Breast Cancer – Risk Factors, Genetics, Screening, Diagnosis

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OBJECTIVES

- Risks of developing breast cancer
- Screening for breast cancer in different subgroups
- Risk reduction strategies
- Diagnosis of breast cancer

CASE 1

- 72 yr old White female presenting with a left breast mass.
- Gravida 2 Para 2.
- Took hormone replacement therapy for 7 yrs (50-57yrs) after natural menopause.
- Her maternal GM had breast cancer at the age of 58. Maternal Aunt had breast cancer at the age of 78.
- Biopsy was consistent with invasive ductal carcinoma.

- What is the most important risk factor predisposing her to developing breast cancer?

AGE

The probability of developing breast cancer in the next 10 yrs for a

40 yr old is 1.5%

70 yr old is 4.1%

CASE 2

- 52 yr old Ashkenazi Jewish female on routine mammogram was found to have bilateral breast mass.
- Gravida 2 Para1.
- Daughter was diagnosed with breast cancer at the age of 30. Mother had ovarian cancer at the age of 45.

- What is her greatest risk factor for developing breast cancer?

Family History

- 5-10% of all breast cancers are associated with cancer predisposition syndromes

RISK FACTORS

Age

Family History

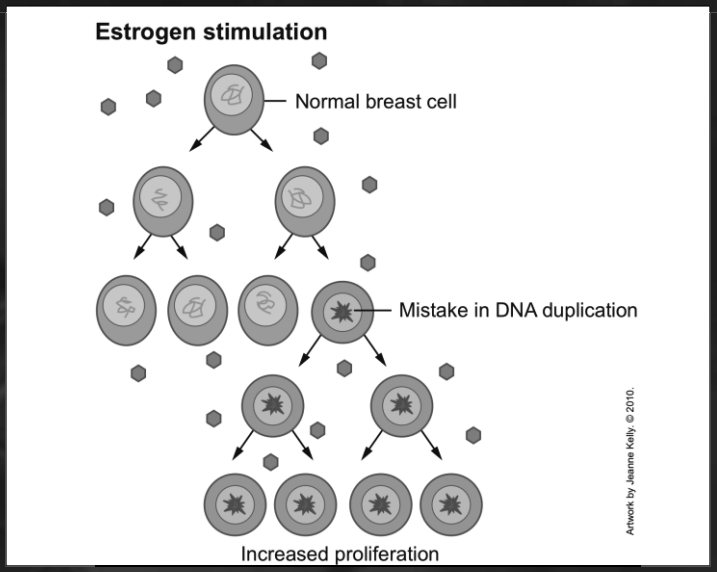
Prolonged Estrogen Exposure

1-1st relative=1.8 fold
2-1st relatives=2.93 fold

Relative < 40 yrs= 5.7 fold

Exposure to ionizing radiation
Abnormal breast biopsies
Obesity
Alcohol

Estrogen-Induced Proliferation and Spontaneous New Mutations

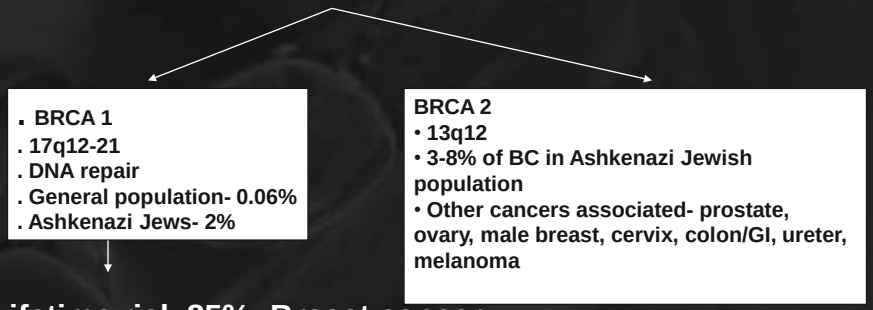


Summary of established risk and protective factors for breast cancer

Risk factors (increased hormone exposure)
Early menarche
Late menopause
Alcohol consumption
Post-menopausal obesity
Hormone replacement therapy
Protective factors (decreased hormone exposure)
Young age at first full term pregnancy
Prolonged lactation
Exercise

Genetic syndromes and breast cancer

- **Hereditary Breast and Ovarian Cancer Syndromes (80% of all inherited breast cancer)**



Lifetime risk 85%- Breast cancer
45% for ovarian cancer
58-fold increase in risk for male breast cancer

BRCA1

- Tumor suppressor gene on chromosome 17
- Autosomal dominant transmission
- Protein has role in genomic stability
- >600 different mutations reported

BRCA2

- Tumor suppressor gene on chromosome 13
- Autosomal dominant transmission
- Protein has role in genomic stability
- ~450 different mutations reported

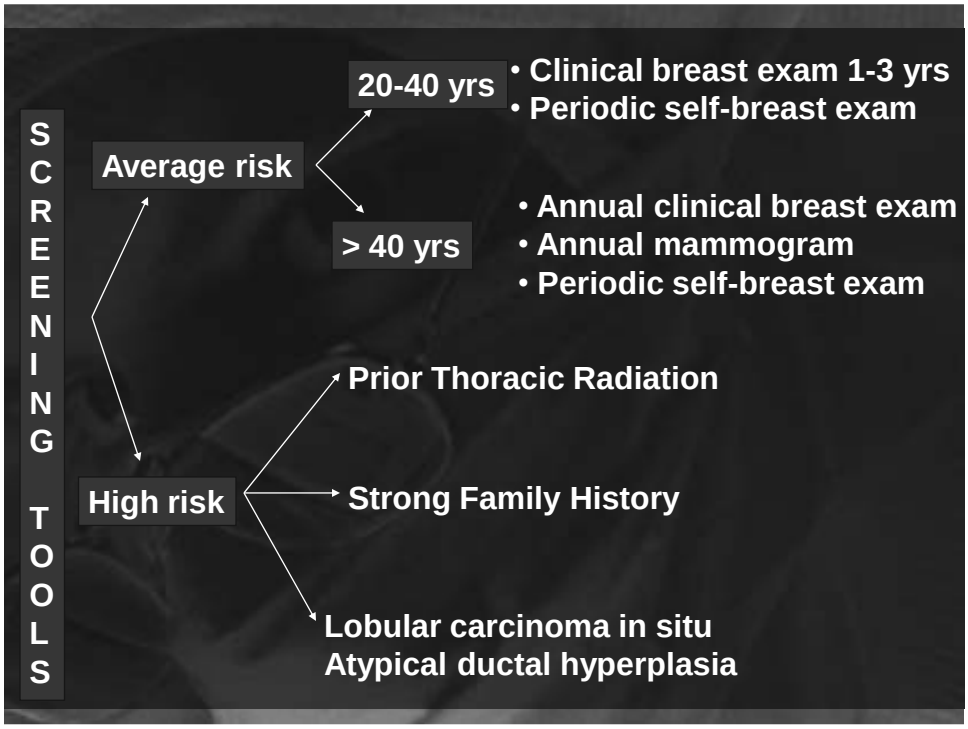
OTHER GENETIC SYNDROMES

- Multiple hamartomas-
- Sarcomas, brain tumors
- Melanocytic Macules in the lips
- Diffuse gastric cancer
- Ataxia, Immunodeficiency.
- Cowden's Syndrome (10q22-33)
- Li Fraumeni syndrome (TP53)
- P-J syndrome (19p13.4- STK11/LBK1)
- Hereditary Diffuse Gastric Cancer (CDH1)
- Ataxia-Telangiectasia (ATM gene)

ALERT SIGNS: Young breast cancers in family, Bilateral cancers, Triple negative cancers, Other cancers in young relatives, skin lesions.

Why should we attempt to identify these high risk women?

- Improved screening measures
- Referral to High-risk breast cancer clinic
  - Consideration of chemoprophylaxis
- Genetic counseling
- Risk reduction strategies
  - Avoid excess estrogen exposure
  - Exercise
  - Moderate alcohol intake



HIGH-RISK BREAST CANCER SCREENING

AGE < 25 y →
- Annual clinical breast exam
- Periodic breast self-exam

AGE > 25 y →
- Clinical breast exam every 6-12 months
- Periodic breast self-exam
- Annual mammogram beginning

↓

Age 25- Hereditary breast ovarian cancer syndromes
8-10yrs after RXT
5-10 yrs prior to youngest breast cancer case

- Consider MRI as an adjunct
- Consider risk reduction strategies

Annual MRI Screening

- BRCA mutation
- First-degree relative BRCA carrier
- Lifetime risk 20-25% or greater

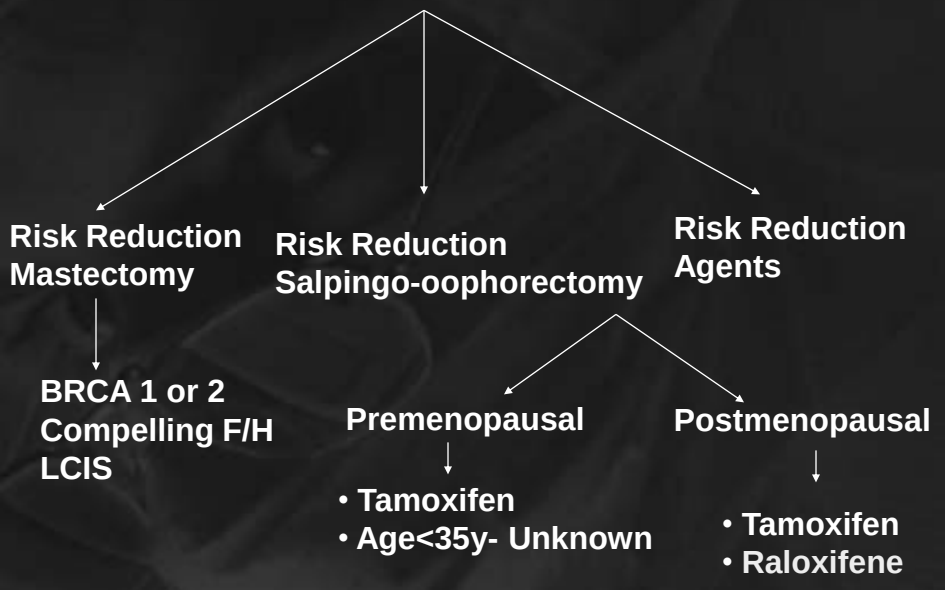
Questionable indications-

Radiation to chest between ages 10 and 30
Other cancer genetic syndromes
Lifetime risk of 15-20%
Biopsy proven LCIS/ADH
Women with extremely dense breast on mammography
Women with personal history of breast cancer or DCIS

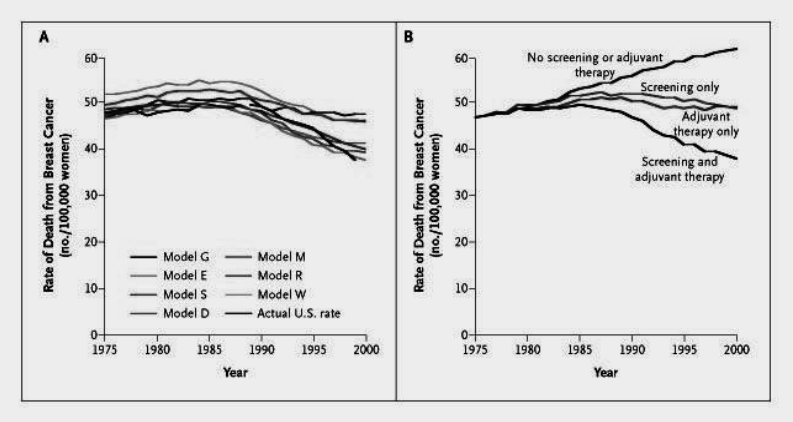
Recommend against MRI screening- Women with a lifetime risk < 15%

Saslow D et al. ACS guidelines for breast screening with MRI as an adjunct to mammography. Can J Clin 57,2007
Bleicher et al Review. MRI in breast cancer: Role in detection, diagnosis, and staging. Oncology 2007

RISK REDUCTION STRATEGIES



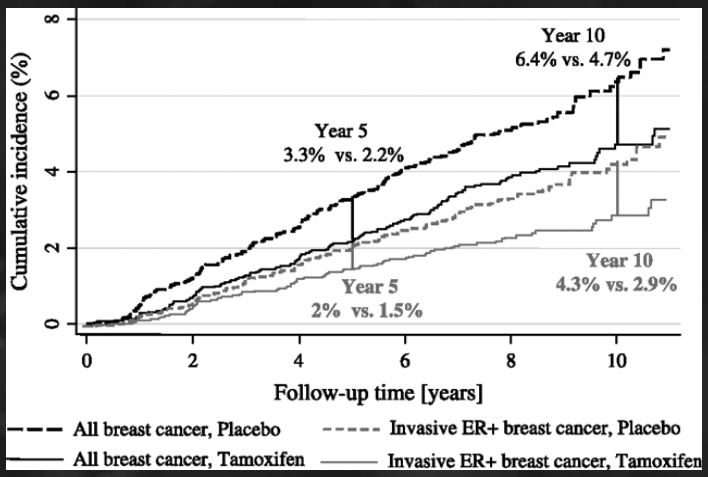
IMPACT OF RESEARCH ON BREAST CANCER SCREENING AND RISK-REDUCTION



Estimated reduction in US overall breast cancer mortality is 28-65%
(Breast cancer mortality RR >50 y- 0.78 and 40-49 y- 0.85)

Berry et al NEJM 2005

Cumulative incidence rates for all breast cancers and invasive estrogen receptor (ER)-positive breast cancers according to treatment arm



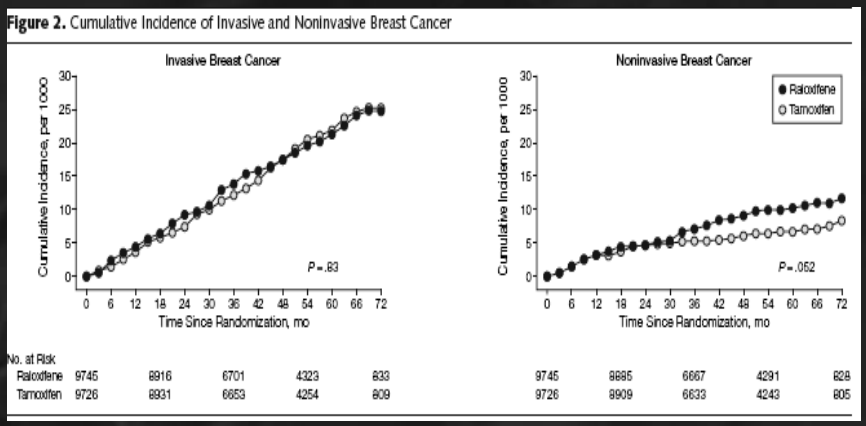
Cuzick, J. et al. J. Natl. Cancer Inst. 2007 99:272-282;
doi:10.1093/jnci/djk049

CONCLUSION

- **Use of 5 yr tamoxifene reduces the risk of developing breast cancer by 50%**
- **10 yr FU Tamoxifen prevention studies- 27-39%RR in ER +ve tumors**

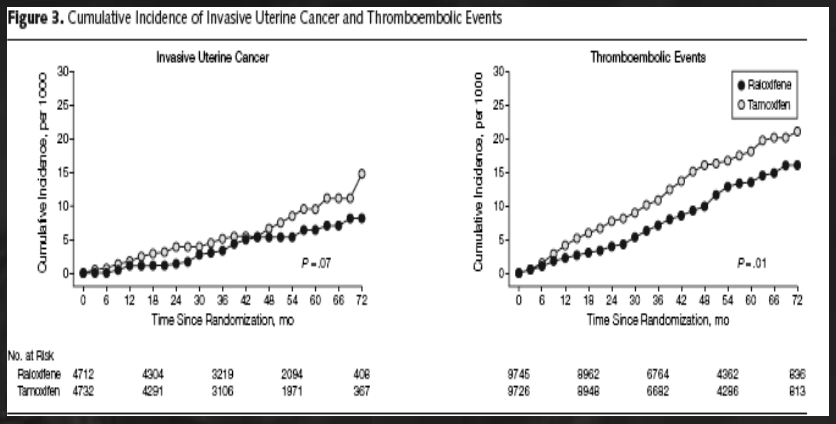
STAR Trial

The NSABP study of tamoxifen and raloxifene (STAR) P-2 trial



Vogel et al, JAMA, 2006

Side-effect profile



Current recommendation: for PM women is 5 yrs of raloxifene

Vogel et al, JAMA, 2006

How to identify these pts in your practice?

- **Gail model risk**

  http://www.cancer.gov/bcrisktool/

  Review: Gail et al Weighing the risks and benefits of tamoxifen treatment for breast cancer prevention JNCI 1999 19(2) 1829-46

<u>Quick pickup:</u>

Family history
Multiple biopsies
LCIS
Bilateral breast cancers

CASE # 3

- **45 yr old AA female presents with a large right breast mass. She had TAH/BSO at the age of 32 and has been on HRT since then. Mass measures 5cm and 2 lymph nodes are palpable in the R axilla. She has no other symptoms.**
  - **What is the clinical staging?**
  - **How do you confirm your diagnosis and staging?**

Clinical/TNM staging

- **Stage I - Node negative, Tumor ≤ 2cm**
- **Stage II - Node positive, Tumor size 2-5 cm**
- **(T > 5cm + node negative)**
- **Stage III - Tumor > 5cm, node positive- matted LN, Internal mammary LN, SCLN.**
- **Inflammatory breast cancer**
- **Stage IV - Distant metastases.**

DIAGNOSIS

- Core needle biopsy is the preferred method
- Sentinel LN biopsy is the preferred method for axillary staging
- Bone scan - indicated for localized symptoms or elevated alkaline phosphatase
- CT scans - Not routinely indicated
- Consider in locally advanced tumors
- Tumor markers - No role at all.

SENTINEL LYMPH NODE BIOPSY

SLN is the first node to receive lymphatic drainage from the area with the breast tumor- Most likely to harbor metastases in the axilla. Current techniques- Isosulphan blue dye, detection of radiolabelled technetium sulfur colloid with a hand-held probe or both

SENTINEL LYMPH NODE BIOPSY

- Predictive power is the same as ALND
- Better QOL with less complications
- Long-term effects unknown

New Diagnosis of Breast Cancer

- Risk factors
- Confirmation of diagnosis
- Stage of disease
- Biology and prognostic and predictive factors

Breast Cancer Treatment and Survivorship

Maryam B. Lustberg, MD, MPH
Assistant Professor of Internal Medicine
The Stefanie Spielman Comprehensive Breast Center
The Ohio State University Comprehensive Cancer Ctr.
The Ohio State University's Wexner Medical Center

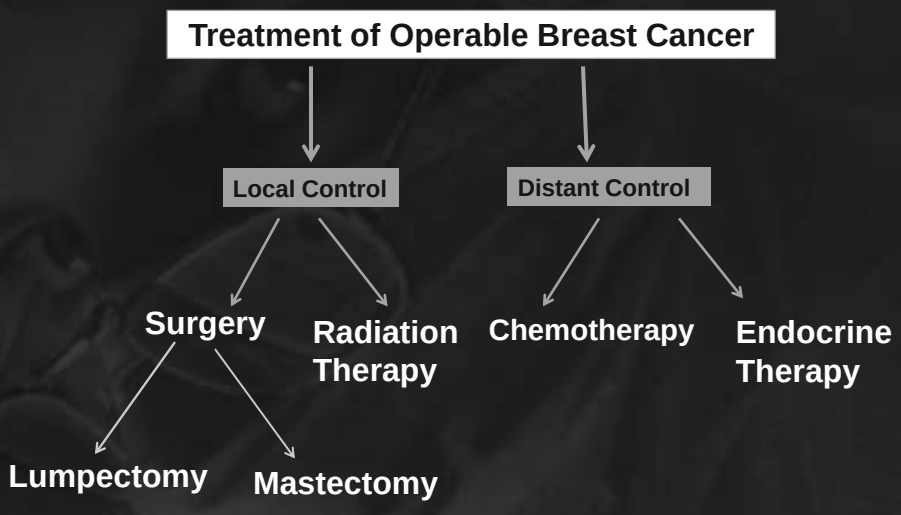
Objectives

- Discuss the most common treatment modalities in breast cancer
- Review common toxicities experienced by breast cancer survivors
- Discuss breast cancer survivorship care in the primary care setting

Initial Presentation

- The majority of breast tumors found on screening mammograms
- Rest are found by clinical breast exams and patient/partner awareness of a breast abnormality
- Other imaging modalities: US and MRI

Breast cancer treatment modalities



Factors Influencing Surgical options

- What factors influence the type of surgery therapy selected?
  - -size of tumor, grade
  - -lymph node involvement
  - -metastatic disease
  - -patient age and co morbidities
  - -contraindication to radiation therapy
  - -Patient preference
- How do different breast cancer subtypes influence therapy choices?
  - -Triple negative breast cancer
  - -HER2 positive breast cancer

Primary Therapy: Breast Surgery

- Lumpectomy with needle localization
- Mastectomy (simple mastectomy, modified radical mastectomy, radical mastectomy
- Negative margins
- Evaluation of axilla
  - -Axillary node dissection
  - -Sentinel node evaluation:
    - -Z0011 Randomized trial (Giuliano et al JAMA 2010)

Breast Cancer Systemic Therapy Options Individualizing care

- Endocrine Therapy
- Chemotherapy
- Biologics (Trastuzumab)
- Experimental therapies
  - Anti-angiogenesis: bevacizumab
  - Bisphosphonates (zoledronic acid)
  - Rank ligand monoclonal antibodies (denosumab)
  - PARP inhibitors

Endocrine Therapy

- ER and/or PR positive only
- Pre-menopausal
  - Tamoxifen
  - Ovarian suppression
- Post-menopausal
  - Aromatase inhibitor
  - Tamoxifen
  - Sequential therapy

Tamoxifen

- SERM (selective estrogen receptor modulator)
- Agonist and Antagonist activity
- 20 mg daily for 5 years
- Recommended for pre-menopausal women and in select post-menopausal patients

Tamoxifen – Potential Benefits

- Decrease contralateral invasive and non-invasive hormone receptor positive breast cancers by approximately 50%
- Significantly improved disease free and overall survival with 5 years of therapy
- Improves bone density in post-menopausal women
  - P1 trial – fracture RR 0.68

Tamoxifen - Toxicity

- Hot flashes – approx 80%, 30% severe
  - CYP2D6
- Endometrial cancer (7 cases/10,000 treated women)
  - Higher risk in women > 50 y/o, obesity
  - Progressive risk with time of exposure
- Uterine Sarcoma (1 – 8 cases / 10,000)
- Venous thromboemolism (10 cases/10,000)
- Net bone loss in pre-menopausal women
- Cataracts

Sources of estrogen in Premenopausal and Postmenopausal Women

- Ovaries: in premenopausal
- Aromatase (Cyp 19) in postmenopausal women
  -present in adipose tissue, adrenal glands, breast tissue

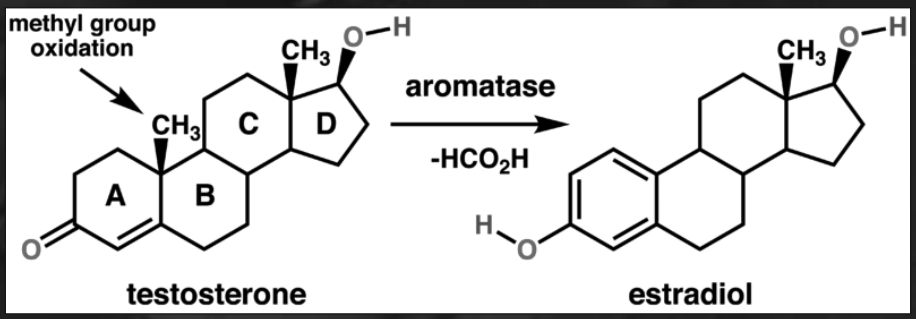


Image from http://www.wikipedia.org/

Aromatase Inhibitors (AIs)

- FDA approved for postmenopausal women with ER/PR + breast cancer
- 2005, ASCO recommended that optimal endocrine therapy included AI as initial therapy or after therapy with tamoxifen based on superior disease free survival relative to tamoxifen.
- Three approved drugs in this class:
  Non-steroidal (anastrazole, letrozole)
  Steroidal (exemestane)

Toxicities of AIs

- Hotflashes (30-50%)
- Arthralgias (30%)
- Vaginal dryness and atrophy (20-30%)
  - Intravaginal estrogen at low doses prescribed after discussion with patient
- Bone loss
- Fractures
- Cardiovascular toxicities?

Fractures with AIs

Trial	N	F/U (mo)	Treatment	Clinical Fracture Rate (%)
AI vs. TAM				
ATAC	9366	100	ANA vs. TAM	11.0 vs. 7.7 [p<0.001]
BIG 1-98	4922	51	LET vs. TAM	8.6 vs. 5.8 [p<0.01]
AI after 2-3 years of TAM				
IES	4724	58	EXE vs. TAM	7.0 vs. 5.0 [p=0.003]
ABCSG8/ ARNO	3224	28	ANA vs. TAM	2.0 vs. 1.0 [p=0.015]
AI after 5 years of TAM				
MA-17	5187	30	LET vs. Placebo	5.3 vs. 4.6 [p=0.25]

68. Cuzick J, Sestak I, Baum M, et al: Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol 11:1135-41, 2010

69. Coates AS, Keshaviah A, Thurlimann B, et al: Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol 25:486-92, 2007

70. Coombes RC, Kilburn LS, Snowdon CF, et al: Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 369:559-70, 2007

71. Jakesz R, Jonat W, Gnant M, et al: Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 366:455-62, 2005

72. Goss PE, Ingle JN, Martino S, et al: Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst 97:1262-71, 2005

Breast Cancer Systemic Therapy Options Individualizing care

- **Endocrine Therapy**
- **Chemotherapy**
- **Biologics (Trastuzumab)**
- **Experimental therapies**
  - **Anti-angiogenesis: bevacizumab**
  - **Bisphosphonates (zoledronic acid)**
  - **Rank ligand inhibitors (denosumab)**
  - **PARP inhibitors**

General Chemotherapy Recommendations

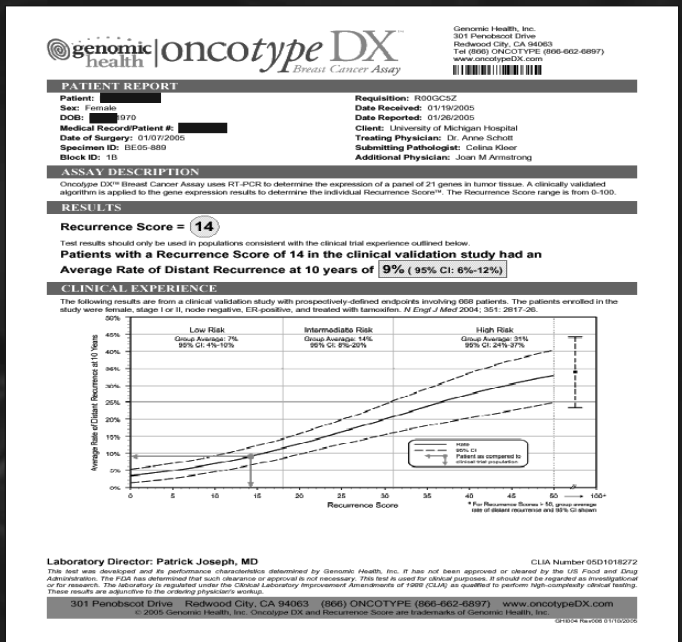
- ER +/- PR positive
  - ≤ 0.5 cm or grade 1 0.6 -1.0 cm – no chemo
  - 0.6 – 1.0 cm grade 2/3 or any grade > 1 cm – consider Oncotype DX
  - LN + Consider chemotherapy, Consider Oncotype DX
- Triple negative (ER-, PR-, HER2-)
  - < 0.5 cm – no chemo
  - 0.6 – 1.0 cm – consider chemo
  - ≥ 1.0 cm or LN+ – recommend chemo
- Her-2 positive
  - < 0.5 cm no chemo
  - 0.6 – 1.0 cm consider chemo + trastuzumab
  - ≥ 1 cm or LN+ - recommend chemo + trastuzumab

Chemotherapy for Hormone Receptor Positive Breast Cancer

- Lymph node involvement
- Lymph node negative
  - Consider based on prognostic factors, age, co-morbidities
  - Adjuvant! online program
  - Oncotype Dx testing

Individualizing therapies

- **Multigene tests: Tests in which samples of tissue are studied to look at the activity of many genes at the same time. These tests may help predict risk of recurrence as well as benefit from chemotherapy**
- **Oncotype DX is the most commonly used assay in the United States for this purpose**



genomic health | oncotype DX™ Breast Cancer Assay

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063
Tel (866) ONCOTYPE (866-662-6897)
www.oncotypeDX.com

PATIENT REPORT

Patient: [redacted]
Sex: Female
DOB: [redacted]970
Medical Record/Patient #: [redacted]
Date of Surgery: 01/07/2005
Specimen ID: BE05-889
Block ID: 1B

Requisition: R00GC5Z
Date Received: 01/19/2005
Date Reported: 01/26/2005
Client: University of Michigan Hospital
Treating Physician: Dr. Anne Schott
Submitting Pathologist: Celina Kleer
Additional Physician: Joan M Armstrong

ASSAY DESCRIPTION

Oncotype DX™ Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. A clinically validated algorithm is applied to the gene expression results to determine the individual Recurrence Score™. The Recurrence Score range is from 0-100.

RESULTS

Recurrence Score = 14

Test results should only be used in populations consistent with the clinical trial experience outlined below.

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%)

CLINICAL EXPERIENCE

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.

Laboratory Director: Patrick Joseph, MD

CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. It has not been approved or cleared by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. These results are adjunctive to the ordering physician's workup.

301 Penobscot Drive Redwood City, CA 94063 (866) ONCOTYPE (866-662-6897) www.oncotypeDX.com

GH1604 Rev008 01/10/2006

Chemotherapy Regimens

Node positive

- **Dose dense Adriamycin/Cytoxan (AC) q 2 weeks with growth factor support + Weekly Paclitaxel x 12 or Paclitaxel q 2 weeks**
- **Taxotere/cytoxan q 3 weeks x 4 doses**

Node negative

- **AC x 4 doses**
- **TC x 4 doses**

Toxicity from Chemotherapy

- **Most common: Fatigue and hair loss**
- **Nausea**
- **Diarrhea/constipation**
- **Mouthsores**
- **Neuropathy**
- **Chemotherapy induced ovarian failure**
- **Infection/neutropenic fever**
- **Therapy related bone loss**
- **Rare: cardiomyopathy, treatment related MDS/leukemia**

Chemotherapy induced ovarian failure (CIOF)

- Greatest risk >50% in women ages 40 or older
- Young women not done with childbearing at risk
- Consultation with fertility specialist recommended.
- Insufficient evidence that concurrent GnRH agonist therapy protective

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- Experimental therapies
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  - Bisphosphonates (zoledronic acid)
  - Rank ligand inhibitors (denosumab)
  - PARP inhibitors

HER2-neu Oncogene

- Located chromosome 17q21
- Encodes a 185 kd transmembrane glycoprotein. Tyrosine kinase-like activity
- Overexpression (or amplification) in 20-25% of tumors
- Independent adverse prognostic factor
- Trastuzumab is the first monoclonal antibody FDA approved for HER2 positive disease. Other HER2 targeted therapies include lapatinib, pertuzumab, and TDM-1.

Chemotherapy +Trastuzumab

- Addition of trastuzumab to chemotherapy, decreases recurrences by 50% and improves survival by 30%
- AC TH vs TCH
- Reversible cardiotoxicity with trastuzumab (4-8%)
- Serial cardiac monitoring with trastuzumab every 3 months in the adjuvant setting

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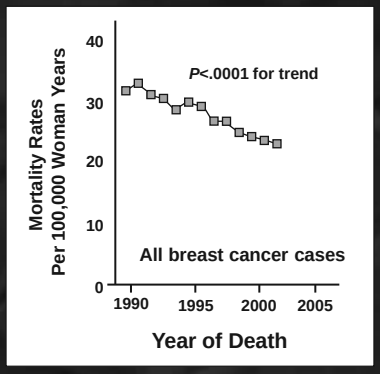
Individualizing Therapy in Breast Cancer

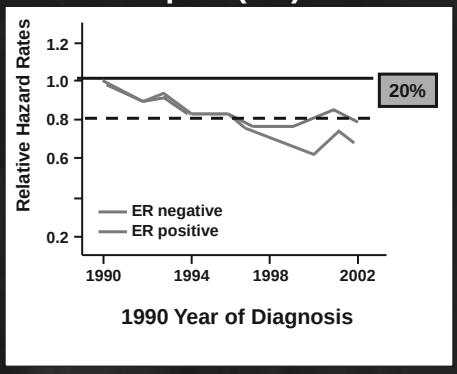
- **As a consequence of both early screening and adjuvant therapies, more women are living with breast cancer than ever before.**

Declining Deaths from Breast Cancer

Age-Adjusted Breast Cancer Mortality Rates Among Women With Invasive Breast Cancer (1990-2003)



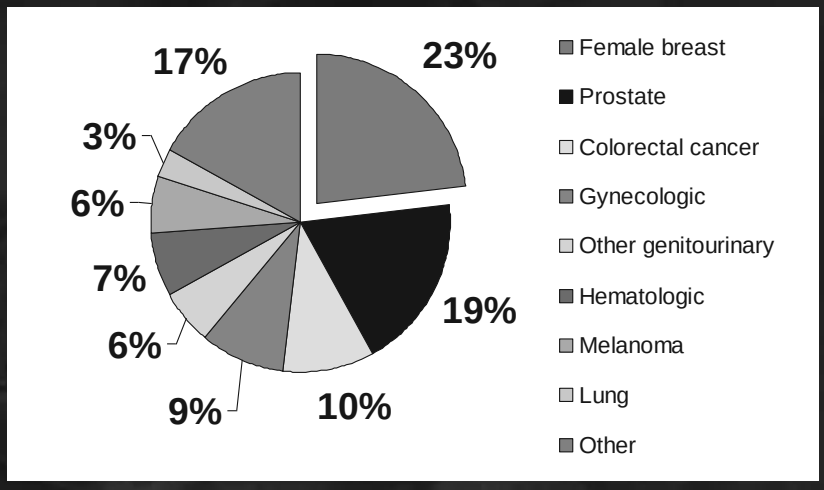
Relative Hazard Rates of Breast Cancer Mortality According to Estrogen Receptor (ER) Status



Jatoi I et al. *J Clin Oncol.* 2007;25:1683-1690.

10 Million+ US Cancer Survivors

Approximately one-fourth are breast cancer survivors



Wolff AC et al. *J Clin Onc*. 2007;25:118-145.

Partnership Between Primary Care Physicians and Oncologists

- Importance of close collaboration between primary care providers and oncologists to optimize breast cancer survivor care
- Treatment summary and care plan
- James/ Stefanie Spielman Comprehensive Breast Center will be organizing workshops on this topic in the future

Key follow up milestones Breast cancer and primary care go hand in hand

- Annual mammograms
- Routine oncology visits
- Bone density every 2 years in postmenopausal women on AIs
- Annual pap and pelvic for women on tamoxifen
- Annual flu shot
- Colonoscopy after age 50
- Blood pressure monitoring
- Cholesterol monitoring
- Vaccines up to date
- Weight management
- Smoking cessation
- Increase physical activity