BREAST CANCER

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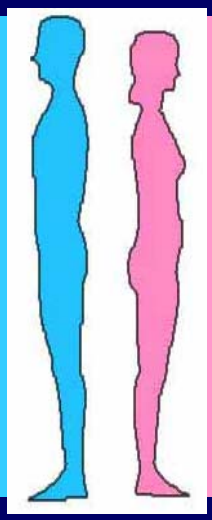
Background

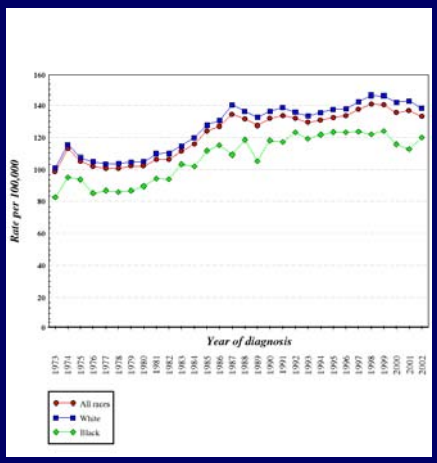
- Breast cancer is the most common cancer among women in the U.S.
- Second leading cause of cancer death among women in the U.S.
- Women have a 1 in 9 lifetime risk of developing breast cancer.

Estimated New Cancer Cases
10 Leading Sites by Gender

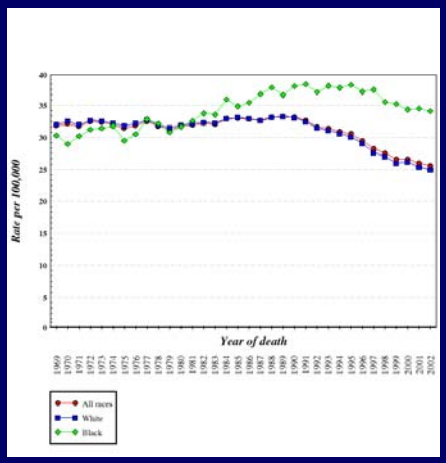
Prostate 31%	31% Breast
Lung & bronchus 14%	13% Lung & bronchus
Colon and Rectum 10%	11% Colon and Rectum
Urinary bladder 6%	6% Uterus
Non-Hodgkin's lymphoma 5%	4% Ovary
Melanoma of skin 5%	4% Non-Hodgkin's lymphoma
Oral cavity & pharynx 3%	4% Melanoma of skin
Kidney & renal pelvis 3%	2% Urinary bladder
Leukemia 3%	2% Pancreas
Pancreas 2%	2% Thyroid
All other sites 18%	21% All other sites



SEER Breast Cancer
Incidence and Mortality Data



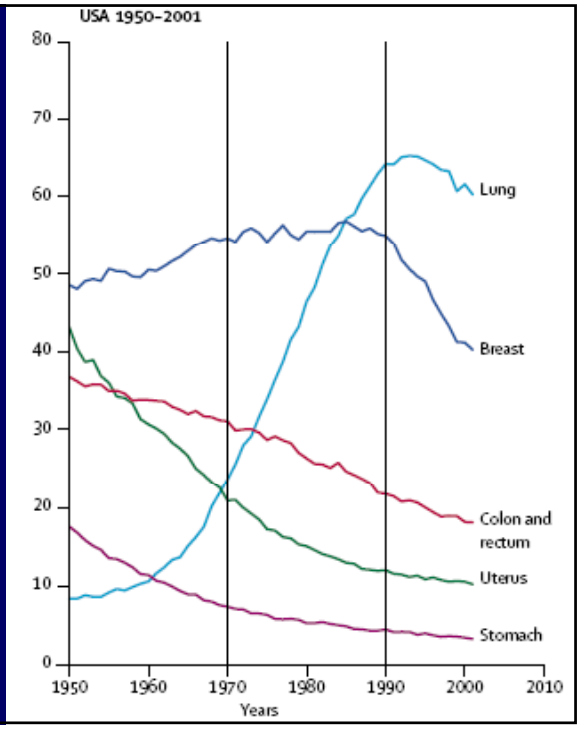
INCIDENCE



MORTALITY

Trends since 1950 in age-standardised death rates comparing breast and selected other types of cancer, among women in the USA

EBCTCG. *Lancet* 2005; 365: 1687

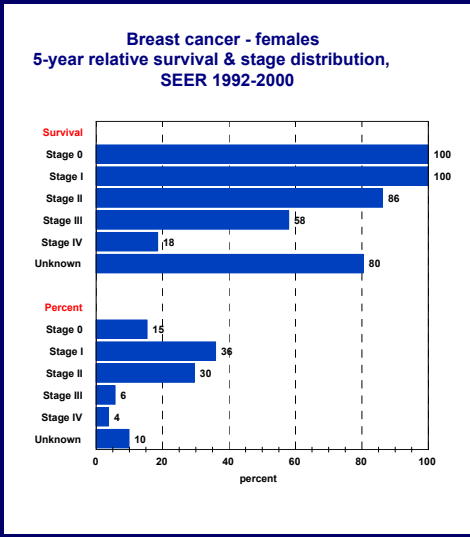


Stages of Breast Cancer

- **Stage 0**: Cancer cells are present in either the lining of a breast lobule or a duct, but they have not spread to the surrounding fatty tissue or DCIS.
- **Stage I**: The tumor is <2 cm, the lymph nodes are not involved.
- **Stage II:** The tumor can range from 2-5 cm in diameter or <4 lymph nodes are involved.
- **Stage III**: Locally advanced cancer; tumor may be larger than 5 cm in diameter or >4 LN.
- **Stage IV:** Known as metastatic; cancer has spread to other parts of the body, such as bone, liver, lung, or brain.

Breast Cancer: 5-year Relative Survival and Stage Distribution, 1992-2000

- About 15% of breast cancer diagnoses are *insitu* disease
- 5-year survival for early stage breast cancer is very good

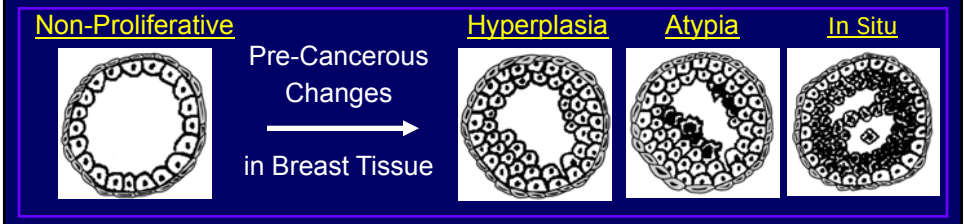


Breast Cancer Risk Factors

Risk Factor	Relative Risk
Alcohol intake (>2 drinks/day)	1.2
Body mass index	1.2
HRT use (>5 years)	1.3
Early age of first menstrual period (<12 years)	1.3
Late menopause (>55 years)	1.2-1.5
Age at first birth (>30 years or no children)	1.7-1.9
Current age (≥ 65 years)	5.8
Benign breast disease	5-20
Prior breast cancer	6.8
Family history	
2nd degree relative with breast cancer	1.5
1st degree relative, age>50	1.8
1st degree relative, age<50	3.3
Prior Exposure to Radiation	5-80x
BRCA1/2 mutation carrier	15-200

Benign Breast Disease

Dupont et al. Cancer, 1993



RR 1.0	1.5-2.0	4.0-5.0	10-20

Breast Cancer Risk Assessment: Gail Model

Gail et al. JNCI, 1989

- Age
- Race
- Age of first menstrual period
- Age of first live birth
- Number of first degree relatives with breast cancer
- Number of breast biopsies
  - Presence of atypical hyperplasia

www.cancer.gov/bcrisktool

Breast Cancer Risk Assessment: Gail Model

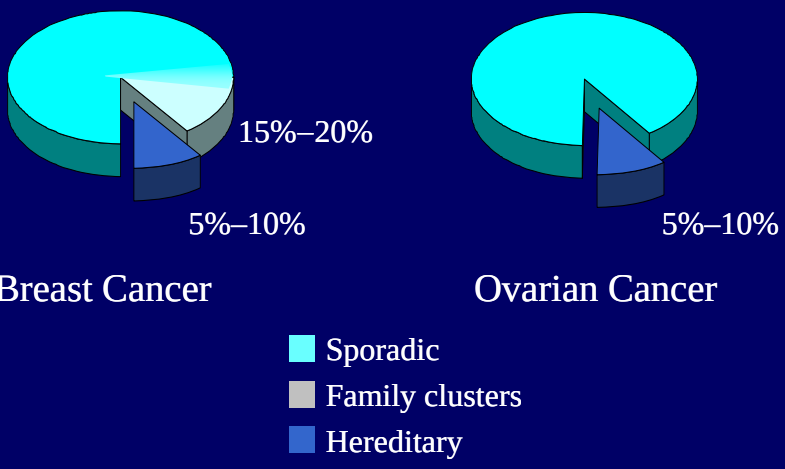
Gail et al. JNCI, 1989

• Age	45
• Race	White
• Age of first menstrual period	13
• Age of first live birth	32
• Number of first degree relatives with breast cancer	1
• Number of breast biopsies	1
– Presence of atypical hyperplasia	No

www.cancer.gov/bcrisktool

5-Year Risk = 2.6%
Lifetime Risk = 21.9%

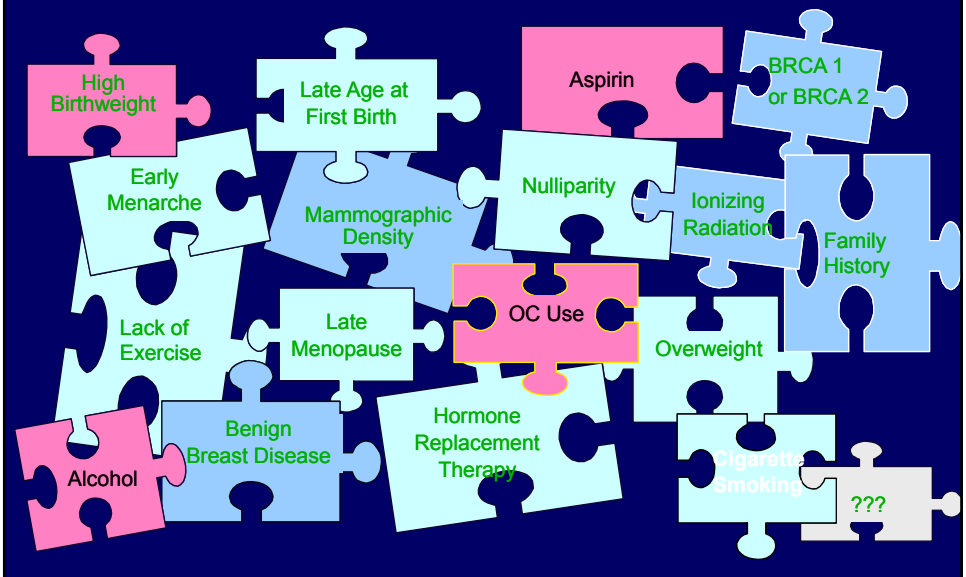
How Much Breast and Ovarian Cancer Is Hereditary?



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

Risk Factors Related to Breast Cancer



Comparing Relative Risk to other Risk Factors

< 2-Fold	> 2-Fold	4 to 6-Fold
Early Menarche Never Pregnant Never Breastfed Late Age at First Birth Late Menopause Lack of Exercise Overweight Alcohol Hormone Use (HRT, OC)	Family History Benign Breast Disease	Mammographic Density

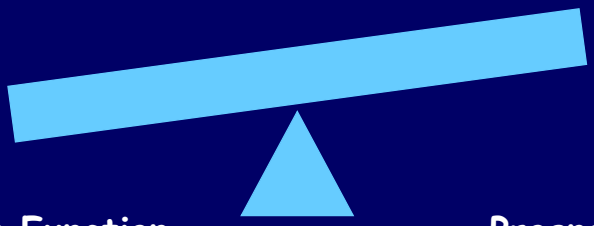
Multi-modality Treatment of non-metastatic Breast Cancer

- Local therapy
  - Surgery
  - Radiation therapy
- Systemic therapy
  - Endocrine manipulations
  - Chemotherapy
  - Novel Therapies

Adjuvant Systemic Therapy for Breast Cancer: Decision making

Risks:
Adverse Events

Benefits:
Risk Reduction



Organ Function,
Age, Co-morbidities

Prognostic &
Predictive Factors

Adjuvant Systemic Therapy for Breast Cancer: Decision Making

- Prognostic Factors
  - Estimate outcome *independent* of systemic treatment
  - Reflect tumor biology: Who should be treated?
- Predictive Factors
  - Reflect a relative resistance or sensitivity to specific therapy
  - What specific treatment(s) should be offered to an individual?

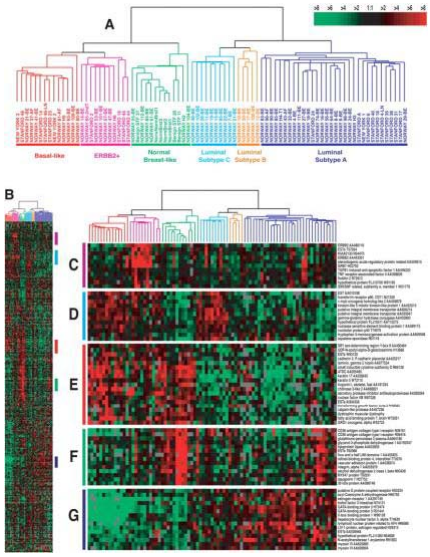
Breast Cancer Prognostic Factors

Strength	Marker
Strong	TNM Stage Axillary Nodal Status Tumor Size
Moderate	Tumor Grade Lymphatic or Vascular Invasion
Weak	ER Content PR Content
Investigational	HER2, Gene arrays, Proteomics Novel imaging

Breast Cancer Predictive Factors

- Accepted
  - Age
  - ER
  - Grade
  - HER2
- Investigational
  - Gene arrays, proteomics
  - Novel imaging

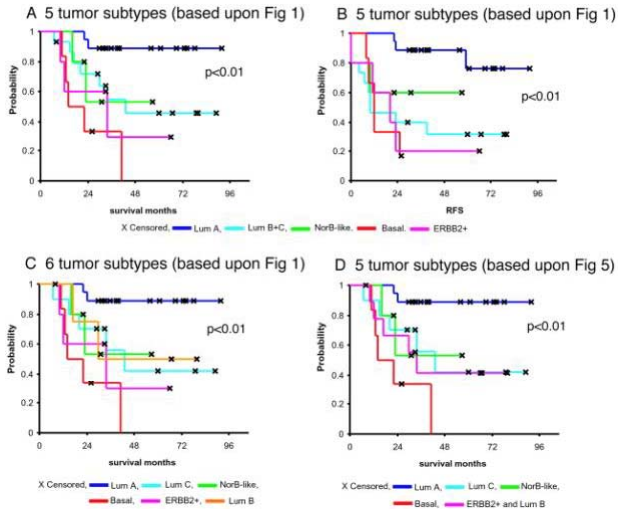
Breast Cancer Subtypes



Sørlie, Therese et al. (2001) Proc. Natl. Acad. Sci. USA 98, 10869-10874

PNAS

Breast Cancer Subtypes



Sørlie, Therese et al. (2001) Proc. Natl. Acad. Sci. USA 98, 10869-10874

PNAS

OncotypeDX Recurrence Score (RS) Assay Predicts Distant Relapse Rates at 10 Years if Five Years of Tamoxifen

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

CD68

BAG1

INVASION
Stromolysin 3
Cathepsin L2

HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

RS = + 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

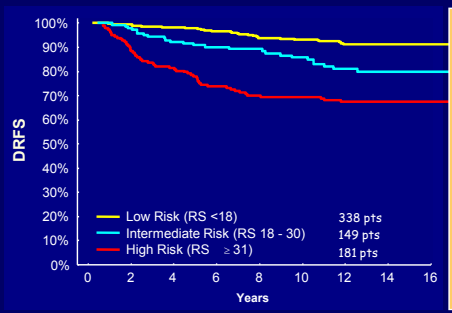
Category	RS (0 – 100)
Low risk	RS < 18
Intermediate risk	RS ≥ 18 and < 31
High risk	RS ≥ 31

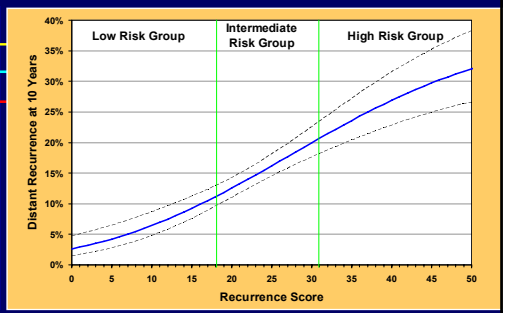
Paik S, et al. NEJM 2004

Validation Study of Oncotype DX

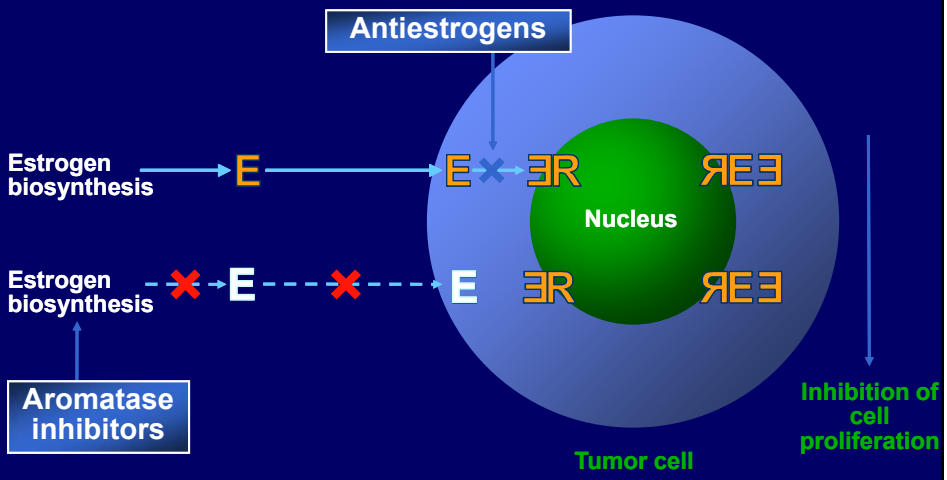
Tamoxifen treated patients from NSABP B-14 (N=668)

Performance exceeded standard measures of patient age, tumor size





Inhibition of Estrogen-Dependent Growth

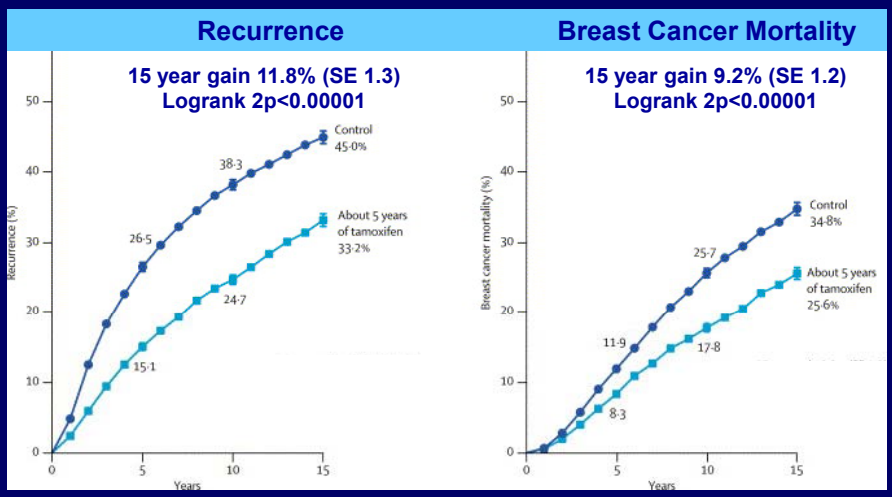


Tamoxifen: Oxford Overview Data

- Effective in all hormone receptor positive women:
  - ER+/PR+ > ER-/PR+ > ER+/PR-
- Regardless of age, stage, tumor grade
- Optimal duration: 5 years
  - 5 ys > 2 ys, but 10 ys not > 5 ys

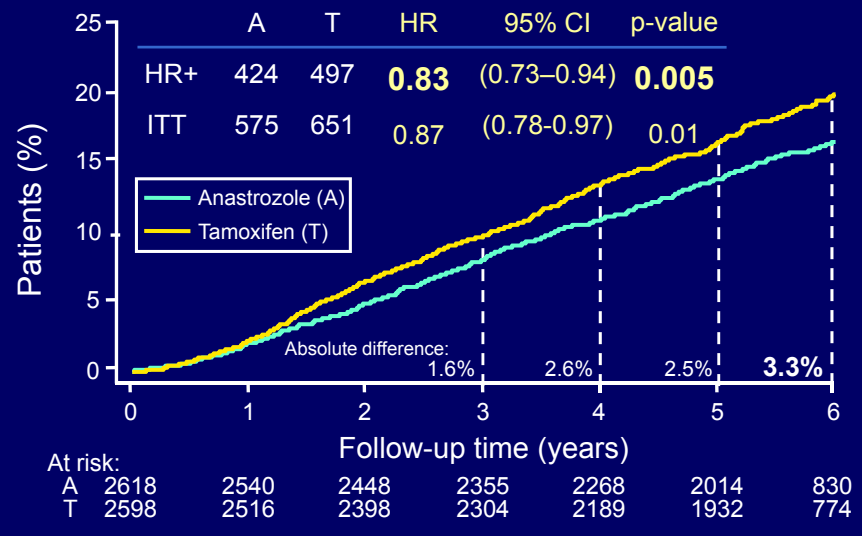
EBCTCG. *Lancet* 2005; 365: 1687–1717

5 years of Tamoxifen vs. Not: 15-year Probabilities of Recurrence and Breast Cancer Mortality (ER-positive/ unknown, n = 10,386)



EBCTCG. *Lancet* 2005; 365: 1687–1717

ATAC: Disease-Free Survival



DFS includes all deaths as a first event

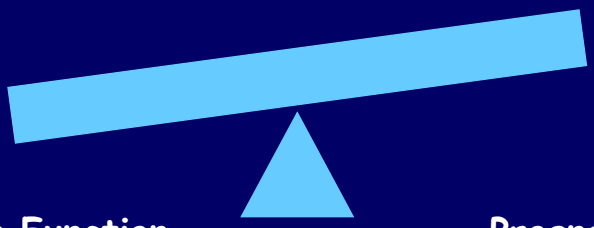
Adjuvant Chemotherapy

1. Who should be treated?
2. Which regimen?
3. What duration?
4. How intense?
5. When to administer?

1. Who should be Treated?

Risks:
Adverse Events

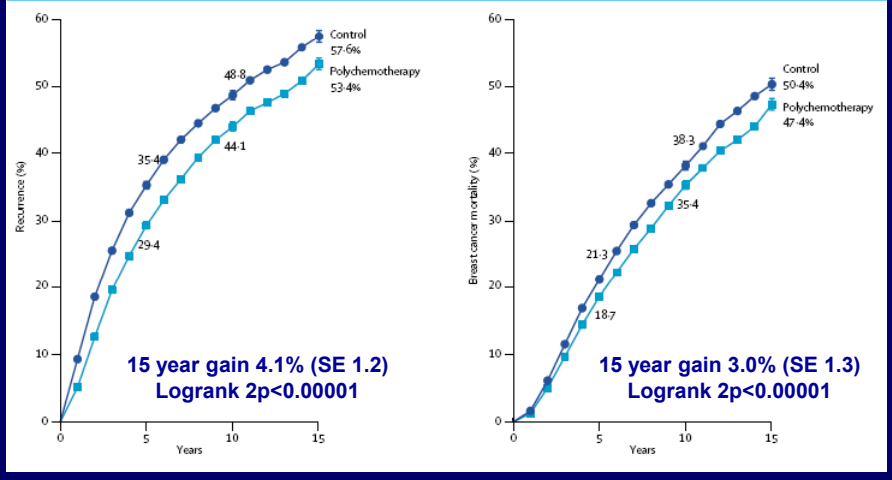
Benefits:
Risk Reduction



Organ Function,
Age, Co-morbidities

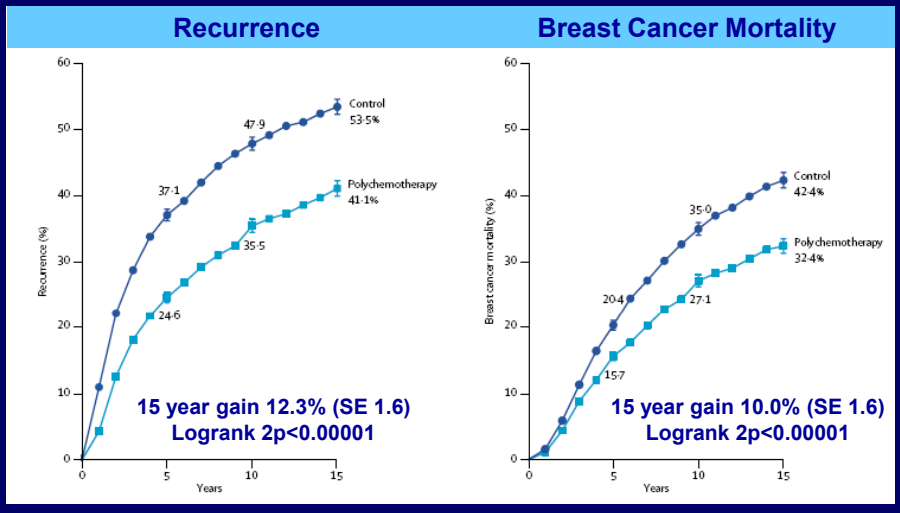
Prognostic &
Predictive Factors

Polychemotherapy vs. Not, by Entry Age: 15-year Probabilities of Recurrence and Breast Cancer Mortality (Age 50-69)



EBCTCG. *Lancet* 2005; 365: 1687–1717

Polychemotherapy vs. Not, by Entry Age: 15-year Probabilities of Recurrence and Breast Cancer Mortality (Age <50)



EBCTCG. *Lancet* 2005; 365: 1687–1717

2. Which Regimen? Results from the Oxford Overview

- Polychemotherpay is superior to single agent chemotherapy
- Anthracycline-based therapy is superior to CMF-based therapy
- All women gain benefit but younger women, and those with poorly differentiated, hormone receptor negative-tumors more likely to benefit

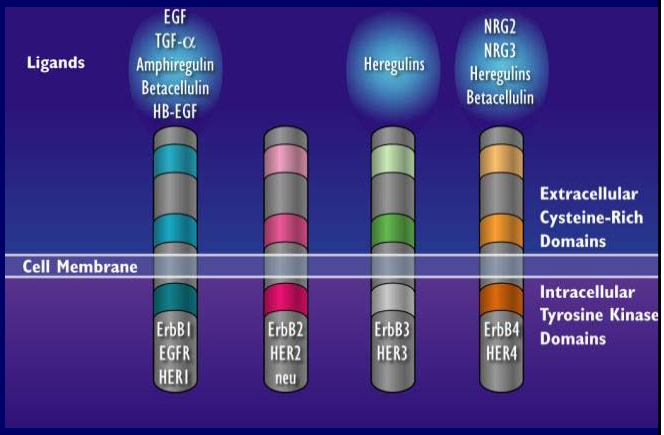
Stearns & Davidson. Diseases of the Breast 2004. 3rd Ed. Chapter 54. Tables 1-3

Common Breast Cancer Treatments

- Endocrine Therapies
  - Tamoxifen
  - Aromatase Inhibitors
  - Other
- Chemotherapy
- Novel Therapies
  - Trastuzumab (Herceptin)

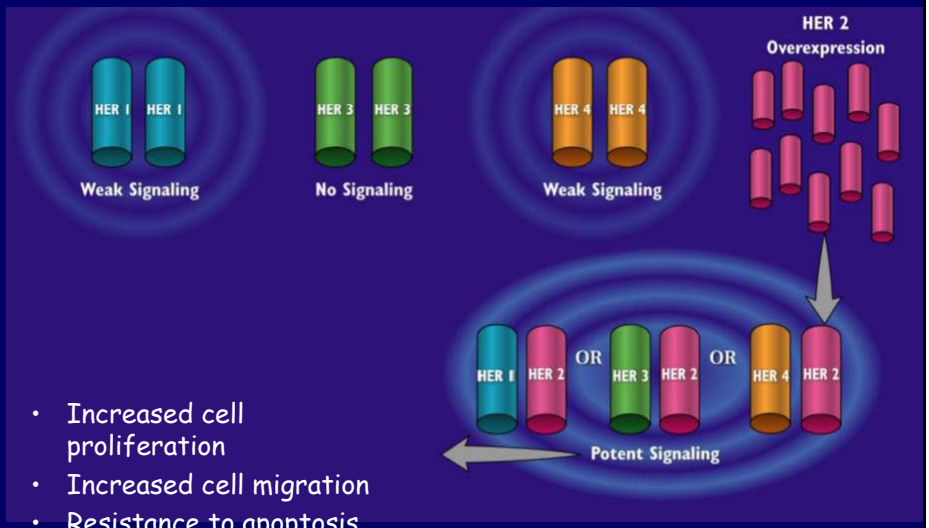
Trastuzumab Targets the Human Epidermal Growth Factor Receptor 2 (HER2)

- The HER2 gene is localized to chromosome 17q
- HER2 is a tyrosine kinase transmembrane growth factor receptor



Fernandes et al, *Cancer Lett* 1999; Moghal et al, *Curr Opin Cell Biol* 1999; Yarden et al, *Nat Rev Mol Cell Biol* 2001

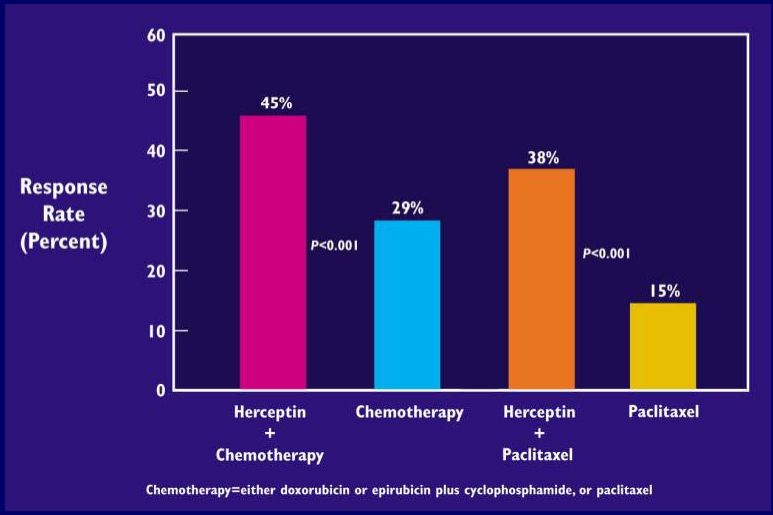
HER2 Overexpression Leads to Increased Signaling



- Increased cell proliferation
- Increased cell migration
- Resistance to apoptosis

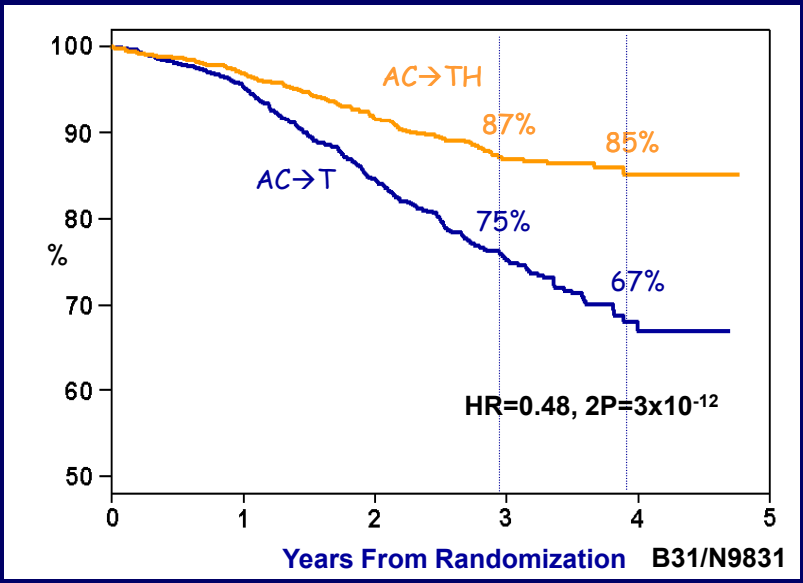
Yarden et al, *Nat Rev Mol Cell Biol* 2001

Trastuzumab Plus Chemotherapy Increased Response Rates

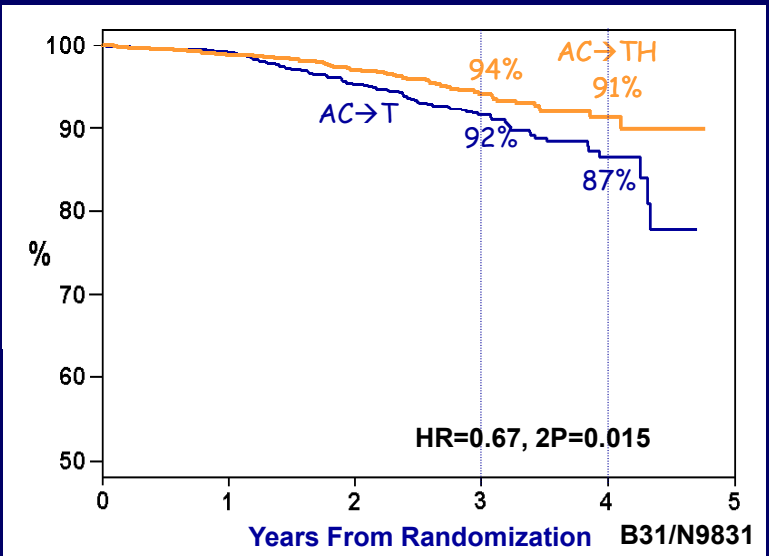


Slamon et al, *N Engl J Med* 2001

B-31/N9831 Disease-Free Survival



B-31/N9831 Overall Survival



Metastatic Breast Cancer: Goals of Therapy

- Cure
- Improve overall survival
- Improve time to progression
- Improve symptoms related to the disease
- Improve quality of life

Therapeutic options

- Endocrine therapies
- Chemotherapy
- Novel therapies
- ✓Supportive Therapy
  - Local therapy: surgery, radiation
  - Bisphosphonates
    - For women with skeletal metastases
    - Reduces pain/risk of fracture/RT requirements
  - Symptom management

Monitoring Response

- History and physical
- Tumor markers
- Imaging
  - Standard: CT, bone scan, MRI
  - Emerging: PET, functional imaging
- Circulating cells
- Other

Conclusions and Future Directions

- Many therapies available to women with metastatic breast cancer
  - Improve overall survival, time to progression, QOL
  - Well tolerated
- Individualized treatment
- Optimal dose, schedule, combination
- Numerous emerging novel therapies

Thank You