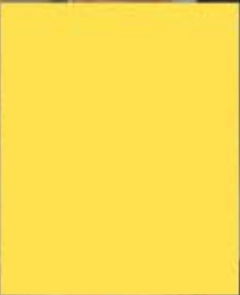




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Breast Cancer



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Breast Cancer

Excess Estrogen Exposure

Nulliparity or late pregnancy	+
Early menarche	+
Late menopause	+
Cystic ovarian disease	+
External estrogens exposure	+



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Breast Cancer

Excess Estrogen Exposure

Alcohol use	+
Phytoestrogens	?
Smoking	? No
Abortion	No
BCPs	No
Infertility treatment	?
Night work	+ (? Melatonin)



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Breast Cancer Etiology

- Diet issues
- Disease of western cultures
- Studies are not all consistent
- Current obesity epidemic
- Recent reports of earlier menarche

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Breast Cancer Etiology

- Pregnancy – 7% reduction for each
- Breast feeding – 4% reduction for 12 months
- Exercise – protective to a degree

Single Greatest Risk Factor

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Breast Cancer

- Biggest Risk Factor
 - American women with breasts

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Breast Cancer

Types by pathology

Invasive ductal	70%
Invasive lobular	5-10%
Ductal carcinoma (non-invasive) in situ	20%
Lobular carcinoma (non-invasive) in situ	<5%

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Breast Cancer

- Types by Pathology
 - Inflammatory
 - Rapid growth in dermis of skin
 - Curable with aggressive multimodality treatment
 - Paget's Disease
 - In situ malignancy of the nipple
 - Can have underlying disease also

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Breast Cancer Prognosis

- Grading System
 - Based on how malignant cells appear
 - Size of cells and nucleus
 - Number of cell dividing
 - Other visual characteristics

Helpful 100 years old
Subjective to a degree

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Breast Cancer Prognosis

Grading System

Grade 1	Slow, good prognosis
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Grade 3	Fast, worst prognosis
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Grade 2	In between
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Breast Cancer Prognosis

TNM Staging System

T – Size of Tumor

T₁ - < 2 cm

T₂ - 2-5 cm

T₃ - >5 cm

T₄ - Advanced changes

N – Status of Lymph Node

N₀

N₁

N₂

M – Status of Metastases

M₀ – No distant disease

M₁ – Distant disease

Helpful but 100 years old.



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Breast Cancer Prognosis

Biologic Characteristics

Estrogen receptor	+ good
Progesterone receptor	+ good
Her-2 status	+ bad

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Breast Cancer Prognosis

- Grade 1 $T_{1A}N_0M_0$ ER+, PR+, her2- = 95% cure
- Grade 3 T_4N_2 ER-, PR-, her2- = 20% cure

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Breast Cancer

- Types of Biology
 - ER+, PR+, her 2 negative
 - ER+/-, PR+/-, her 2 positive
 - ER-, PR-, her 2 negative
 - Each carry different prognosis

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Breast Cancer Prognosis

- Onco Type Dx
 - One of several genetic analysis
 - Specific for ER+ tumors
 - Very helpful in lower risk situations

RESULTS

Breast Cancer Recurrence Score = 26

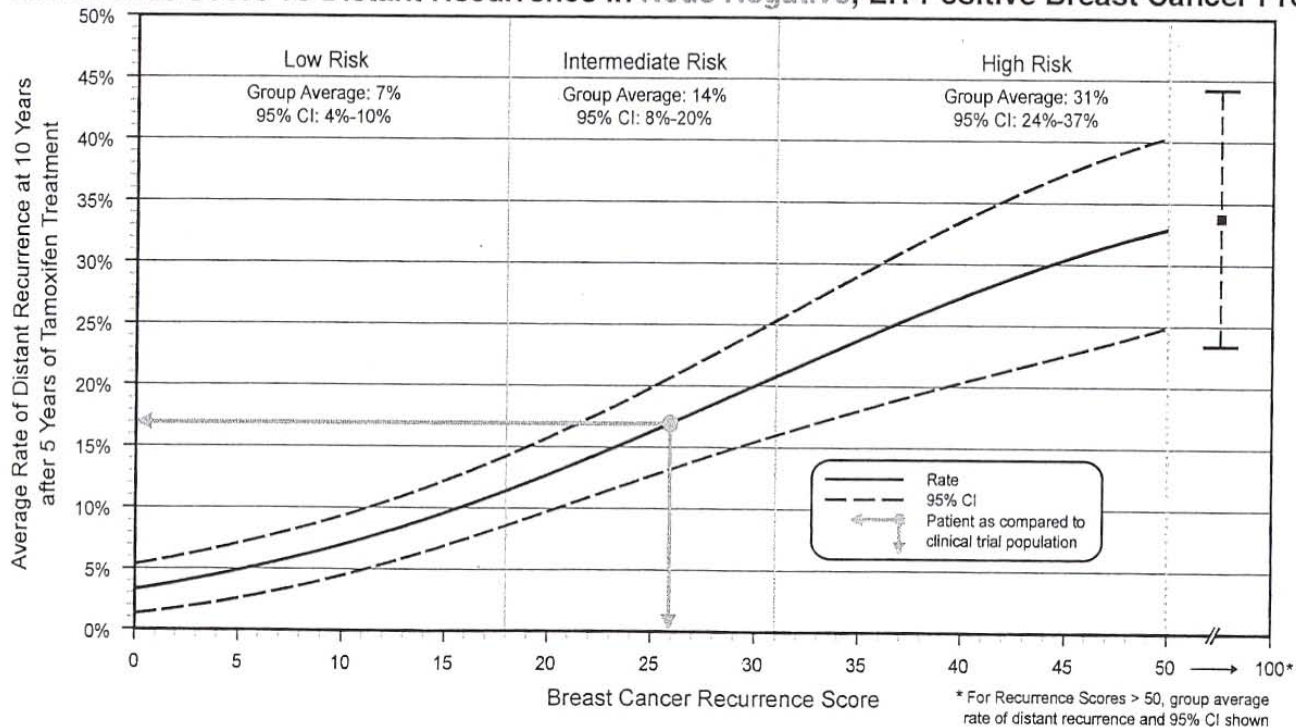
The findings summarized in the Clinical Experience sections of this report are applicable to the patient populations defined in each section. It is unknown whether the findings apply to patients outside these criteria.

CLINICAL EXPERIENCE: PROGNOSIS FOR NODE NEGATIVE, ER-POSITIVE PATIENTS

The Clinical Validation study included female patients with Stage I or II, Node Negative, ER-Positive breast cancer treated with 5 years of tamoxifen. Those patients who had a Recurrence Score of 26 had an Average Rate of Distant Recurrence of **17% (95% CI: 13%-21%)**

The following results are from a clinical validation study of 668 patients from the NSABP B-14 study. *N Engl J Med* 2004; 351: 2817-26.

Recurrence Score vs Distant Recurrence in Node Negative, ER-Positive Breast Cancer Prognosis



Node Negative

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Breast Cancer

- BRCA 1 & 2 gene mutations
 - Most common cause of inherited breast cancer up to 85% penetrance
 - Earlier age onset 20% < 40, 50% < 50
 - Higher incidence of bilateral breast cancer
 - High rate in Ashkenazi Jewish descendants
 - Debate concerning prognosis

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Breast Cancer

- BRCA 1 & 2 mutations
 - Loss of suppressor oncoprotein
 - Treatment generally the same vs. sporadic cancer
 - Testing of DNA available and expensive

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Breast Cancer

- BRCA 1
 - Younger than BCRA-2 or in general
 - 40%-60% development of ovarian cancer
 - 2-3 fold risk for other cancers
 - Male breast and prostate association

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Breast Cancer Screening

- Exam
- Self exam
- Mammogram
- Ultrasound
- MRI
- Needle biopsy

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Breast Cancer

- Surgical Treatment
 - Lumpectomy equals mastectomy (in most circumstances)
 - Complete resection necessary
 - Post lumpectomy radiation usually
 - Local control vs. cure

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Breast Cancer

- Surgical Treatment
 - Nodes now sentinel sampled
 - Only positive sentinel nodes need more surgery
 - ? Benefit of removing positive nodes
 - Role of surgery in stage 4 disease

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Breast Cancer

- Radiation therapy
 - After lumpectomy usually
 - After mastectomy >5 cm or 3 N+
 - After mastectomy for earlier stage?

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Breast Cancer

- Neoadjuvant and Adjuvant treatment
 - Neoadjuvant treats tumor before surgery
 - Adjuvant treats after local therapy
 - Each can be chemo, antiestrogens or both
 - Adjuvant attempting to kill cells already spread
 - Can reduce risk by 5-20%
 - Choice of treatment based on risk

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Breast Cancer Treatment

- Metastatic disease
 - Treatable, not curable
 - Anti-estrogen therapy if ER+
 - Chemotherapy if ER- or after failure

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Breast Cancer

- ER+ disease
 - Tamoxifen blocks estrogen entry
 - Aromatase inhibitor block adrenal production
 - Arimidex, Femara, Aromasin
 - Foslodex blocks estrogen
 - Progesterone does something?
 - Estrogen can work after above treatments
 - At times years of benefit or none

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Treatment Metastatic Breast Cancer

- ER+ (40-80%) (Luminal A&B)
- Antiestrogen therapies – 5
- Chemotherapy – 10
- HER2+ (20%) increased growth factor receptors
 - Trastuzumab (herceptin), lapatinib (tykerb) with chemotherapy
 - Herceptin and lapatinib with antiestrogens
- Triple negative (20%)
 - Chemotherapy only
 - PARP inhibitors



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Treatment Metastatic Breast Cancer – ER+

- Favorable response rate
 - ▣ ER+ strongly, PR+ strongly
 - ▣ Long disease-free interval
 - ▣ Bone only involvement
- Drugs
 - ▣ Tamoxifen
 - ▣ Aromatase inhibitors (Femara, Arimidex, Aromasin)
 - ▣ Fulvestrant (Faslodex)
 - ▣ Progesterone (Megace)
 - ▣ Estrogen (DES)

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Treatment Metastatic Breast Cancer

Chemotherapy

- ❑ Multiple drugs available
- ❑ No regimen is curative
- ❑ Two together better response rate
- ❑ Two together more toxicities
- ❑ All work by inhibiting cell division
- ❑ None exclusively attack breast cancer cells



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Treatment Metastatic Breast Cancer

HER2+ (3+ IHC, FISH amplified)

- Herceptin + chemotherapy
 - Increased response rates 20% more
 - Increased disease free interval 3-5 months
 - Increased survival 3-5 months
- Established role in first line therapy
- Use in additional lines of therapy under study
- Adds minimal toxicities
- Adds substantial cost

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Transtuzumab (Herceptin)

- Monoclonal antibody
- Inhibits HER2, a growth factor receptor
- Few side effects except cardiac
- Can cause congestive heart failure
- Not used with anthocyclines
- Very expensive

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Lapatinib (Tykerb)

- ❑ Inhibits HER1/2 & EGFR receptors
- ❑ Can work in herceptin failures
- ❑ Can be synergistic with herceptin
- ❑ Can be synergistic with chemotherapy
- ❑ May reduce brain metastasis
- ❑ Currently approved with xeloda in 2nd line Rx
- ❑ Can be given orally

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Triple Negative Breast Cancer

ER-, PR-, HER2-

- ❑ Molecular profile similar to BRCA disease
- ❑ Loss of ability to repair DNA damage
- ❑ PARP-1 is a DNA binding protein involved in repair
- ❑ PAPP-1 inhibitors are synergistic with chemo
- ❑ Not yet clinically approved (? Soon)

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Treatment Metastatic Breast Cancer

Chemotherapy Bevacizumab (Avastin)

- ❑ Monoclonal antibody
- ❑ Binds and inhibits vascular endothelial growth factor receptor
- ❑ Limits blood flow to the tumor
- ❑ Synergistic with chemotherapy
- ❑ Little action on its own
- ❑ Standard care of colon & lung cancer

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Treatment Metastatic Breast Cancer

Chemotherapy – Bevacizumab

- ❑ Approved with chemotherapy 2008
- ❑ Increased response rates and disease free survival
- ❑ Additional studies now question its value
- ❑ Decision by FDA Sept 2010
- ❑ Toxicities can be severe/fatal
- ❑ Usually fairly well tolerated



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