BREAST CANCER
From Diagnosis to Treatment: The Role of Primary Care

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Essentials of Primary Care
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Incidence

• Most commonly detected cancer in U.S. women
  – 1 in 8 women will be diagnosed with breast cancer in their lifetime
  – 5.6% of women will develop breast cancer between their 50th-70th birthdays

• Incidence increases with age
  – Median age at diagnosis = 61;
  – Nearly half (47%) diagnosed in women over age 65;
  – 52% of breast cancer mortality occurs in this age group

Mandelblatt, JGIM 2005
Incidence

Age-adjusted overall incidence: 126.1 per 100,000 per year

Differs by race/ethnicity

- White: 130.6
- Black: 117.5
- Latina: 90.1
- Asian/PI: 89.6
- AI/Alaska Native: 75.0

SEER Data 2001-2005
Stage at Diagnosis

- Stage at diagnosis:
  - 61% diagnosed are localized to site
  - 31% diagnosed with regional extension
  - 6% diagnosed with distant metastases
  - 2% unknown stage

Black and Latina women more likely to be diagnosed at later stage

Li et al, Arch Int Med, 2003;163
Mortality

• 2nd most common cause of cancer death in women

Overall age adjusted death rate 25.0 per 100,000 per year

Differs by race/ethnicity

• White 24.4
• Black 33.5
• Al/Alaska Native 17.1
• Latina 15.8
• Asian/PI 12.6

• 5-year survival overall 88.7%; Whites 89.9%; Blacks 77.1%

SEER Data 2001-2005
Recent Decline in Incidence

- Decline in incidence of breast cancer since 2000
  - 3.1% decrease between 2001-2005 (SEER data)

- Decrease associated with decline in HRT use
  - HRT declined 2000-2002: 7% per year; 2002-2003: 34%
  - 2000-2003 invasive breast CA down by 5% per year
  - 2001-2003 ER+ invasive breast CA down 13% per year
  - No decrease in DCIS incidence

  Kerlikowske et al, JNCI 2007;99

- Decline in incidence has been less for African American women than for white women: less HRT use?

  Smigal et al, CA Cancer J Clin 2006;56
Risk Factors

• Non-modifiable
  – Age (incidence increases with age)
  – Early menarche (before age 11)
  – Late menopause (after age 54)
  – Family History (first degree relative <age 50; multiple 1\textsuperscript{st} and 2\textsuperscript{nd} degree relatives; ovarian cancer; prostate cancer)
  – Breast density (modifiable?)
Mammographic Breast Density

- Women with **high breast density** (>50% dense area on mammographic image) have **3-5x greater risk** of breast cancer than women with **low breast density** (< 25% dense area)
  
  Byrne et al JNCI 1995;87

- Modifiable? Breast density
  - Decreases with age, menopause
  - Higher BMI: lower breast density
  - Earlier parity: lower breast density
  - HRT: higher breast density

Increase in density over time is associated with increase in breast ca risk;
Decrease in density over time is associated with decrease in breast ca risk

Kerlikowske JNCI 2007;99
Modifiable Risk Factors

Parity

– late parity (>40) / nulliparity: higher risk
– African-American women dual association: higher parity (more births) associated with higher risk among younger (<45) & lower risk among older women

BMI

– post-menopausal high BMI: higher risk;
– for Latinas obesity associated with risk across age groups
Modifiable Risk Factors

HRT use
- 5-years combined HRT associated with 26% increased risk of post-menopausal invasive breast ca
  
WHI, JAMA, 2002;288

Alcohol intake
- >1 drink per day
- Linearly associated with risk of breast cancer
Risk Reduction

- Low fat diet and exercise with aim of goal BMI post-menopause
- Limit alcohol intake to max 1 drink daily
- Limit HRT use for women with severe symptoms and keep to 2 years use
- Consider having first child before age 30
BRCA Mutations

• Increased risk of carrying BRCA1 and BRCA2 mutations associated with:
  – Younger age of diagnosis
  – More 1\textsuperscript{st} and 2\textsuperscript{nd} degree relatives with breast & ovarian cancer

• General population: BRCA mutations account for 5-10\% of breast cancers
  – Highest among Ashkenazi Jewish women
  – Also found in Africans, African-American, Chinese, Latina, white women without Ashkenazi heritage
Risk Reduction in Very High Risk Women

• Genetic Testing – BRCA 1 & BRCA 2

• SERMS
  – BCPT 1998 showed 5-yrs tamoxifen reduced risk of invasive breast ca 49% -- increased endometrial ca, VTE
  – STAR trial 2006 showed raloxifene equal to tamoxifen in reducing risk of invasive breast cancer – increased VTE

• Prophylactic Mastectomy
SCREENING

- Disease has high prevalence: Yes
- Disease has serious consequences: Yes
- Detectable preclinical phase – microcalcifications
- Treatment for pre-symptomatic disease is more effective than after symptoms develop – unclear in case of DCIS
- Screening reduces cancer mortality: Several studies have shown that screening mammography can reduce mortality
  - RCTs have not shown a mortality reduction in women in their 40’s
Test Issues

- Increased density of pre-menopausal breast tissue leads to decreased sensitivity

- Cumulative risk of false positive result: 49% after ten mammograms
  - False positive rates higher for women in their forties than for women age 50-69

Elmore et al NEJM 1998
Test Issues

• More cases discovered by mammography in women in their forties are ductal carcinoma in situ (DCIS) than in women in their fifties (40-45% vs. 20%)
  – Clinical significance of DCIS is unclear
  – Only 20% will progress to invasive cancer over 10 years and those that do progress will do so slowly
USPSTF

- Recommends screening mammography with or without clinical breast examination every 1-2 years for women aged 40 and older
  - Data are most clear for women aged 50-69
  - For women in their forties the evidence is weaker
  - Benefit to women aged 70 and older if life expectancy not compromised by co-morbid disease

- Evidence insufficient for or against clinical breast examination alone

- Evidence insufficient for or against teaching or performing routine breast self-examination
Screening in High Risk Women

- Women w/ BRCA or >20% lifetime risk of breast cancer
  - Lower sensitivity of mammography in younger women
  - High tumor growth rate
  - Atypical mammography changes in women with BRCA mutations

- MRI
  - Sensitive method of breast imaging and has been used as a diagnostic tool in women with breast cancer
  - Not influenced by breast density
  - Specificity is variable
  - Expensive

- Ultrasound
  - Less sensitive than MRI
  - Time consuming for physician (and thus access/expense an issue)
  - Specificity is variable
High Risk Screening

- 236 Canadian women aged 25-65 with BRCA1 and BRCA2 mutations had 1-3 annual screening examinations
  - MRI, ultrasound, mammography annually
  - Clinical breast examination every 6 months
- 22 cancers detected
  - 6 DCIS
- All four screening modalities combined had a sensitivity of 95% vs. 45% for mammography plus clinical breast exam

Warner et al JAMA 2004
## High Risk Screening

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>77%</td>
<td>95%</td>
</tr>
<tr>
<td>Mammography</td>
<td>36%</td>
<td>99.8%</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>33%</td>
<td>96%</td>
</tr>
<tr>
<td>Clinical Breast Exam</td>
<td>9%</td>
<td>99%</td>
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High Risk Screening

• Ultrasound study:
  – 2,809 women from 21 sites; 1 year follow-up
  – Heterogeneously dense breasts at least 1 quadrant
  – Mammogram and physician-performed u/s (random order; blinded)
  – 41 cancers
    • 8 seen on both
    • 12 seen on mammogram alone
    • 12 seen on ultrasound alone (29%)
    • 9 seen on neither

Berg et al, JAMA 2008
High Risk Screening

Specificity concerns

• 233 suspicious u/s findings led to biopsy
• 20 (8.6%) were breast cancer
• False-positive diagnoses:
  – Mammography alone 116
  – Mammography + Ultrasound 275
Abnormal Mammogram

American College of Radiology BIRADS category (breast imaging reporting and data system)

- **0**: indeterminate → rapid follow-up with imaging (spot-compression views +/- u/s)
- **1**: negative → routine follow-up
- **2**: benign finding → routine follow-up
- **3**: low chance malignancy (~2%) → short interval follow-up (3-6 months repeat mammo)
- **4**: >2-95% chance malignancy (a: low; b: intermediate; c: moderate) → biopsy
- **5**: ≥95% chance malignancy, usually invasive → biopsy
Abnormal Mammograms

- Adequate communication of abnormal results improves receipt of appropriate follow-up
  
  Poon et al, JGIM 2004

- Minority women report lower rates of adequate communication, and are less likely to know their abnormal mammogram results
  
  Zapka et al, Prev Med 2004
Delays in Diagnosis

- 20-40% women undergoing breast ca diagnosis experience delays to diagnosis or treatment

- Delay of $\geq 3$ months (symptoms to treatment) associated with 12% lower 5-year survival (compared to less delay)
  - Most of this attributable to later stage disease
  
  Richards et al, Lancet 1999

- African-American women are more likely to suffer delays than White women

  Elmore et al, Med Care 2005
Delays in Diagnosis

• Causes of delays
  – Scheduling difficulties
  – Physician inaction (not contacting patient; not ordering follow-up tests)
  – Inadequate communication of abnormal results and need for follow-up
  – Language barriers
  – Patient inaction (lack of knowledge / understanding, fear, anxiety)
Palpable Mass: Clinical Evaluation

• Primary Care: 16% women age 40-69 have breast concern over 10-year period

• Breast CA found in:
  – 11% of women complaining of a breast lump
  – 4% of women with any breast complaint

Barton et al, Ann Int Med 1999

• Most common diagnosis: cysts, fibroadenomas

• Malpractice awards: delayed cancer diagnosis due to negative clinical exam and/or mammogram
Palpable Mass: Clinical Evaluation

• Physical Exam: classic characteristics of CA
  – Single lesion
  – Hard
  – Immovable
  – Irregular borders
  – Large (≥ 2 cm)

• But, many cancers are soft & cystic, moveable, regular, and < 2cm

• Most benign lesions are also single
Palpable Mass: Clinical Evaluation

Younger Women <30-35

• Dominant Mass on physical exam?
  – No, average risk woman → return in 2-3 months for re-exam
  – No, high risk woman → refer to breast surgeon/clinic

– Yes, but average risk woman & exam not concerning
  → RTC 3-10 days after next menses
  → If still palpable, then further work-up

– Yes, high risk woman or exam concerning → ultrasound or FNAB
Palpable Mass: Clinical Evaluation

• Diagnostic mammography not very useful in younger women – order if other results suggest malignancy

• Ultrasound first if mass does not feel cystic:
  – Simple cyst → no further invasive work-up
  – Complex cyst or solid mass → FNA, core needle, or excisional biopsy

• FNAB first if mass feels cystic:
  – Clear fluid & mass disappears
    → f/u exam in 4-6 weeks to check for recurrence,
    → if recurs then refer
  – Bloody fluid or cellular material, send for cytology,
    → if inadequate sample then refer
    → If atypical or suspicious for ca, then core or excisional biopsy indicated
Palpable Mass: Clinical Evaluation

Older women >30-35

• Diagnostic mammography to evaluate mass & search for occult malignancy elsewhere in same breast
  – In study of >41,000 diagnostic mammograms for women with self-reported breast lump
    Sensitivity 87.3
    Specificity 84.5
    Barlow et al JNCI, 2002

• Mammography misses 10-20% of breast cancers

• Addition of ultrasound to mammogram, negative predictive value = 97%
  Moy et al, Radiology 2002
Palpable Mass: Clinical Evaluation

- “Triple Diagnosis” misses very few cancers
  - physical exam
  - mammography
  - skilled FNAB

- If all 3 negative → f/u exam q3-6 months x 1 year

- If all 3 suggestive of malignancy → refer for definitive treatment

- If any one test suggestive of malignancy → core or excisional biopsy
Staging Work-up

• Specimen mammography
  – Lesions excised under mammographic localization
  – Palpable lesions associated with microcalcifications

• Operative findings
  – Size of primary tumor
  – Chest wall invasion
  – Regional metastases

• Post-excision mammography
  – 3-5 weeks after excision
  – Complements specimen mammography & histologic margin assessment
  – Residual calcifications found in up to 24% should be removed
Hormone Receptors and HER2

Assay for estrogen, progesterone receptors and HER2

– Perform on core biopsy specimen
– If negative on core specimen, should be repeated at definitive surgery:
  • up to 15% of cases with negative markers on biopsy specimen will be positive on larger surgical specimen

• ER/PR + cancers responsive to hormonal treatment (tamoxifen / aromatase inhibitors)

• Over-expression of HER2/neu oncogene
  – worse prognosis
  – responsive to trastuzumab (Herceptin)
Stages

• **Stage 0**
  – **LCIS**: increased risk of developing invasive ca later in life (up to 30-40% lifetime risk)
  – **DCIS**: 25-50% of untreated cases become invasive, but no mortality risk in and of itself

• **Stage 1**: tumor <2cm, no lymph node involvement

• **Stage II**: tumor 2-5cm or any size tumor with non-matted axillary lymph node involvement

• **Stage IIIa**: tumor <5cm or significant matted axillary lymph node involvement

• **Stage IIIb**: inflammatory breast cancer

• **Stage IV**: tumor spread beyond breast, axilla, and internal mammary LN, and may be metastatic to lungs, bone, liver, brain
Metastatic Work-up

- Mets are rare without symptoms
- Physical exam – skin, breasts, lymph nodes, abdomen
- Diagnostic bilateral mammography; possible breast u/s or mri
- CBC, LFTs
- Chest x-ray; possibly CT pre-radiation
- Staging CT – liver, pelvis, chest – and bone scan in stage III disease
Initial Treatment

• DCIS:
  – Lumpectomy +/- radiation if localized
  – If multifocal / extensive possibly possibly mastectomy
  – Tamoxifen x 5 years

• Early Stage Invasive
  – Lumpectomy + whole breast radiation vs. mastectomy
  – For HR+ tumors 5 years of anti-estrogen therapy
    Post-menopausal women: aromatase inhibitors (AI)
      • Superior to tamoxifen in disease-free survival, time to recurrence, and time to distant recurrence
      • Fewer adverse events than tamoxifen

  – For HER2+ tumors – trastuzumab with or without anti-estrogen therapy and chemotherapy

ATAC, Lancet 2005
BIG, NEJM 2005
Poor Prognosis Tumors

- Triple negative tumors
  - ER- / PR- / HER2-
  - Unresponsive to anti-estrogen therapy and trastuzumab
  - Neo-adjuvant chemotherapy
  - Clinical trials investigating immune modulators and receptor-blockers for growth factors

- African Americans, Latinas and BRCA1 carriers more at risk for triple negative tumors
Surveillance After Therapy

Goals:

– Early recognition & treatment
  • disease recurrences
  • second primary breast cancers

– Screening for therapy related complications

– Detection of symptoms consistent with metastatic disease
Surveillance After Therapy

• Intensive surveillance vs. follow-up with regular physical exams & mammography
  – No survival or quality of life benefit
  De Bock et al J Clin Oncol 2004

• H&P
  – ASCO: q 3-6 months x 3 years, then annually (no data to guide this)
  – Focus history on symptoms of local recurrence
    • New lumps or skin changes
    • Axillary discomfort / mass
    and on possible metastases to bones, liver, lung, brain, sub-q tissue
Surveillance After Therapy

- H&P continued
  - Physical exam
    - Thorough bilateral breast exam, diagram of affected breast and post-op/post-radiotherapy changes
    - Axillary & supraclavicular lymph nodes
    - Arm girth exam for lymphedema
    - Palpation of spine, sternum, ribs, pelvis for bone tenderness
    - Lung exam for decreased breath sounds/effusions
    - Cardiac
    - Abdominal exam for RUQ tenderness / hepatomegaly
    - Neurologic exam

- Testing should be guided by symptoms and findings

- Women taking tamoxifen need gyn exam / possible emb for any vaginal bleeding
Surveillance After Therapy

- Ipsilateral local recurrence: 1-2% per year
- Contralateral 2\textsuperscript{nd} primary .5-1% per year (non-BRCA carriers)

- Only retrospective evidence to support use of mammography to prevent local recurrence or new primary

- ASCO guidelines:
  
  Post breast-conserving therapy:
  - first mammography 6 months after radiotherapy
  - Subsequent mammo q 6-12 months, once stability of findings, then annually