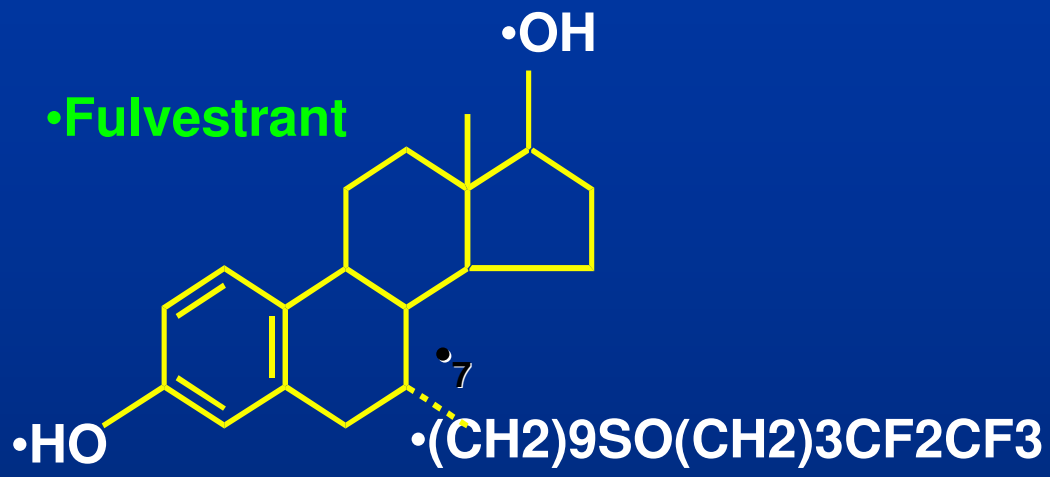
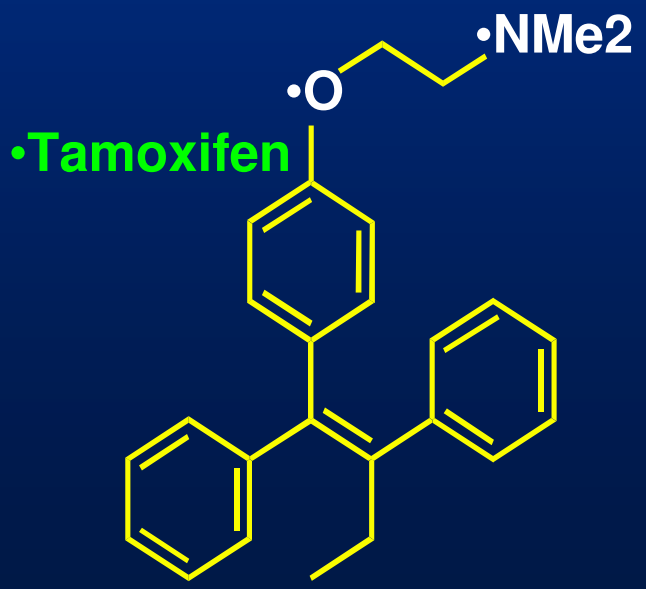
The Drugs

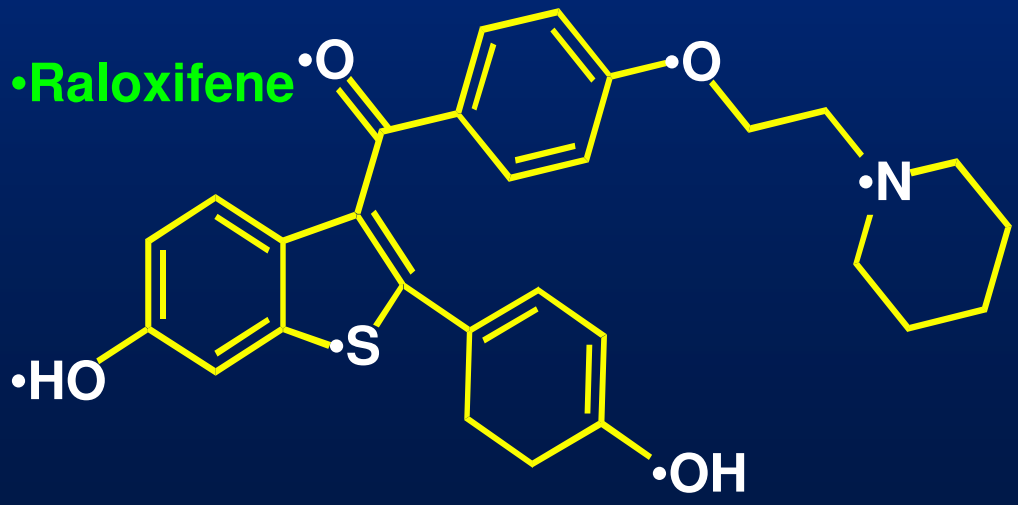
- **SERM/SERD**
  - Tamoxifen
  - Raloxifene
  - Fulvestrant
- **AIs**
  - Anastrazole
  - Letrozole
  - Exemestane
- **Other**
  - LHRH agonists
  - Estrogens, Progestins

Chemical structures

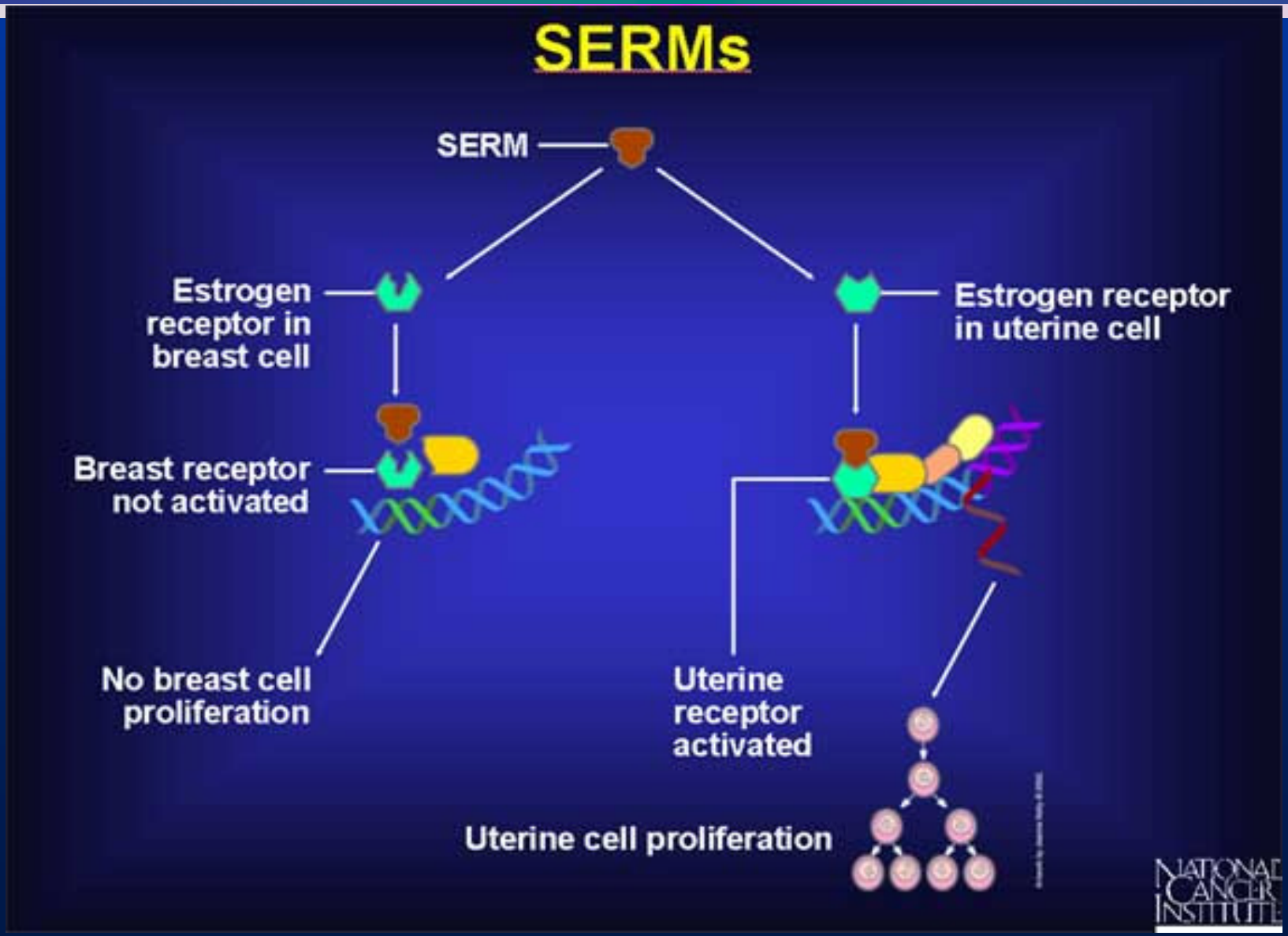








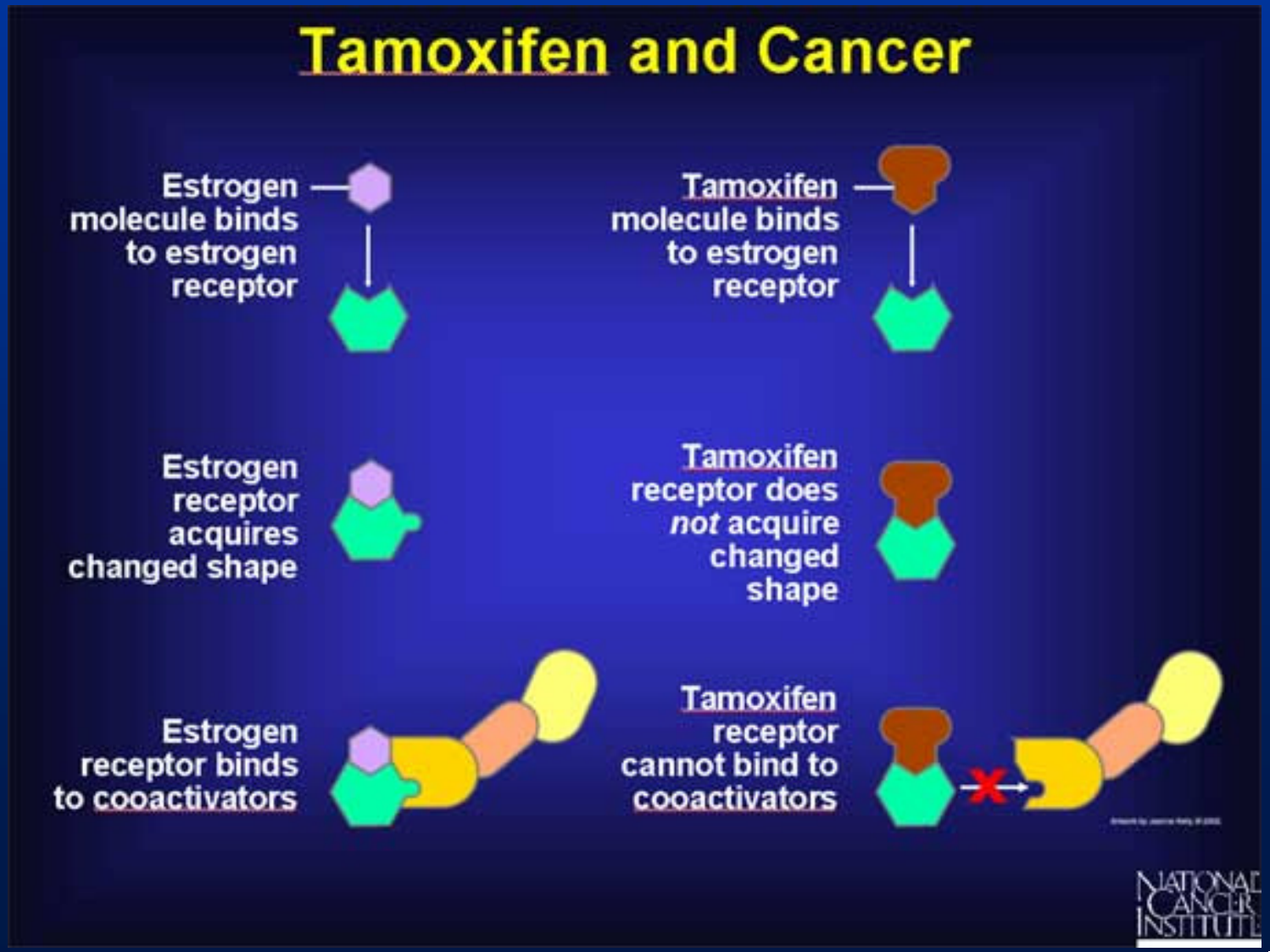
"Selective" Estrogen Receptor Modifiers



Tamoxifen

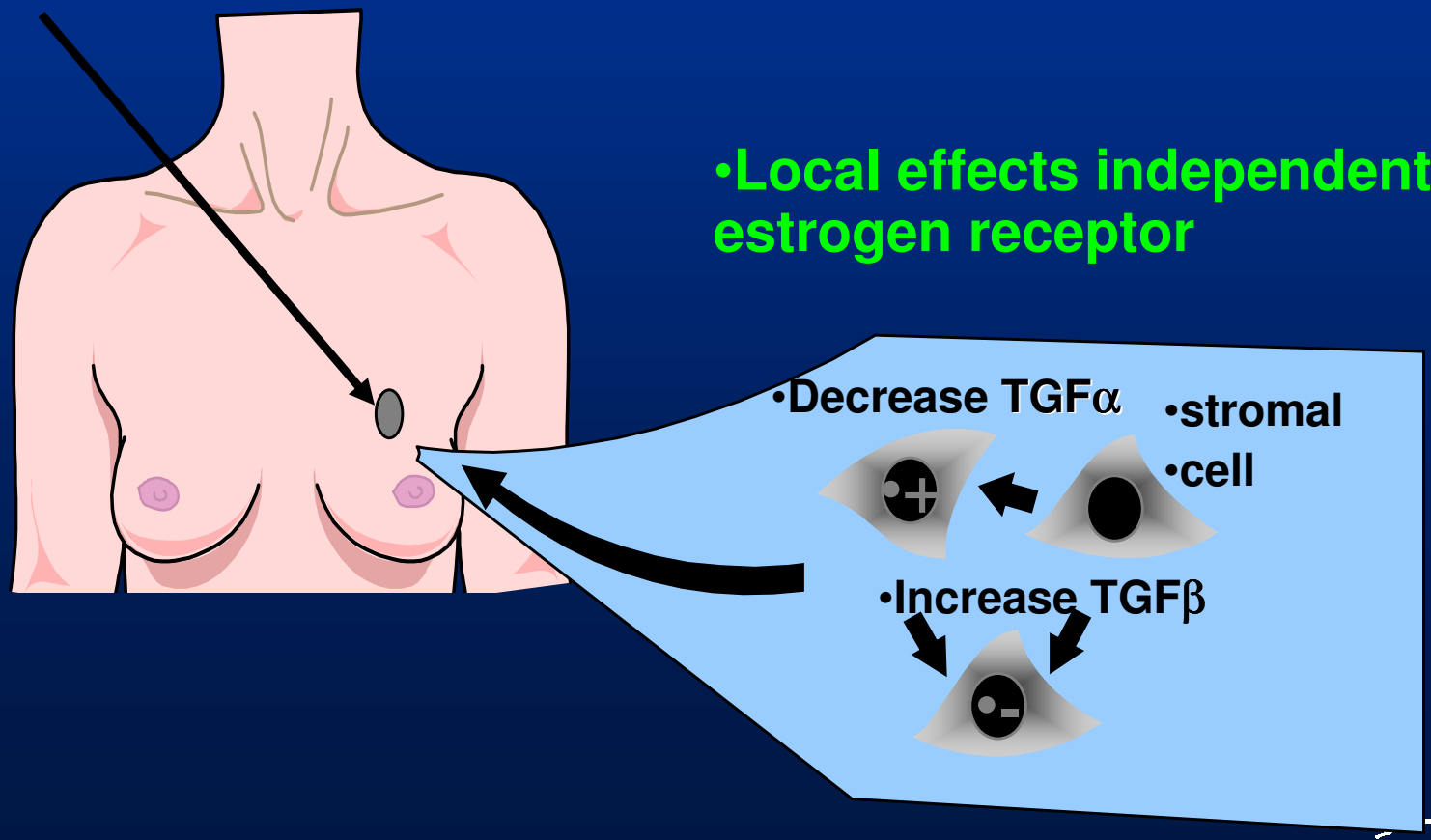
- Developed in 1966 as an oral contraceptive.
- Uh-oh: induced ovulation.

Tamoxifen (SERM)

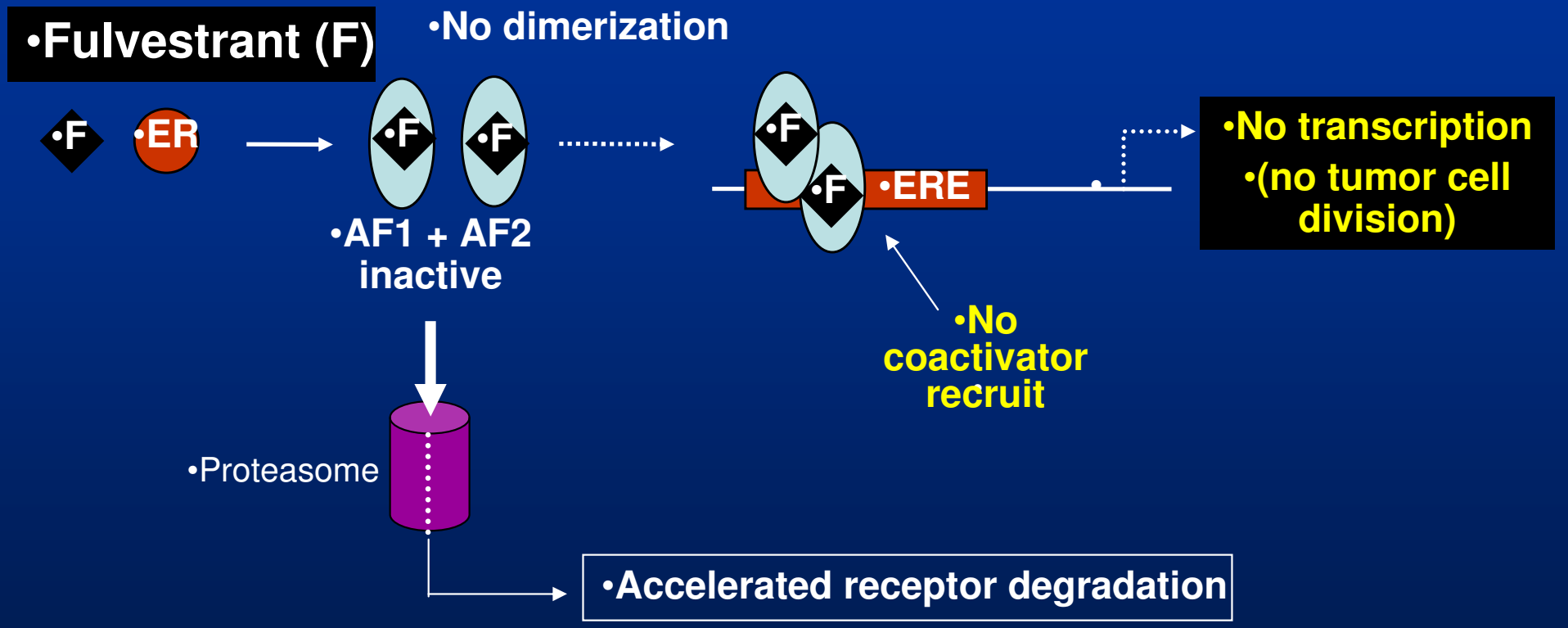


Other Actions of Tamoxifen

- Antiestrogen effects



Fulvestrant (SERD)



•Wakeling AE et al. *Endocr Relat Cancer* 2000

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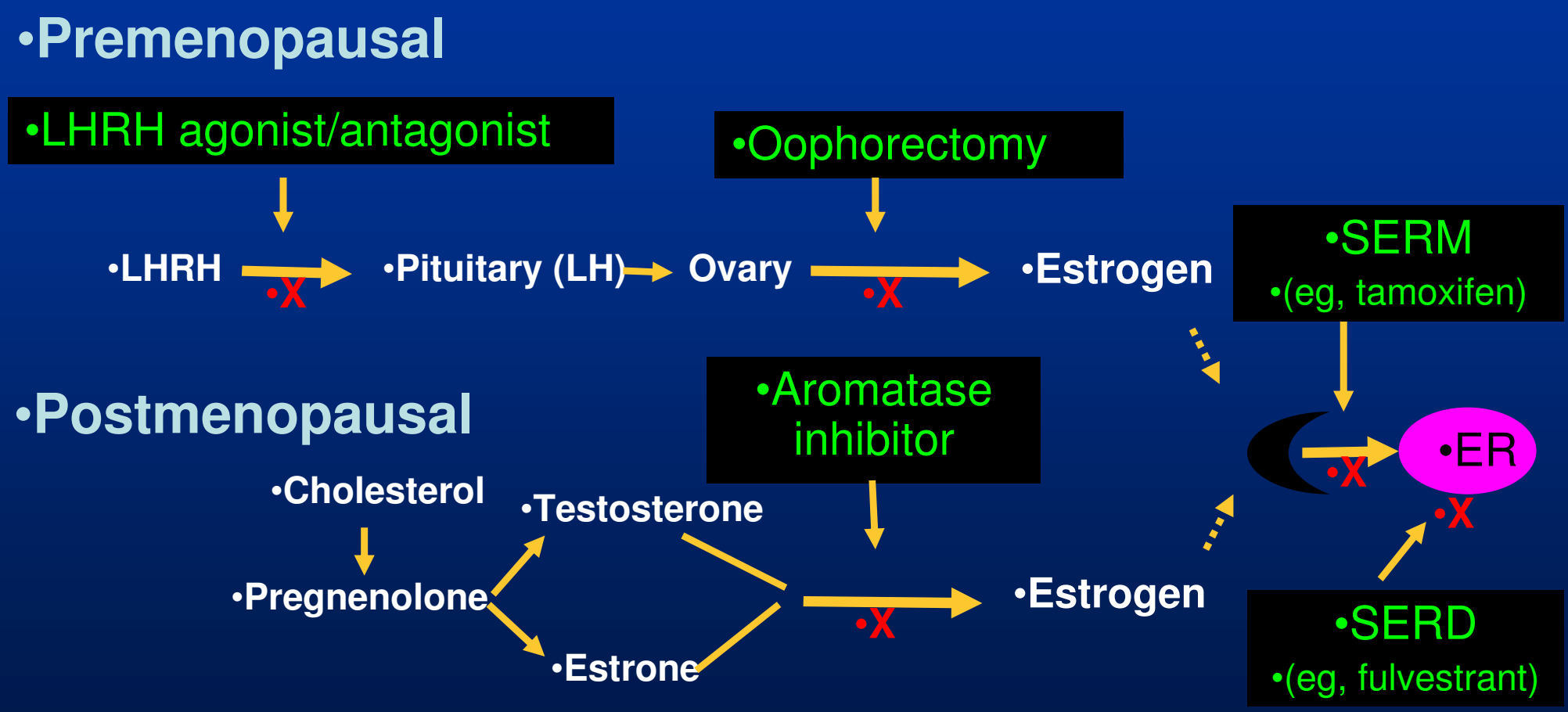
The Drugs

- SERM/SERD
  - Tamoxifen
  - Raloxifene
  - Fulvestrant
- AIs
  - Anastrazole
  - Letrozole
  - Exemestane
- Other
  - LHRH agonists
  - Estrogens, Progestins

Targets of Inhibition



•LH, luteinizing hormone; SERM, selective estrogen receptor modulator; SERD, selective estrogen receptor down-regulator.

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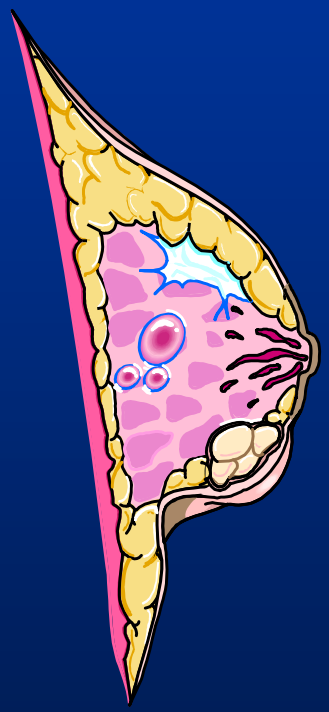
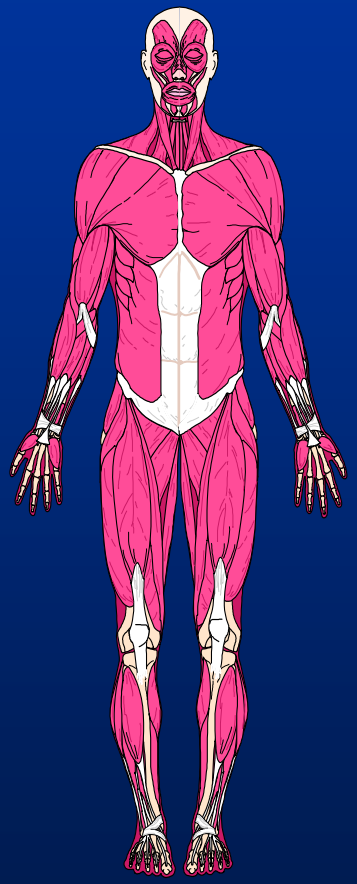
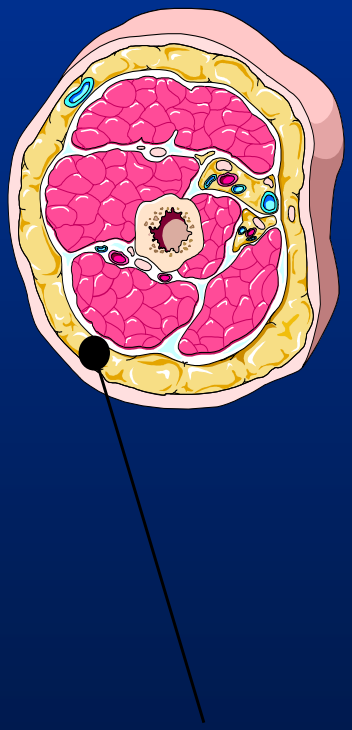
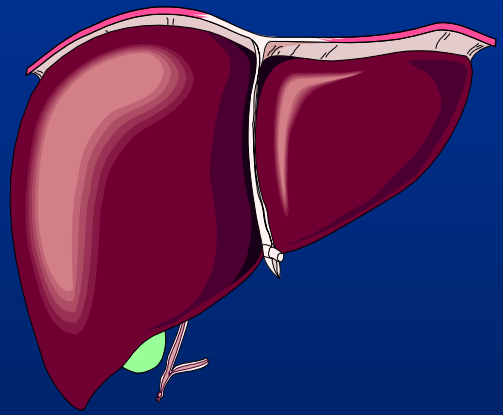
Peripheral Aromatization









- Breast
  - tumor
- Muscle
- Fat
- Liver

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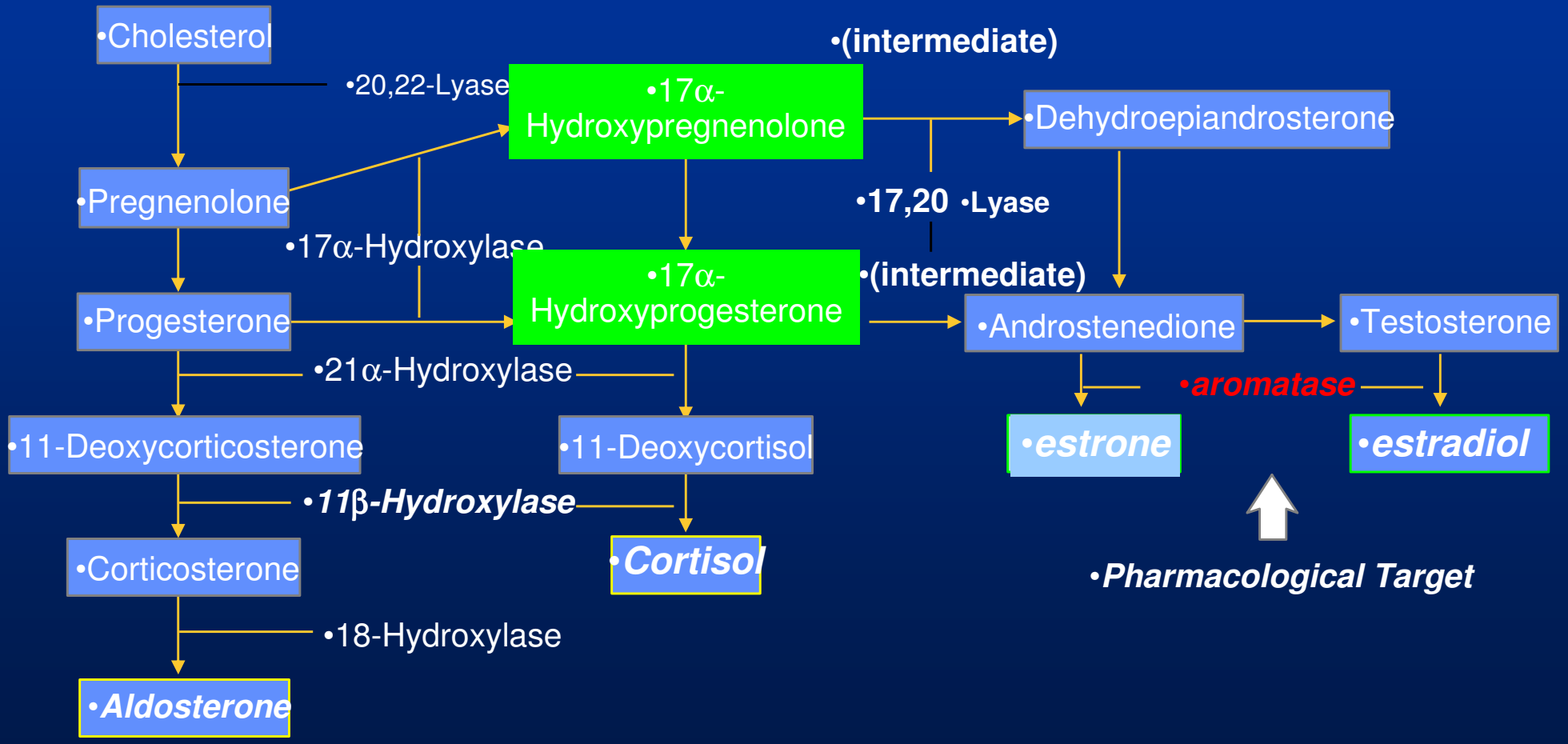
Aromatase inhibitors

- **Aminoglutethimide was developed as an anti-epileptic**
- **Shown to inhibit estrogen production in 1977**
- **The non-steroidals AI reversibly bind the substrate binding site**
  - Letrozole, anastrazole
- **The steroidal AIs irreversibly bind the substrate binding site**
  - exemestane

Estrogen Synthesis 301



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Aromatase inhibition within the breast tumor

•P-450 Aromatase

•+ NADPH-cytochrome P-450 reductase

•ANDROGENS ⟶ ESTROGENS

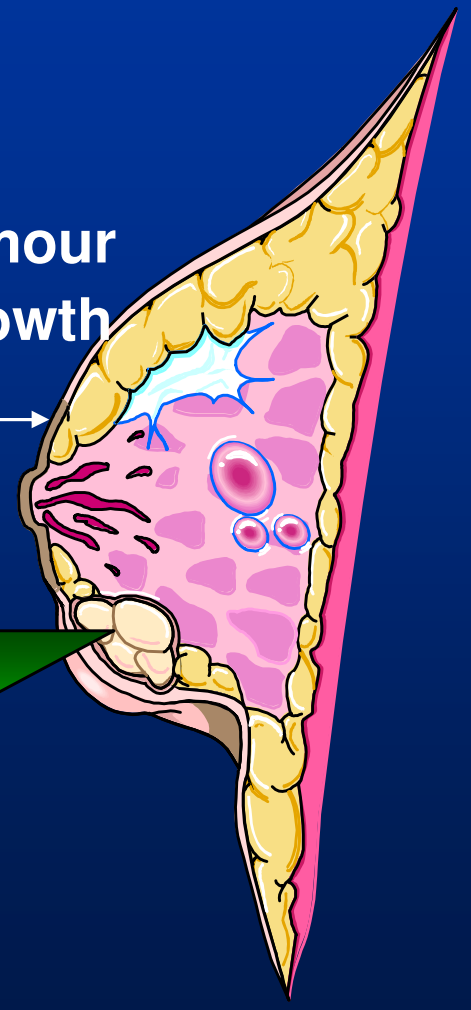
•(Testosterone, androstenedione, •16-OH-testosterone)

•(estradiol, estrone)

•Aromatase Inhibitors

•tumour

•growth



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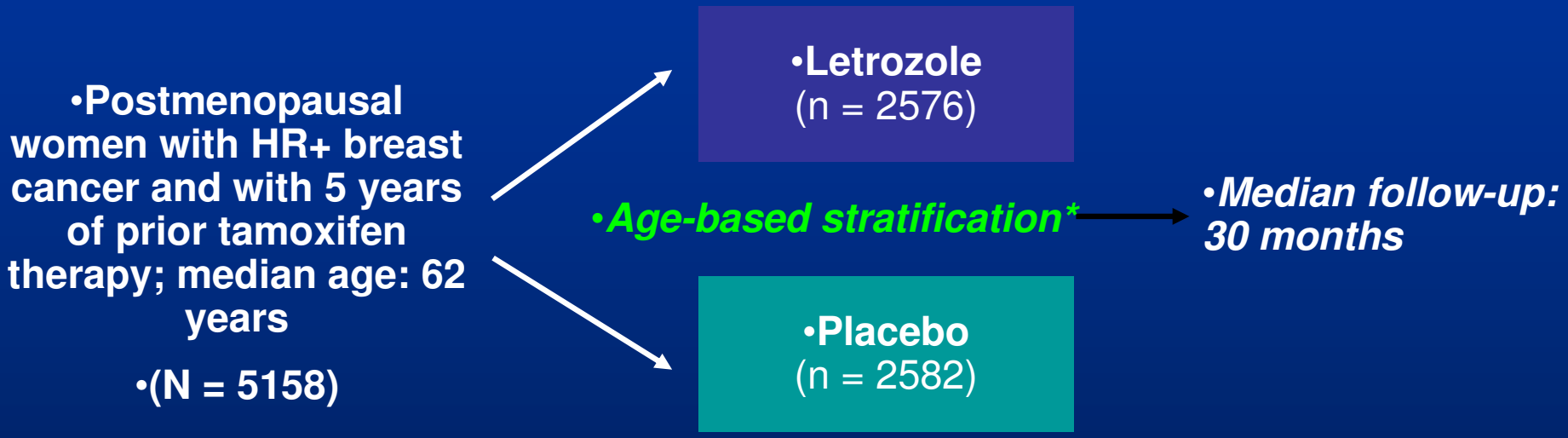
Adjuvant Endocrine Trials

- Initial Adjuvant Tamoxifen x 5yrs
- Initial Adjuvant AI x 5 yrs
- Switching: Tam 2-3yrs followed by AI 2-3 yrs
- Extended therapy: Tam x 5yr followed by AI x 5years

MA.17: Letrozole After 5 Years of Tamoxifen



- In preliminary analyses, letrozole therapy significantly improved OS and decreased risk of recurrence by 42% compared with placebo

•* ≤ 60 yrs < 60 years; 61-69 years; ≥ 70 years.

•Muss HB, et al. SABCS 2006. Abstract 102.

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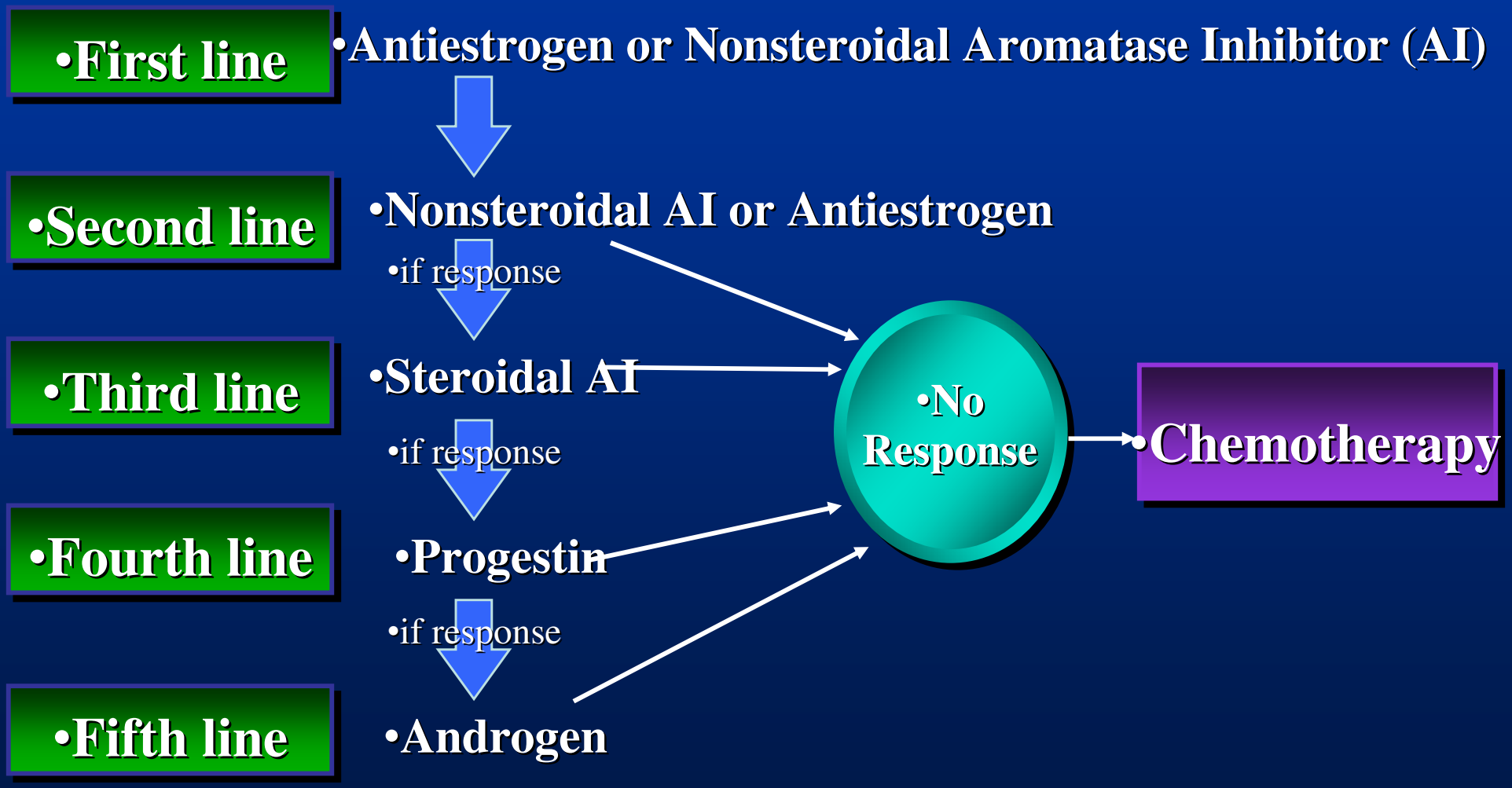
2009 Update

- OS benefit to extended therapy in node positive pts
- DFS benefit larger in women who were premenopausal at the time of entry
- WORSE QOL in premenopausal women on letrozole
- Cognitive function better on letrozole compared to tamoxifen (BIG-98)

Hormone positive post-menopausal Metastatic Breast Cancer



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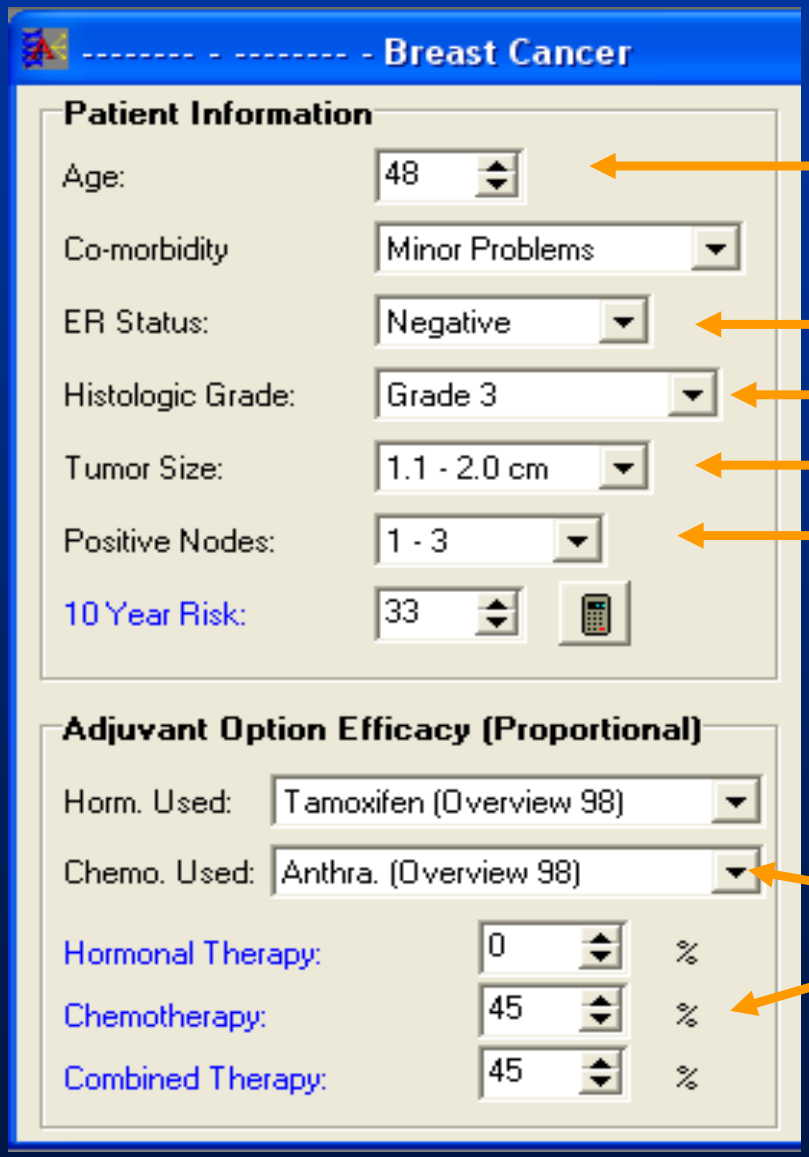
Chemotherapy: When?

- We believed, based on clinical trials, that every woman with a tumor >1cm should be offered chemo. We have learned that biologically less-aggressive tumors, particularly those that are ER+, are more effectively treated with hormonal blockade and may not gain any benefit from chemo. The trick is deciding who gets what!

Chemotherapy: When?

- **Absolute Indications:**
  - ER negative tumor
  - Age <= 35
  - HER2 + tumor
  - Inflammatory breast cancer
  - Positive lymph nodes (?)
  - “Large” tumor (how large?)

•www.adjuvantonline.com



•Adjuvant! input Data

- •Age = 48yr
- •Health: Default is 'minor probs'
- •ER = negative
- •Grade = 3
- •T-size = 1.5cm
- •Nodes = 2+ of 11

•Treatment Choice and Efficacy

- •Chemo choice: Anthracycline based
- •Efficacy from literature: 45%

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Chemotherapy: When?

The Common and Problematic Example:

- ER+, low grade tumor
- Postmenopausal
- 2.2cm
- 0 lymph nodes

Oncotype DX

- **A multigene assay to predict recurrence of Tamoxifen-treated, node-negative breast cancer (Paik NEJM 204)**
- **21 genes - proliferation (5), invasion (2), HER 2 (2), Estrogen (4) , 3 others and 5 reference genes with a Recurrence Score (RS) algorithm**
- **For node negative, Tam treated (JCO 2007):**
  - –Luminal A = low risk oncotype DX
  - –Luminal B = mod/high risk

RESULTS

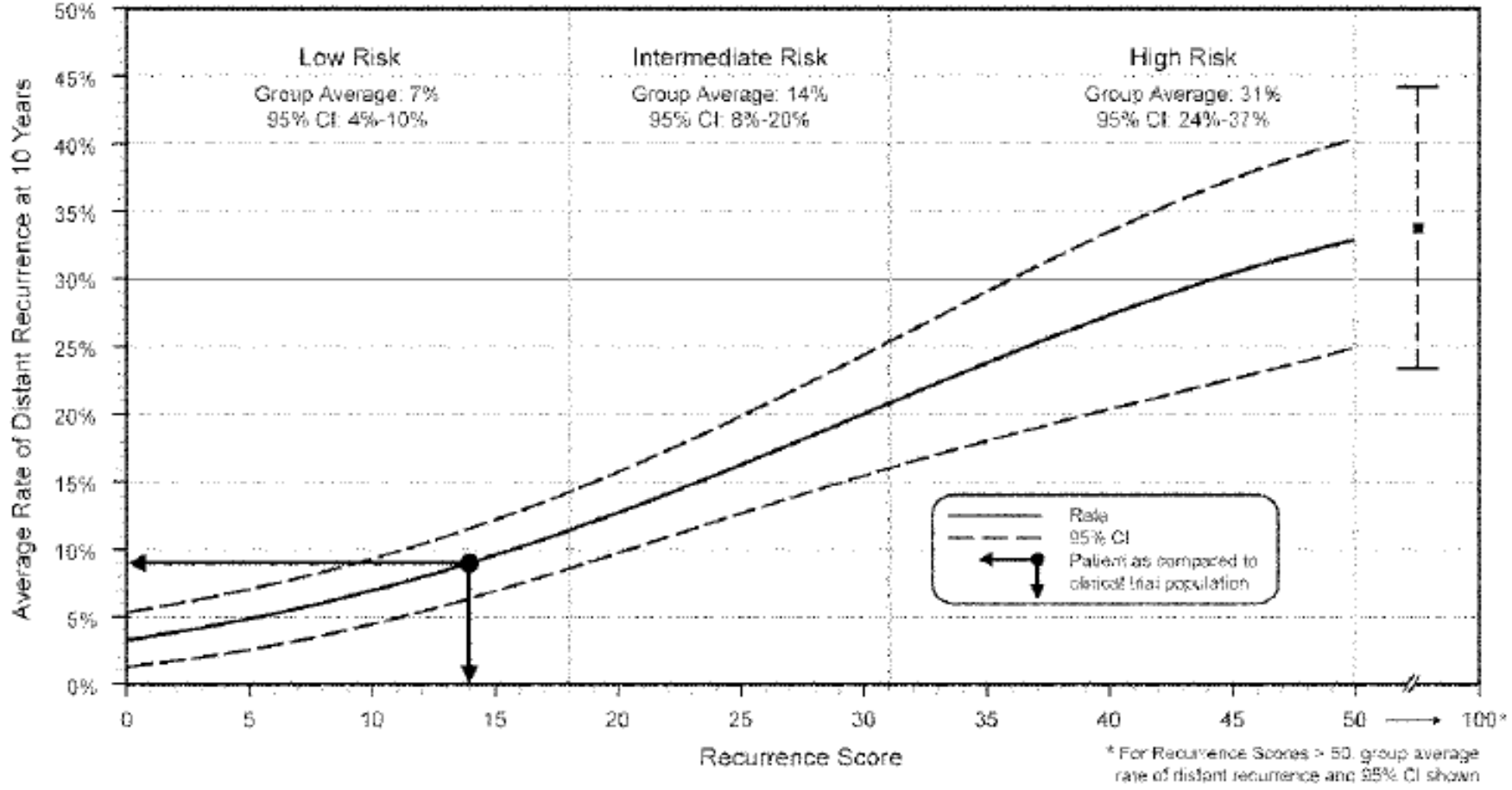
Recurrence Score = 14

Test results should be interpreted using the information in the Clinical Experience section below, which applies only to patients consistent with this clinical experience.

CLINICAL EXPERIENCE

Patients with a Recurrence Score of 14 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of 9% (95% CI: 6%-12%)

The following results are from a clinical validation study with prospectively-defined endpoints involving 668 patients. The patients enrolled in the study were female, stage I or II, node negative, ER-positive, and treated with tamoxifen. *N Engl J Med* 2004; 351: 2817-26.



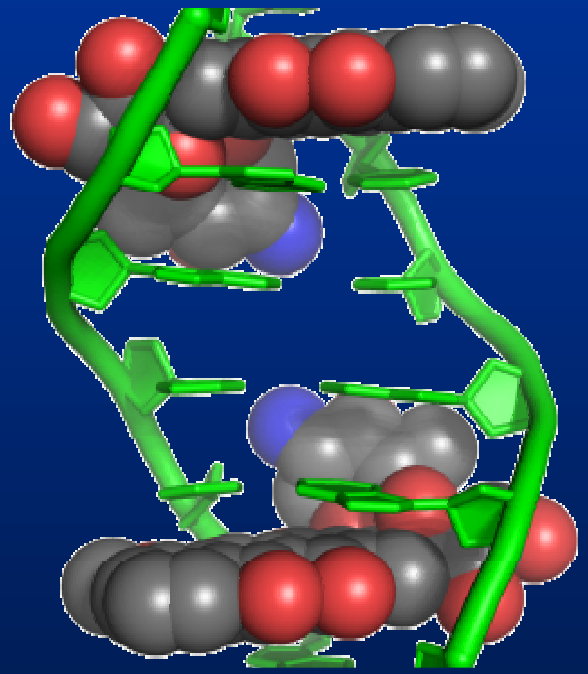
Chemotherapy: What?

- **How do we decide what drugs to give?**
  - Large prospective clinical trial results
  - Consideration of a person's comorbidities and preferences
  - Bias of our training
  - (Insurance coverage…)

Chemotherapy definitions

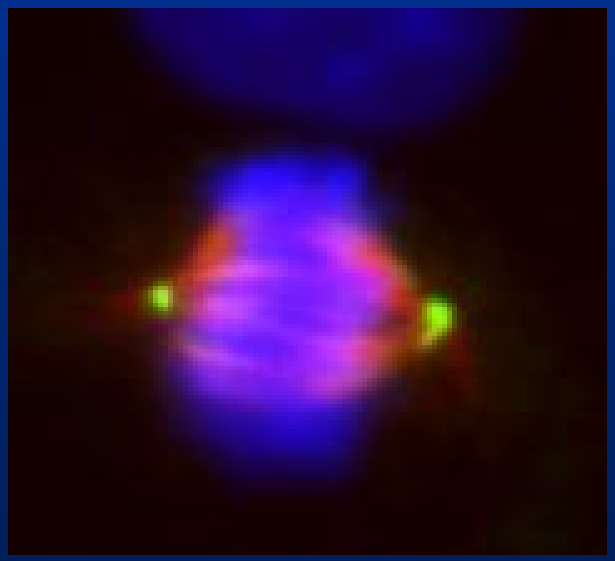
- Anthracycline: Doxorubicin(Adriamycin, A) or Epirubicin (E)
- Taxane: Paclitaxel (P) or Docetaxel (D)
- Platinum: Carboplatinum or Cisplatinum (C or P)
- Others: 5FU (F), Cyclophosphamide (C), Methotrexate (M)

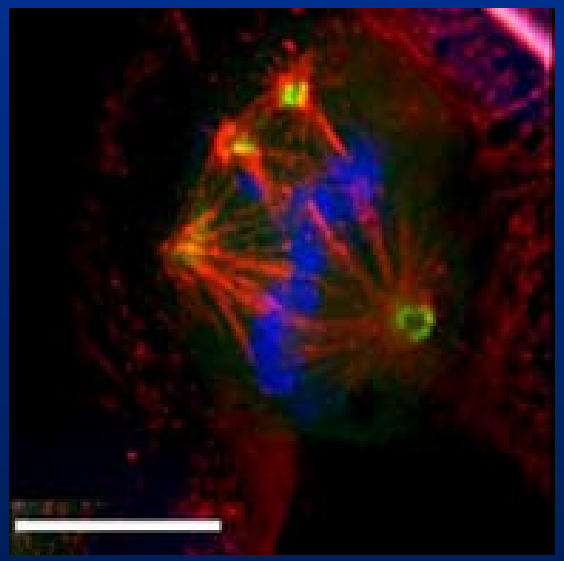
What Do Anthracyclines Do?

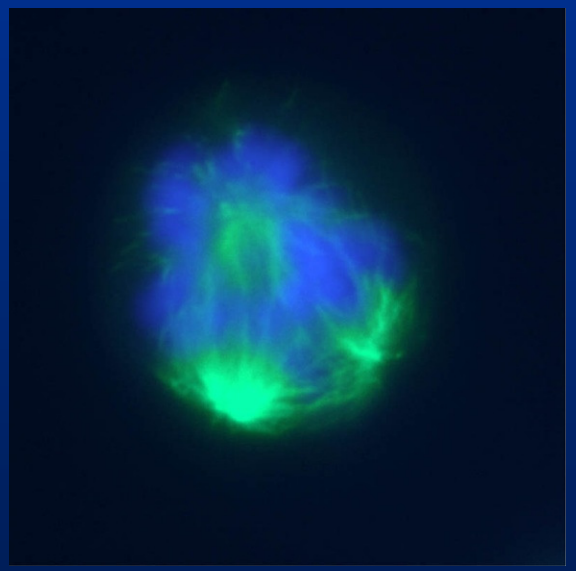


What Do Taxanes Do?

- Promote microtubule formation







- Prevent microtubule dissassembly

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Chemotherapy Evolution

- Every tumor >1cm and/or + lymph nodes needs chemo (CMF or AC)
- Anthracycline-containing regimens are superior though more toxic (AC, FAC)
- Taxane-containing regimens are superior (TAC, AC-T)
- Everybody gets A and T
- Anthracycline-containing regimens may not be necessary in some cancers (HER2+)

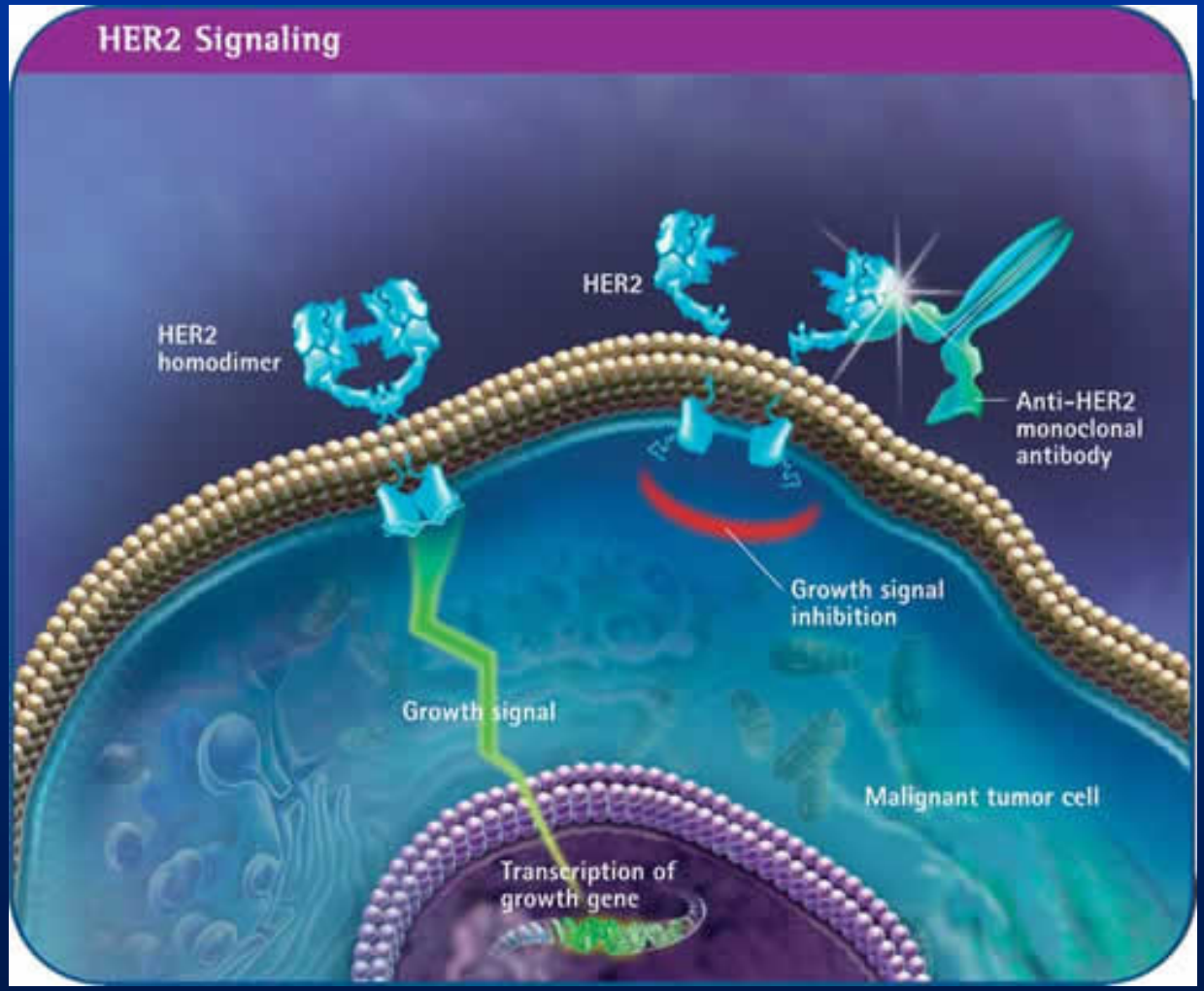
Chemotherapy Evolution

- Some breast cancers may not need ANY chemo (low Oncotype DX score)
- HER2+ breast cancers can be treated with non-anthracycline regimen (TCH)
- Luminal A subtypes don't need taxanes (SABCS 2009)
- We are learning who NOT to treat

Biologic Therapy

- **Monoclonal antibodies**
  - Trastuzumab (Herceptin) 2005
  - Bevacizumab (Avastin)

What Does Herceptin Do?



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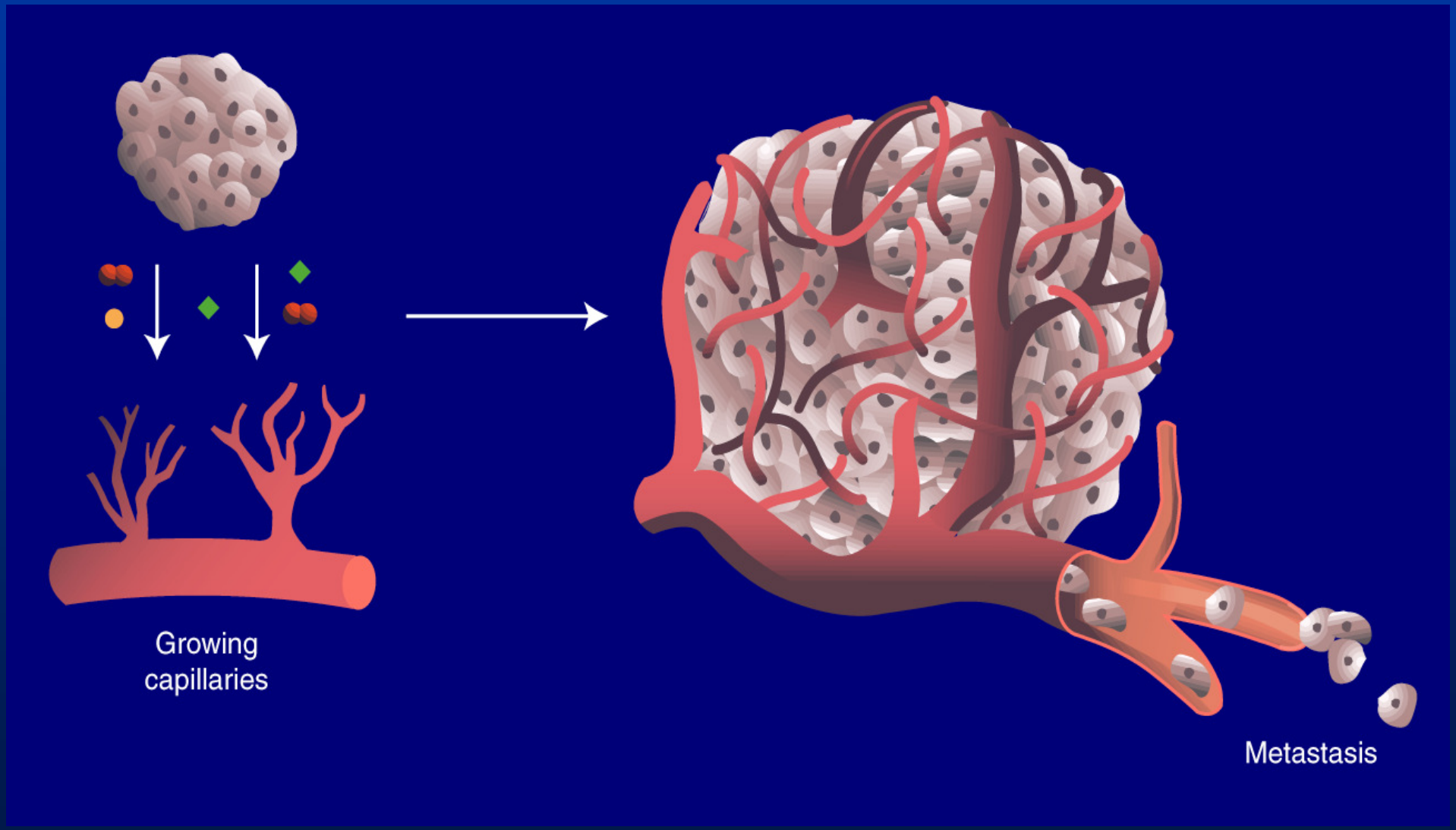
Tumor Angiogenesis



•Bevacizumab (Recombinant Humanized •Monoclonal Antibody to VEGF)

- Humanized to avoid immunogenicity (93% human, 7% murine)
- Recognizes all isoforms of vascular endothelial growth factor, $K_d = 8 \times 10^{-10} M$
- Terminal half life 17-21 days

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Treatment Risks: Cardiac

- **Chemotherapy:**
  - The red drug (Adriamycin)
    - Heart failure in up to 2% of patients, occurs late
    - Higher risk if over age 65
    - Higher risk if high blood pressure, diabetes, smoker
  - Herceptin
    - Heart failure in up to 4% of patients
    - Much higher risk if given with Adriamycin
    - Usually reversible if the drug is stopped
- **Radiation:**
  - If received between 1973 and 1992, higher risk of dying from heart attack with left-sided tumor

Treatment Risks: Other Cancers

- **Chemotherapy risks:**
  - Leukemia (Adriamycin, Cytoxan)
  - Bladder cancer (Cytoxan)
- **Hormone therapy risks:**
  - Uterine cancer (Tamoxifen)
- **Radiation risks:**
  - Lung cancer, skin cancer
  - New breast cancer
  - Angiosarcoma (very rare)

Treatment Risks: Other

- Osteonecrosis of the femoral head from steroids
- Osteonecrosis of the ribs from radiation
- Neuropathy from chemotherapy
- Decreased lung capacity from radiation therapy
- Cataracts from Tamoxifen

To Summarize So Far…

- Systemic therapy can be endocrine, chemo or biologic therapy
- We have been overtreating with chemo; we are learning who not to treat
- Biologic therapy with trastuzumab is now standard for HER2+ tumors
- Ongoing endocrine blockade is important for ER+ tumors

Overview

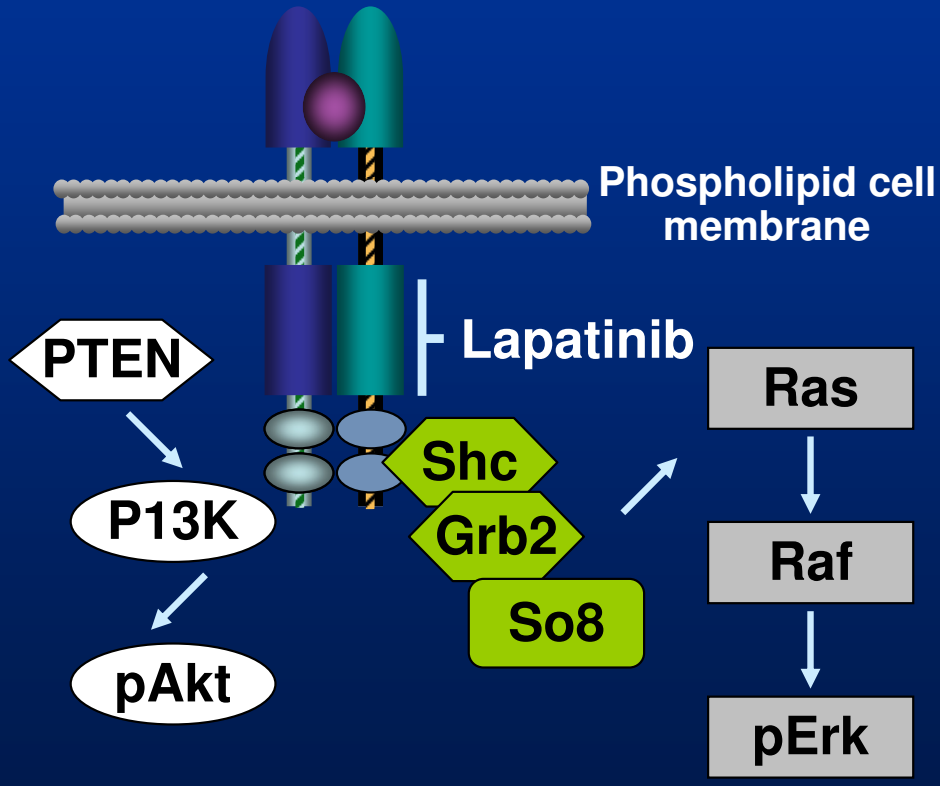
- History
- Causes
- Pathophysiology
- Types and Subtypes
- Treatment Overview
- Systemic Therapy
- On the Horizon

Predictions

- Bisphosphonates will become part of adjuvant therapy to decrease breast cancer recurrence
- Low Oncotype = no benefit chemo even in pts with 4+ lymph nodes
- More biologics with conjugated toxins
- More small molecule inhibitors

Lapatinib: EGFR and HER-2

- **Oral tyrosine kinase inhibitor of ErbB1 and ErbB2**
  - **Blocks signaling through EGFR and HER-2 homo and heterodimers**
  - **Blocks signaling between other ErbB family members**



Rusnak DW, et al. *Mol Cancer Ther*. 2001;1:85-94; Xia W, et al. *Oncogene*. 2002;21:6255-6263.

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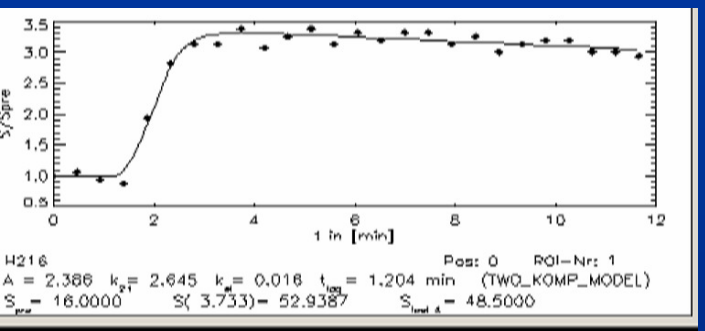
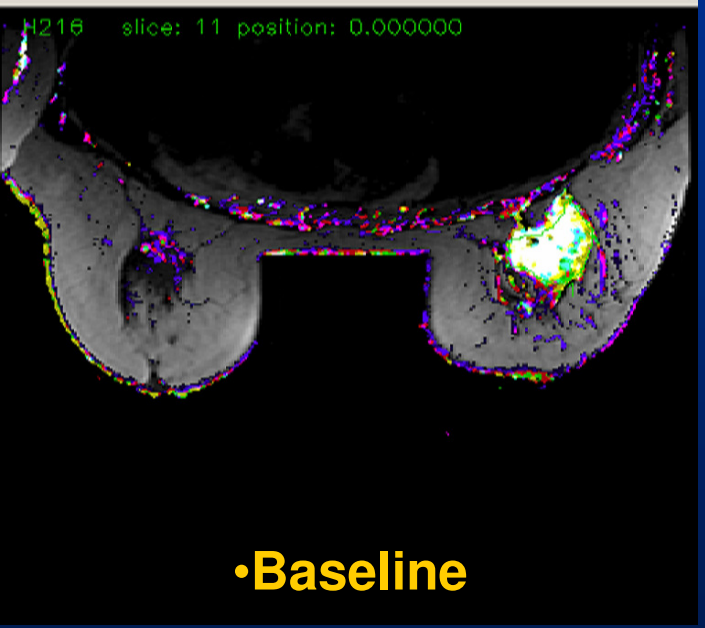
Bevacizumab + Chemotherapy

- **NCI 0173**
  - Bevacizumab alone, then
  - Docetaxel 75mg /m2
  - Doxorubicin 50mg/m2
  - Bevacizumab 15mg/kg
    - All Q3 wks x 6
- **N=21**
  - Partial Response14 (67%)
    - cPR 1
  - Stable Disease 5 (24%)
  - Progressive Disease 2 (9%)

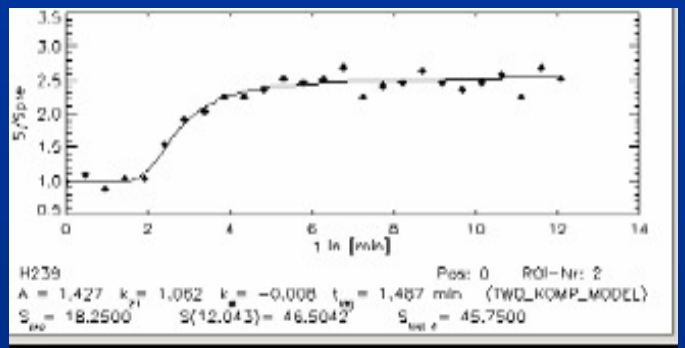
Wedam et al., J Clin Oncol 2006; 24:769

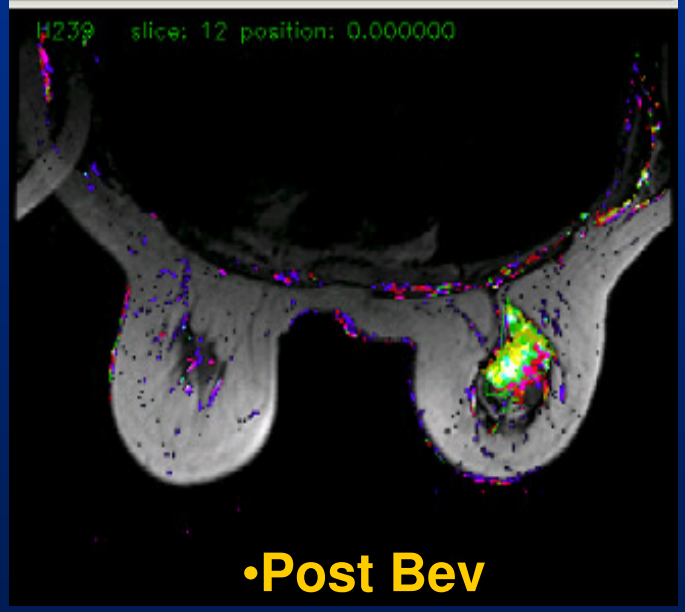
NCI0173: Bevacizumab + Chemo



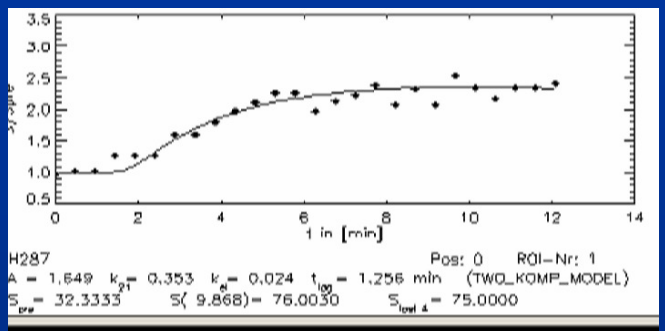


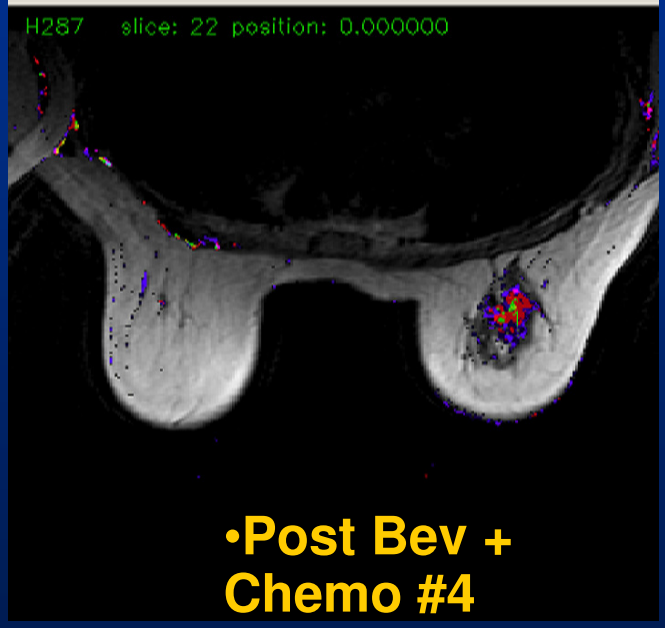
•Baseline





•Post Bev





•Post Bev + Chemo #4

•Increased uptake of contrast in tumor reflecting permeability and flow

Wedam et al., J Clin Oncol 2006; 24:769

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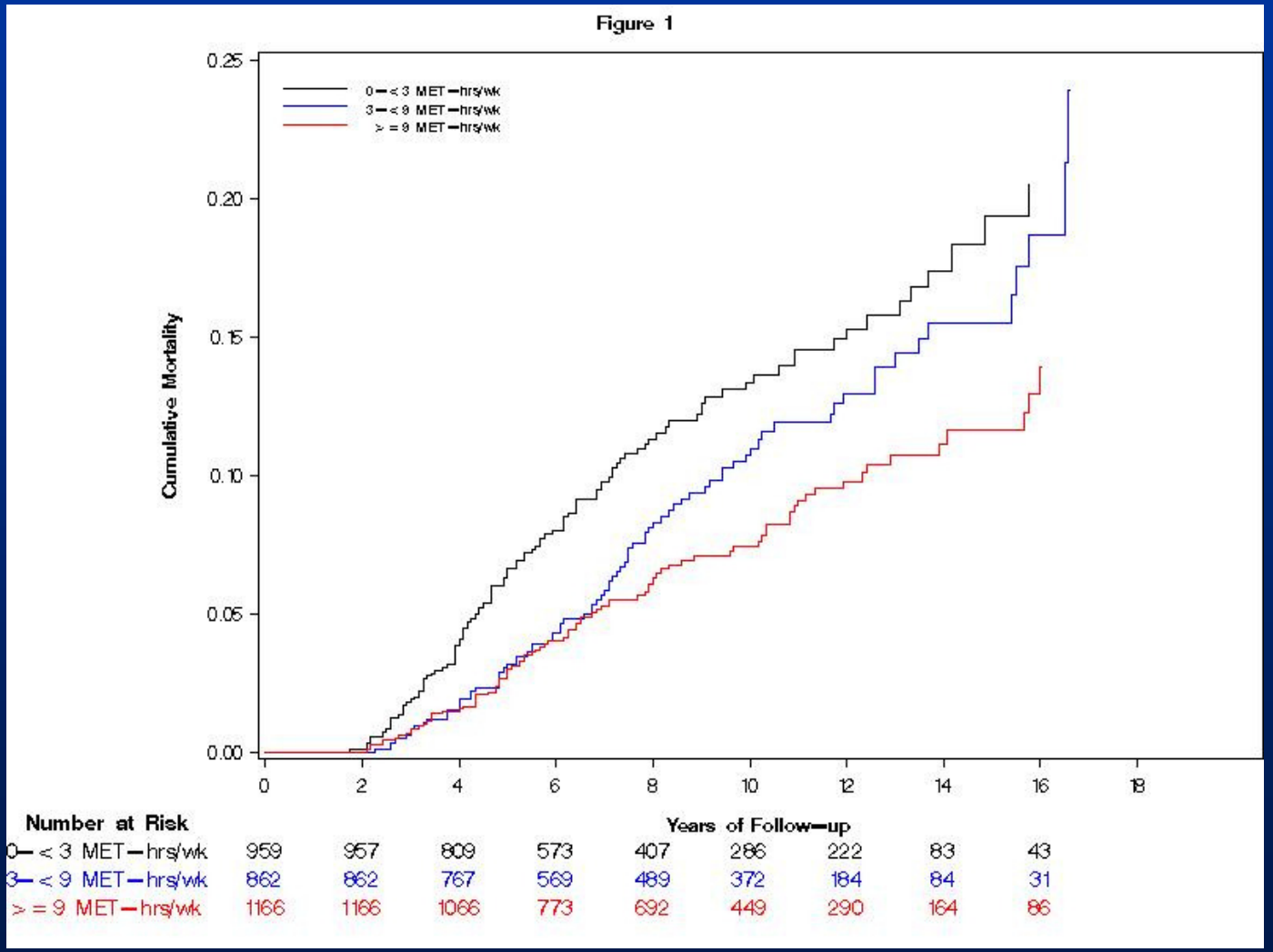
"Is this a good shoe for sitting?"

Mortality curves by exercise level



•Holmes MD, JAMA 2005;293:2479

Conclusions


24 HOUR
FITNESS

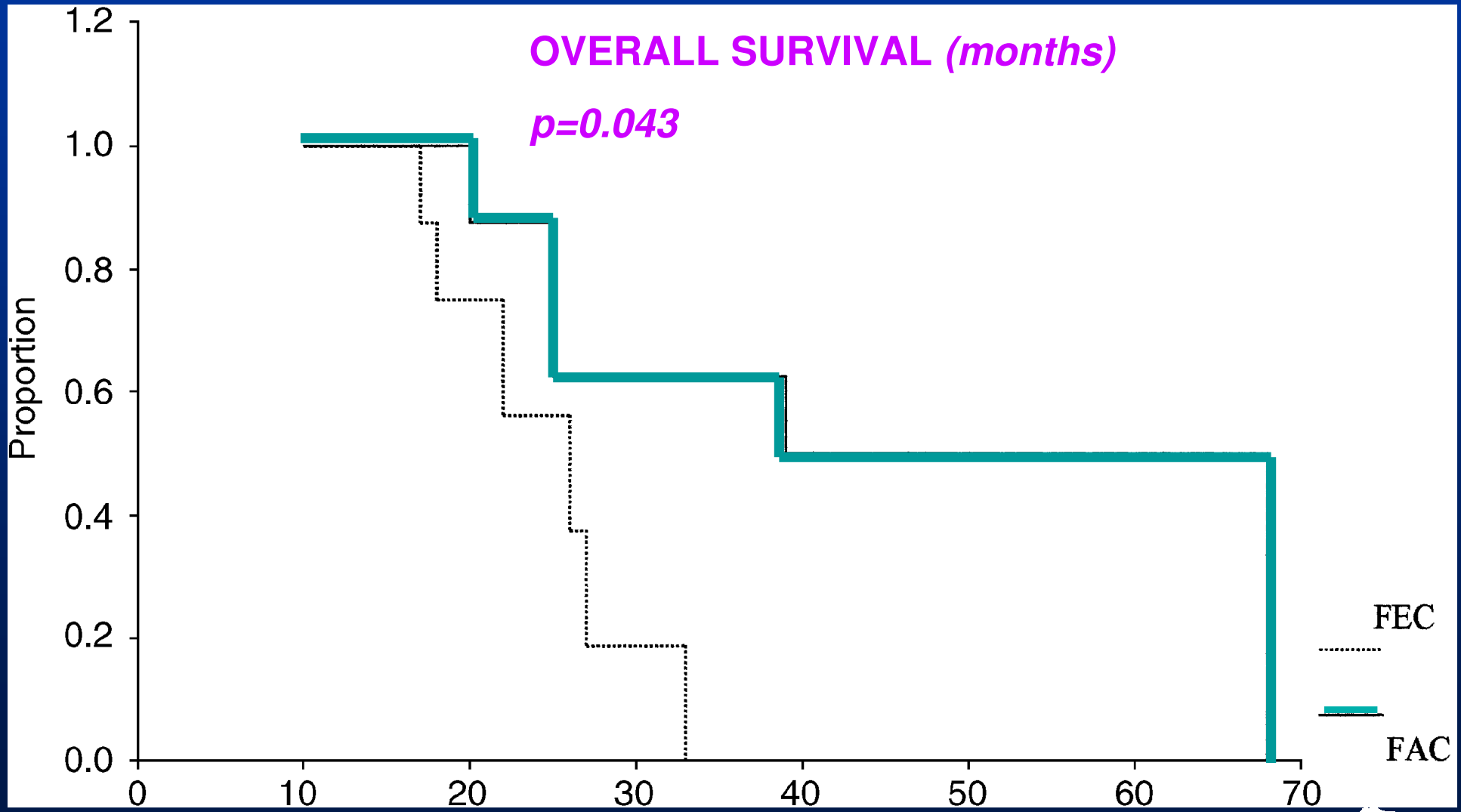
Inflammatory Breast Cancer

- **Presentations you could miss:**
  - Unilateral bruising
  - Unilateral enlargement
  - Unilateral arm swelling/pain
  - Nipple inversion
  - Skin retraction
  - Post-partum “mastitis”

IBC Prognosis

- **Single-institution series** **5yOS:**
  - MDACC n=178 40%
  - Centre H Bequerel n=178 32%
  - Institut Gustav Roussy n=230 42-74% (4yr)

Anthracycline-Based Chemotherapy



The Breast Journal, Volume 9, Number 2, 2003
79Ð85

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Metronomic Chemotherapy

- **SWOG 0012**
  - Adriamycin/Cyclophosphamide q 3wks x 5, weekly paclitaxel x 12
    - vs
  - Weekly Adriamycin (24mg/m2) + daily oral cyclophosphamide x 15 wks, weekly paclitaxel x 12

•IBC pCR: 12% vs 32%

Ellis et al, ASCO 2006

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