Breast Cancer: Selected Topics for the Primary Care Clinician

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Essentials of Primary Care

A Core Curriculum for Ambulatory Practice

OUTLINE

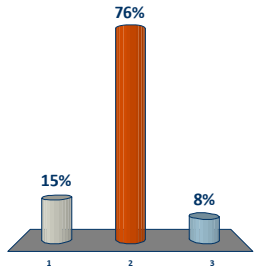
- Incidence and Mortality
- Risk Factors and Risk Reduction/Prevention
- Abnormal Mammograms and Delays in Diagnosis
- Evaluation of a Palpable Mass
- Hormone Receptors and HER2/Neu
- Surveillance After Therapy
- Survival
- (Staging and Initial Treatment)

Case 1

AR, a 60 year old African American woman, presents to your office asking about her risk for breast cancer. She has 2 children, first birth at age 26, menarche at age 12, menopause age 50. Her BMI is 29, she drinks wine with dinner 1-2 glasses/night, and has been taking HRT since age 50. She has a great-aunt who had breast cancer at age 70.

Compared to a White woman with a similar risk profile, is her risk of having breast cancer…

1. The same
2. Higher
3. Lower



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 ca 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:

- 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
AI/Alaska Native	17.1
Latina	15.8
Asian/PI	12.6

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

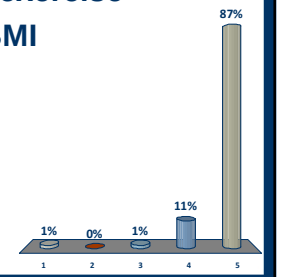
SEER Data 2001-2005

Case 1 continued

- **AR, having learned about the high mortality risk of breast cancer for African American women, now asks you if there is any way she can reduce her risk of breast cancer.**

You tell her she can lower her risk of breast cancer in the following way…

1. **Drink no more than 1 glass of wine/day**
2. **Eat a low fat diet and exercise**
3. **Lose weight to goal BMI**
4. **Stop taking HRT**
5. **All of the above**



Recent Decline in Incidence

- **3.1% decrease between 2001-2005** (SEER data)
- **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**
- **Decrease associated with decline in HRT use**
  - HRT declined 2000-2002: 7% per year;
  - 2002-2003: 34%

  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 1st and 2nd degree relatives;
    - ovarian cancer; prostate cancer

Mammographic Breast Density

- **High breast density (>50% dense area on mammogram) 3-5x greater risk compared to low breast density (< 25% dense area)**

  Byrne et al JNCI 1995;87

- **Modifiable?**
  - 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: more births confers 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 / Prevention

- **Low fat diet and exercise with aim of goal BMI post-menopause**
- **Limit alcohol intake to 1 drink daily**
- **Limit HRT use for women with severe symptoms and keep to 2 years use**

BRCA Mutations

- **Increased risk of carrying BRCA1 and BRCA2 mutations associated with:**
  - Younger age of diagnosis
  - More 1st and 2nd 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

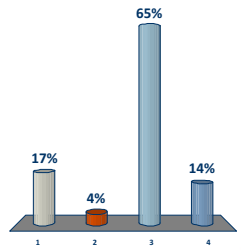
- **Genetic Testing – BRCA 1 & BRCA 2**
- **SERMS**
  - BCPT 1998:
    - 5-yrs tamoxifen reduced risk of invasive breast ca 49% -- increased endometrial ca, VTE
  - STAR trial 2006:
    - raloxifene equal to tamoxifen in reducing risk of invasive breast cancer – increased VTE only
- **Prophylactic Mastectomy**
- **Prophylactic Oophorectomy for women <30**

Case 2

- **Your patient AH, a 56 yo woman, goes for her screening mammogram. A few days later, you get a call from the radiologist. The mammogram shows increased density and possibly a calcification on the right. The radiologist says they are reading it as a BIRADS 0 and the patient should get follow-up, could you please let her know?**

What kind of follow-up does this patient need next?

1. **A repeat mammogram in 3-6 months**
2. **A mammogram at the usual screening interval**
3. **A diagnostic mammogram with spot-compression views**
4. **A referral to the breast surgeon/clinic for a biopsy**



Abnormal Mammogram

- **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

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

Normal

1: negative — routine follow-up

2: benign finding — routine follow-up

Abnormal

0: indeterminate — immediate follow-up
(spot-compression views +- u/s)

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 invasive malignancy — 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

Jones et al, Am J Pub Health 2007

Delays in Diagnosis

- **20-40% women undergoing breast ca diagnosis experience delays to diagnosis or treatment**
- **Delay of ≥ 3 months** (symptoms to treatment) **associated with 12% lower 5-year survival**
  - 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

- **Hospitals disproportionately serving non-English speaking and minority women have longer delays**

Karliner et al, publication in preparation

Delays in Diagnosis

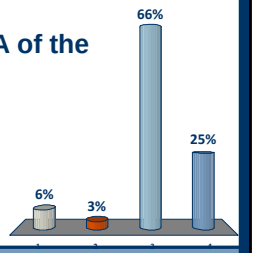
- **Causes of delays**
  - Scheduling difficulties
  - Physician inaction (not contacting patient; not ordering follow-up tests)
  - Inadequate communication of abnormal results and need for follow-up
  - Language barriers
  - Inadequate tracking systems
  - Patient inaction (lack of knowledge / understanding, fear, anxiety)

Case 3

- **You are seeing GL, a 50-year-old Chinese-American woman, for her routine annual exam. She tells you about a new lump she found in her breast, which you feel and find to be firm with regular borders. You send her for a diagnostic mammogram the next week. The mammogram is normal.**

What is your response to the normal mammogram?

1. **Reassure the patient and get another mammogram in 6 months**
2. **Reassure the patient and get another mammogram in 1-2 years**
3. **Send the patient for an ultrasound of mass**
4. **Send the patient for an FNA of the mass**



Palpable Mass: Clinical Evaluation

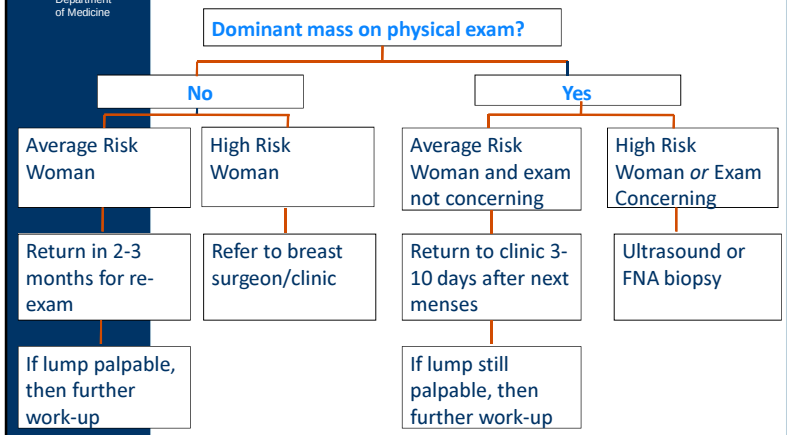
- **Primary Care: 16% women age 40-69 have breast concern over 10-year period**
- **Breast CA found in:**
  - 11% of women complaining of a breast lump
  - 4% of women with any breast complaint

  Barton et al, Ann Int Med 1999
- **Most common dx: 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: Younger Women <30-35



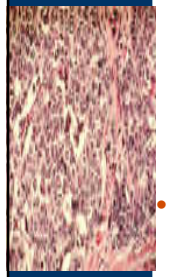
- **Diagnostic mammography not very useful in younger women – order if other results suggest malignancy**
- **Ultrasound first if mass does not feel cystic:**
  - Simple cyst → no further invasive work-up
  - Complex cyst or solid mass → FNA, core needle, or excisional biopsy
- **FNAB first if mass feels 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: 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

- **"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**

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

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**

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**

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 for intensive approach

  De Bock et al J Clin Oncol 2004
- **Testing should be guided by symptoms and findings**
- **Women taking tamoxifen need gyn exam / possible emb for any vaginal bleeding**

Surveillance After Therapy

- **History and Physical**
  - ASCO: q 3-6 months x 3 years, then annually (no data to guide this)
  - Focus history & PE on symptoms/signs of Local recurrence
    - New lumps or skin changes
    - Axillary discomfort / mass

    Possible metastases: bones, liver, lung, brain, sub-cutaneous tissue

Surveillance After Therapy

- **Ipsilateral local recurrence: 1-2% per year**
- **Contralateral 2nd 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:**

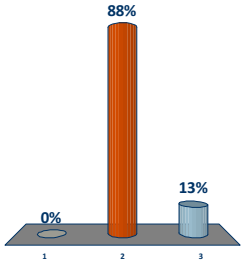
  Post breast-conserving therapy:
  - first mammography 6 months after radiotherapy
  - Subsequent mammo q 6-12 months, once stability of findings, then annually

Case 4

- Your patient TD (72 yo) is diagnosed with Stage I breast cancer. She undergoes lumpectomy and radiation, followed by 5 years of an Aromatase Inhibitor. She comes to see you on the 5-year anniversary of her diagnosis. You congratulate her and tell her…

Her chance of recurrence is now

1. Zero
2. Less than 10%
3. 15-20%



Post-Treatment Survival

- 2,838 women Stage I-III treated w/ adjuvant or neo-adjuvant systemic therapy
- 1985-2001; disease free x 5 years
- Residual disease-free recurrence rate
  - 10 years post-diagnosis 89%
  - 15 years post-diagnosis 80%
- By stage residual risk of recurrence at 10 years
  - Stage I 7%
  - Stage II 11%
  - Stage III 13% Brewster et al JNCI, 2008

Take Home Points

- Highest incidence in white and African American women
- Highest mortality in African American women
- Women with highest breast density have 3-5 fold risk of developing cancer
- Decrease in HRT use has resulted in corresponding decrease in BC incidence
- Delays in diagnosis are common after an abnormal mammogram
- Improved communication of abnormal results improves receipt of appropriate follow-up

- **Evaluation of palpable breast mass differs by age group**
  - Diagnostic mammogragraphy not very useful in younger women (<30-35)
  - Mammography misses 10-20% of breast cancers even in older women (>30-35)
- **Triple-negative tumors have worst prognosis, more common among African Americans, Latinas, BRCA1 carriers**
- **Metastases are rare without symptoms**
- **Surveillance by hx/PE/mammography; other testing should be guided by symptoms**
- **If a woman survives 5-years, her 10-year survival is very good (Stage I-III)**

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; may be metastatic to lungs, bone, liver, brain**

Standard Treatment

- **DCIS:**
  - Lumpectomy +/- radiation if localized
  - If multifocal / extensive 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

    ATAC, Lancet 2005

    BIG, NEJM 2005
  - For HER2+ tumors – trastuzumab with or without anti-estrogen therapy and chemotherapy