BREAST CANCER

George Raptis, M.D., M.B.A
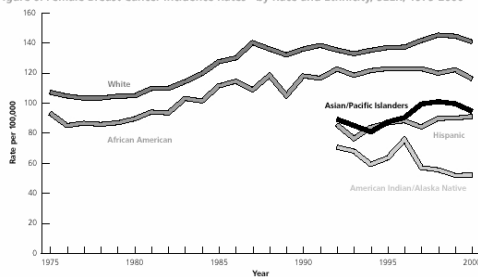
Division of Medical Oncology & Hematology
College of Physicians & Surgeons
Columbia University

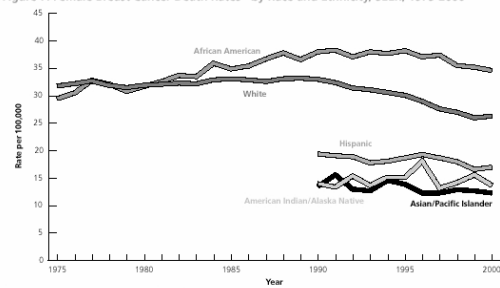## BREAST CANCER
Epidemiology

- Commonest cancer in women
- About 235,000 new cases/year in United States
- About 45,000 deaths/year

Figure 6. Female Breast Cancer Incidence Rates* by Race and Ethnicity, SEER, 1975-2000

*Rates are age-adjusted to the 2000 US standard population.

Figure 7. Female Breast Cancer Death Rates* by Race and Ethnicity, SEER, 1975-2000

*Rates are age-adjusted to the 2000 US standard population.

BREAST CANCER
Epidemiology

- Incidence high in U.S., Canada, Europe, Australia
- Incidence low in Japan, China, Africa
- Migration studies indicate an environmental factor(s)

BREAST CANCER
Epidemiology

Risk *increased* with:
1. Early age first menstrual cycle (menarche < age 12)
2. Late age last menstrual cycle (menopause > age 55)
3. First pregnancy after age 30

BREAST CANCER
Epidemiology
Risk *increased* with:
4. Prolonged use of post
   menopausal estrogen
   replacement therapy
5. Obesity - postmenopausal

BREAST CANCER
Epidemiology
Risk *decreased* with:
1. Late age first menstrual cycle
   (menarche > age 14)
2. Early age last menstrual cycle
   (menopause < age 45)
3. First pregnancy before age 20
4. Breast feeding > 16 months

BREAST CANCER
Epidemiology
Risk *increased* with:
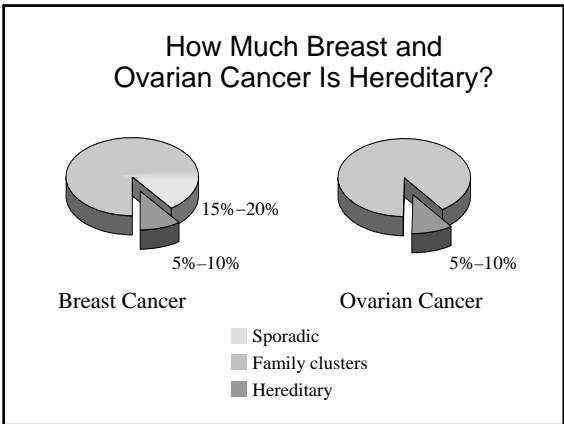**Prolonged used of OCPs / HRT**
Daily alcohol intake
- increased estradiol levels
- other mechanisms – effects on folate

BREAST CANCER
Epidemiology
Risk *increased* with:

Family history breast cancer,
especially first degree
relatives (mother, sister)

How Much Breast and
Ovarian Cancer Is Hereditary?

15%–20%
5%–10%   5%–10%
Breast Cancer   Ovarian Cancer

■ Sporadic
■ Family clusters
■ Hereditary

BRCA1

Tumor suppressor gene on chromosome 17
Autosomal dominant transmission
Protein has role in genomic stability
~500 different mutations reported

■ Nonsense   ● Missense   ◆ Splice-site

Breast Cancer Information Core

BRCA1-Associated Cancers: Lifetime Risk

Breast cancer 50%–85% (often early age at onset)

Second primary breast cancer 40%–60%

Ovarian cancer 15%–45%

Possible increased risk of other cancers (eg, prostate, colon)

BRCA2

Tumor suppressor gene on chromosome 13

Autosomal dominant transmission

Protein has role in genomic stability

~300 different mutations reported

■ Nonsense   ● Missense   ◆ Splice-site
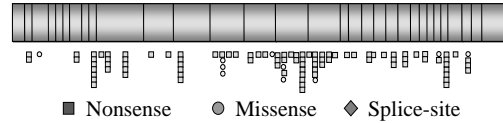
Breast Cancer Information Core

BRCA2-Associated Cancers: Lifetime Risk

breast cancer (50%–85%)   male breast cancer (6%)

ovarian cancer (10%–20%)

Increased risk of prostate, laryngeal, and pancreatic cancers (magnitude unknown)

## Comparing Breast Cancer Risk Estimates in BRCA Mutation Carriers

Breast cancer risk (%)

BRCA1+ carriers (BCLC)

BRCA1+ carriers (Ashkenazi Jews)

General population

Age
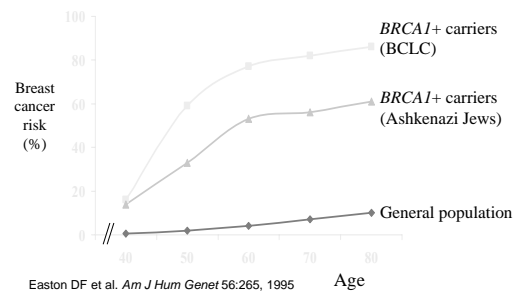
Easton DF et al. *Am J Hum Genet* 56:265, 1995
Struewing JP et al. *N Engl J Med* 336:1401, 1997

Features That Indicate Increased Likelihood of Having BRCA Mutations

- Multiple cases of early onset breast cancer
- Ovarian cancer (with family history of breast or ovarian cancer)
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Male breast cancer

ASCO
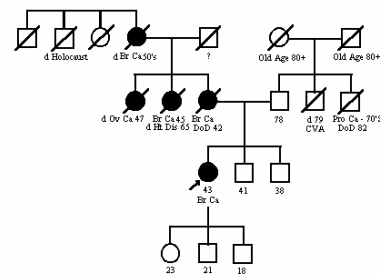
Br Ca = Breast Cancer
Ov Ca = Ovarian Cancer
Pro Ca = Prostate Cancer
Ht Dis = Heart Disease

Causes of Hereditary Susceptibility to Breast Cancer

Gene	Contribution to Hereditary Breast Cancer
BRCA1	20%–40%
BRCA2	10%–30%
TP53	<1%
PTEN	<1%
Undiscovered genes	30%–70%

BREAST CANCER

Epidemiology

Risk *increased* with:

Exposure to Ionizing Radiation

1. Fluoroscopy for monitoring TB therapy in 1940's
2. Atomic bombings 1945
3. Radiation therapy for Hodgkins disease

BREAST CANCER

Epidemiology

Risk *increased* with:

Breast biopsy showing

1. Atypical ductal hyperplasia
2. Lobular carcinoma in situ
3. Ductal carcinoma in situ

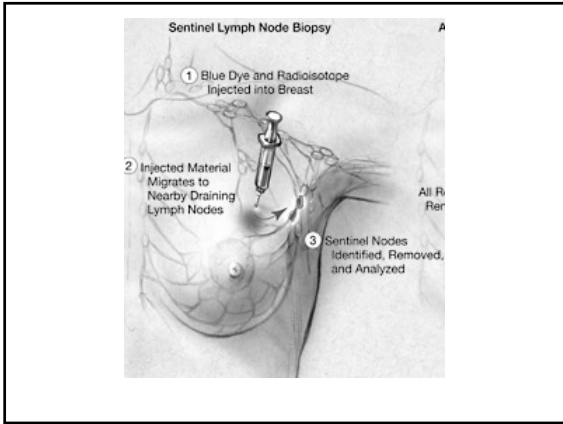## BREAST CANCER

Pathology

1. Description of:
   i. Histological type
   ii. Size of primary
   iii. Axillary nodal metastases
2. Hormone receptors
3. Over expression her-2/neu

Axillary Lymph Node Dissection

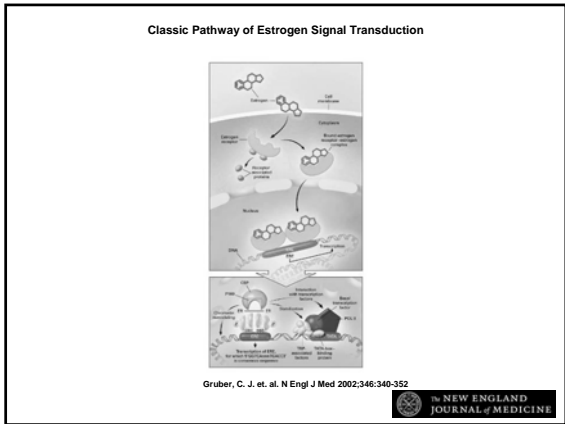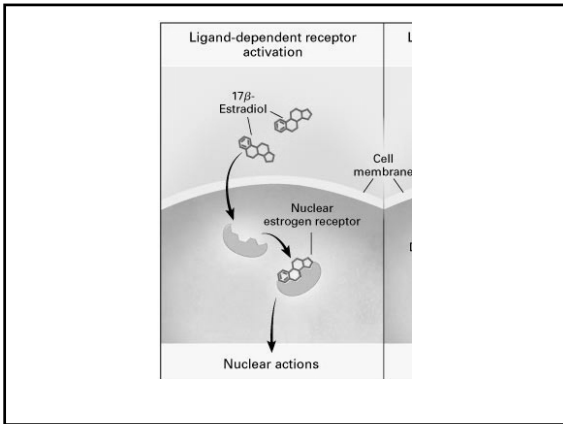All Regional Lymph Nodes Removed and Analyzed
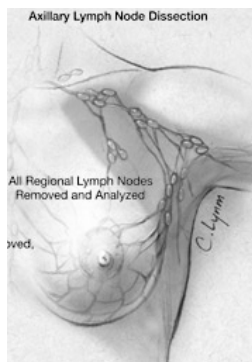
Axillary Dissection

Complications

1. Dysesthesiae and paresthesiae in axillary skin and medial upper arm
2. Arm/hand edema; celulitis
3. Limited shoulder mobility

Sentinel Lymph Node Biopsy

1. Blue Dye and Radioisotope Injected into Breast
2. Injected Material Migrates to Nearby Draining Lymph Nodes
3. Sentinel Nodes Identified, Removed, and Analyzed

BREAST CANCER
Pathology
Hormone receptors
   - steroid binding proteins
1. Estrogen receptors
2. Progesterone receptors

Ligand-dependent receptor activation

17β-Estradiol

Cell membrane

Nuclear estrogen receptor

Nuclear actions

Classic Pathway of Estrogen Signal Transduction

Gruber, C. J. et. al. N Engl J Med 2002;346:340-352

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BREAST CANCER
Pathology
Hormone receptors
1. Measured by immunohistochemical test
2. Expressed as percentage positive cells
3. Over 10% reported as a positive test

BREAST CANCER
Pathology
Hormone receptors
1. Prognostic factor
   - Improved if receptors present
2. Predictive factor
   - If receptors present, hormonal therapy may be effective
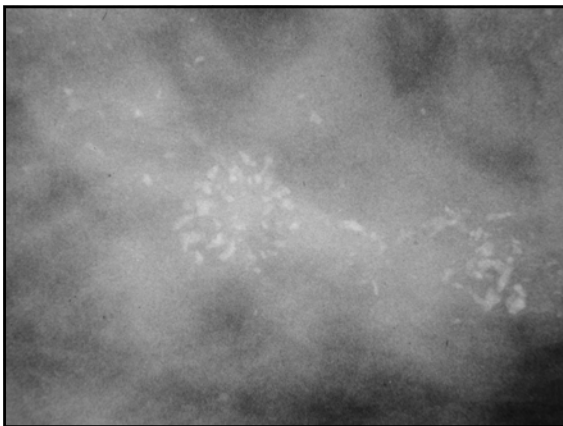
BREAST CANCER
Pathology
Her-2/Neu

1. Prognostic factor
   - Worse if her-2/neu is over expressed
2. Predictive factor
   - If her-2/neu over expressed, may respond to trastuzumab

MANIFESTATIONS
Local tumor growth

i. Changes detectable on imaging studies (mammography, sonography, MRI)
ii. Lump found by patient
iii. Lump found by physician

Diagnostic Methods

- Radiologic
  - Mammography
  - Sonography
  - MRI
- Histologic
  - FNA/core biopsy
  - Stereotactic biopsy
  - Excisional biopsy

MANIFESTATIONS
Mechanisms of spread

i. Direct extension
   - skin, chest wall
ii. Lymphatic
   - axillary, others
iii. Hematogenous
   - skeleton, lungs, liver, CNS, skin, LN, anywhere

BREAST CANCER
TREATMENT

1. Surgery
2. Radiation therapy
3. Medical therapy
   (Pharmaceuticals)

BREAST CANCER
TREATMENT GOALS
1. Control primary
   lesion in breast
2. Control systemic
   micrometastases

TREATMENT PRIMARY LESION

1. Surgery alone
   (total mastectomy)
2. Limited surgery
   (lumpectomy) and
   radiation therapy

Breast Cancer: Primary Surgery Options / Outcomes

- **Halsted:**   **radical mastectomy**
- **Fisher:**   **MRM vs lumpectomy +/- XRT**

Event	MRM	LE	LE+XRT
Recurrence – n(%)	219 (37)	269 (42)	214 (34)
Local	60 (10)	56 (9)	17 (3)
Regional	27 (5)	55 (9)	34 (5)
Distant	132 (22)	158 (25)	163 (26)
Total	371 (63)	408 (64)	391 (62)
Alive/event-free	218(37)	226(36)	237(38)

Fisher et al NEJM October 2002

Overall Survival (Panel A) and Disease-free Survival (Panel B) in the Two Groups

o Mastectomy
(28 of 116 died)
■ Lumpectomy + radiation
(29 of 121 died)
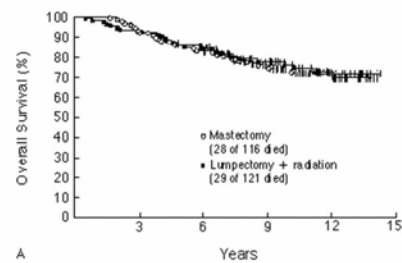
Jacobson, J. A. et. al. N Engl J Med 1995;332:907-911

The NEW ENGLAND JOURNAL of MEDICINE

Breast Cancer: Primary Surgery Options / Outcomes

- Contraindications to MRM:
  - Multifocal / multicentric disease
  - Large lesion relative to breast: poor cosmetic outcome
  - Radiation therapy issues:
    - Active collagen vascular disorder
    - Logistical issues

RISK OF SYSTEMIC METASTASES

1. Lymph node metastases
2. Size primary lesion
3. Degree differentiation
4. Hormone receptor status
5. Her-2/neu expression

Adjuvant Therapy of Breast Cancer

- Risk of metastasis:
  - 1 cm ~ 12% risk
  - 1 LN ~ 6% risk

  Therefore   2.5 cm ~ 30%
  <u>2 + LN ~ 12%</u>
  Risk   ~ 42%

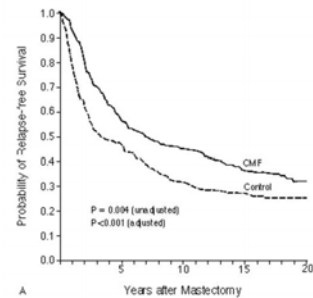## BREAST CANCER

SYSTEMIC ADJUVANT THERAPY
1. All axillary node positive cases
2. Node negative at significant risk

BREAST CANCER

SYSTEMIC THERAPY

1. Hormonally based
2. Chemotherapy
3. Monoclonal antibody
   preparations

Relapse-free Survival (Panel A) and Overall Survival (Panel B) According to Treatment Group

P = 0.004 (unadjusted)
P <0.001 (adjusted)

CMF

Control

A   Years after Mastectomy

Bonadonna, G. et. al. N Engl J Med 1995;332:901-906

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Simulation of Impact of Chemotherapy: (Based on EBCTG Meta-Analysis)

AC→Taxane
AC
CMF
Nil

Years
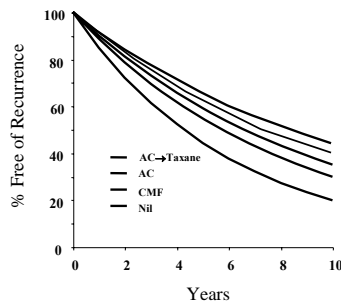
Annual Odds of Recurrence:

Nil = 15%/Yr

CMF = 11.4%
(Reduced by 24%)

AC = 10%
(Reduced by 12%)

AC→T = 7.8%
(Reduced by 22%)

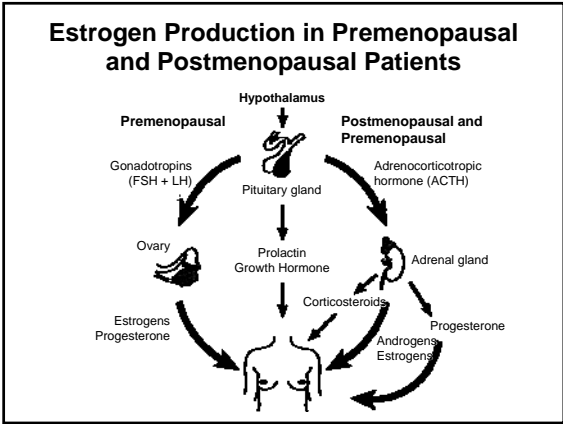
BREAST CANCER

Hormonally Based Therapy

Estrogen acting as a growth factor in tumor cells which express hormone receptors

BREAST CANCER

Hormonally Based Therapy

Reduce estrogen action

1. Block with antagonist
   "selective estrogen receptor modulator"
2. Reduce production
   - pre-menopausal
   - post-menopausal

Estrogen Production in Premenopausal and Postmenopausal Patients
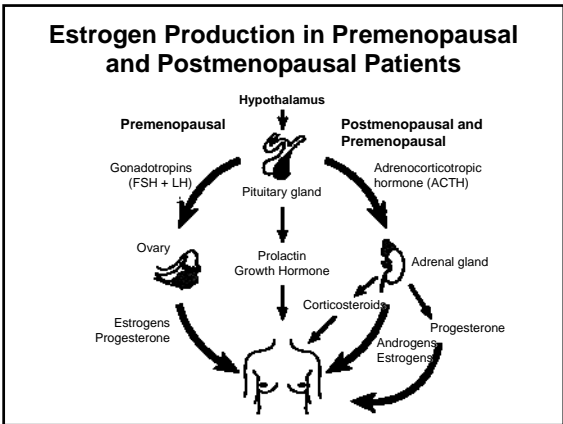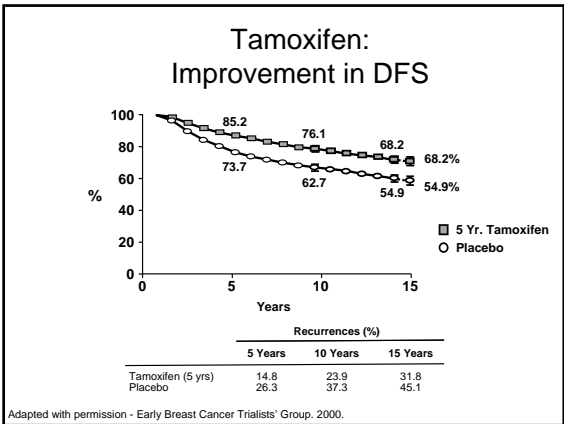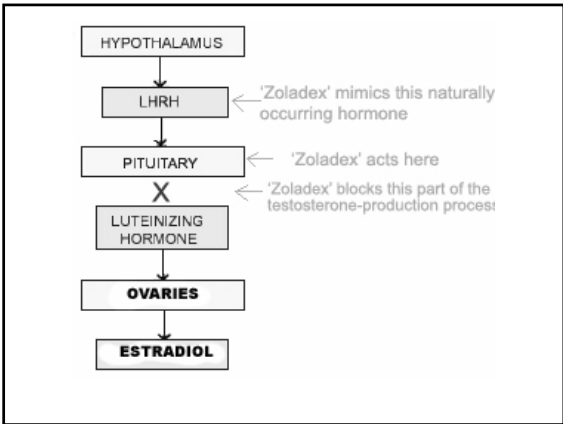

Premenopausal Breast Cancer

Hormonally Based Therapy
Reduce production
1. Surgical oophorectomy
2. Medical oophorectomy
Selective Estrogen Receptor Modulator
1. Tamoxifen

Tamoxifen: Improvement in DFS

	Recurrences (%)		
	5 Years	10 Years	15 Years
Tamoxifen (5 yrs)	14.8	23.9	31.8
Placebo	26.3	37.3	45.1

Adapted with permission - Early Breast Cancer Trialists' Group. 2000.

**Estrogen Production in Premenopausal and Postmenopausal Patients**

Postmenopausal Women

- **Estrogen synthesis**
  - **Occurs in non-ovarian tissue**

- **Concentrations in breast tissue higher than serum**
  - **Equivalent to premenopausal levels**

- **Tumor ER concentrations higher than in pre-menopausal patients**
 - **Increase with age**

Rationale for Aromatase Inhibitors for Breast Cancer Treatment

- **Selective inhibition of all estrogen biosynthesis**
- **No estrogenic effects (compared with antiestrogens, tamoxifen)**
- **Different mode of action from antiestrogens ie non- cross resistant with tamoxifen**
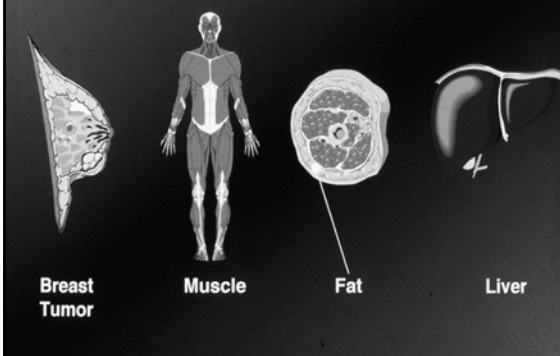- **Few side effects**

Estrogen Production in Premenopausal and Postmenopausal Patients
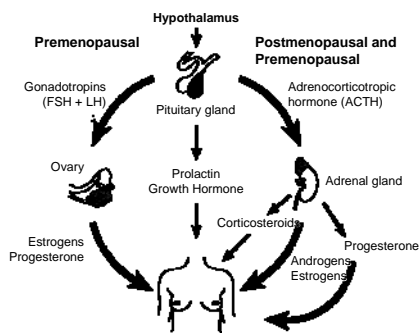
Steroid Biosynthesis
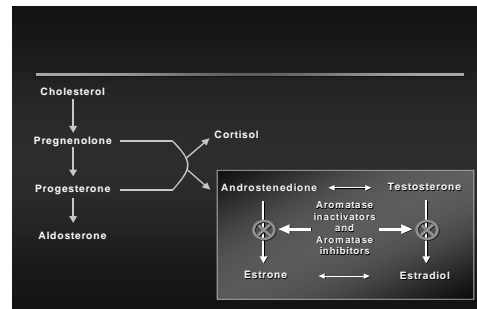
Sites of Peripheral Aromatization

Breast Tumor — Muscle — Fat — Liver

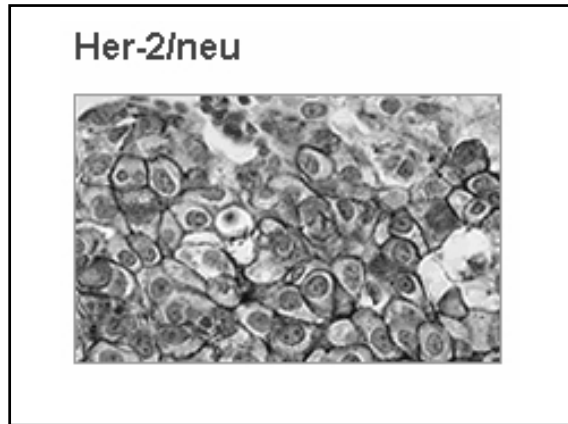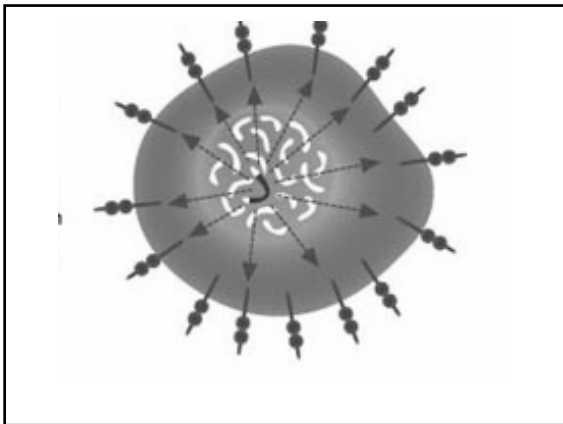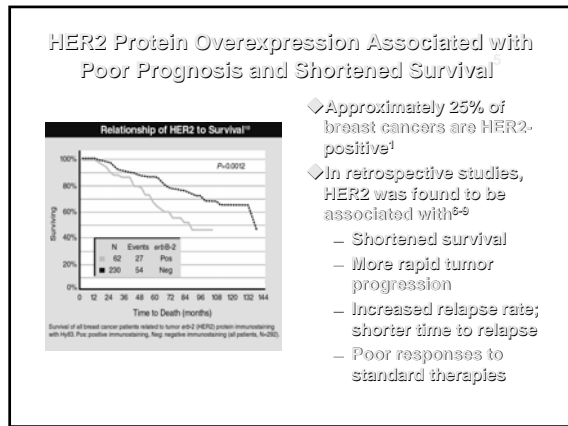## Postmenopausal Breast Cancer

Hormonally Based Therapy

1) Selective estrogen receptor moduator ie tamoxifen
2) Reduce production by aromatase inhibition
   ie anastazole, letrozole, exemestane

Selective Versus Nonselective Aromatase Inhibition

Cholesterol

Multiple steps involving P-450 enzymes and production of steroid intermediates

○ Selective Inhibitors
▬ Nonselective Inhibitors

Aldosterone — Cortisol — Androstenedione

Testosterone

Aromatase ○
Aromatase ○

Estrone → Estradiol

Peripheral aromatization

Federman, DD: The Adrenal. Dale DC, Federman DD, eds. In: *Scientific American Medicine.* Section 3. Subsection IV. ©1997 Scientific American Inc. All rights reserved.

Probability of Recurrence in Receptor-positive Population

	HR	95% CI	*p*-value
AN vs TAM	0.78	0.65–0.93	0.007

Anastrozole
Tamoxifen

Absolute Difference 1.8%
Absolute Difference 2.6%

Proportion with recurrence (%)

Time to event (months)

No. of Pts. at risk	0	6	12	18	24	30	36	42	48	54
AN	2617		2533		2436		2243		1258	602
TAM	2598		2516		2386		2180		1210	574

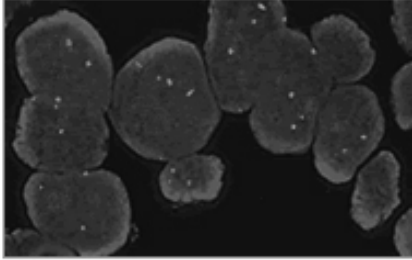* Censoring non-BC deaths before recurrence
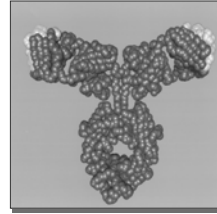

BREAST CANCER

Pathology
Her-2/Neu

1. Transmembrane protein
2. Epidermal growth factor receptor family
3. Activates a tyrosine kinase pathway
4. Over expressed in 25% cases

HER2 Protein Overexpression Associated with Poor Prognosis and Shortened Survival

Relationship of HER2 to Survival

P<0.0012

Surviving

N	Events	erbB-2
62	27	Pos
230	54	Neg

Time to Death (months)

Survival of all breast cancer patients related to tumor erb-2 (HER2) protein immunostaining with Hy63. Pos: positive immunostaining, Neg: negative immunostaining (all patients, N=292).

◇ Approximately 25% of breast cancers are HER2-positive[1]
◇ In retrospective studies, HER2 was found to be associated with[6-9]
  – Shortened survival
  – More rapid tumor progression
  – Increased relapse rate; shorter time to relapse
  – Poor responses to standard therapies

Her-2/neu

Her-2/neu by FISH


Trastuzumab (Herceptin): Humanized Anti-HER2 Antibody

◇ Targets HER2 oncoprotein, which occurs in approximately 25% of patients with breast cancer[1]
◇ High affinity (Kd = 5 nM) and specificity
◇ 95% human, 5% murine
  – Less immunogenicity
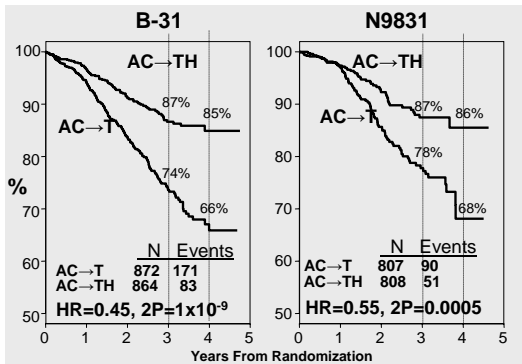 – Increased recruitment of immune effector cells

TRASTUZUMAB

Mechanism of Action

1. Down regulation receptor
2. Antibody dependent cell mediated cytotoxicity
3. Prevents dimerization of receptors, decreasing signal transduction
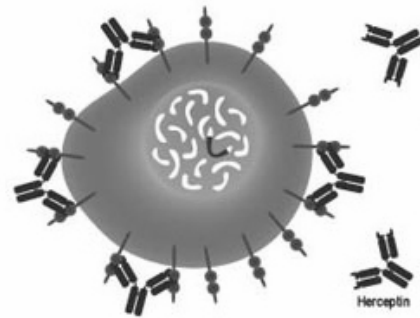
Disease-Free Survival

Questions?

Thank you!