UPDATES IN BREAST CANCER

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Annual Refresher Course for the Family Practitioner
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I HAVE NOTHING TO DISCLOSE
OBJECTIVES

• Discuss trends in breast cancer incidence and mortality
• Identify new methods of risk assessment, screening and detection
• Discuss changes in breast cancer management
• Discuss breast cancer survivorship and the role of the primary care physician
BREAST CANCER IN 2021
### Top 12 most common cancer sites in United States (overall incidence)

<table>
<thead>
<tr>
<th>Site</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>116,300</td>
<td>112,520</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>78,300</td>
<td>69,650</td>
</tr>
<tr>
<td>Prostate</td>
<td>60,190</td>
<td>N/A</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>62,100</td>
<td>40,160</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>42,380</td>
<td>19,300</td>
</tr>
<tr>
<td>Bladder</td>
<td>45,520</td>
<td>34,880</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>N/A</td>
<td>28,230</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>35,470</td>
<td>65,620</td>
</tr>
<tr>
<td>Uterus</td>
<td>30,400</td>
<td>25,060</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,720</td>
<td>27,200</td>
</tr>
<tr>
<td>Pancreas</td>
<td>12,720</td>
<td>40,170</td>
</tr>
</tbody>
</table>

### Top eight cancer sites (death)

<table>
<thead>
<tr>
<th>Site</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>72,500</td>
<td>63,220</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>28,630</td>
<td>24,570</td>
</tr>
<tr>
<td>Pancreas</td>
<td>24,640</td>
<td>22,410</td>
</tr>
<tr>
<td>Breast</td>
<td>520</td>
<td>42,170</td>
</tr>
<tr>
<td>Liver &amp; Intrahepatic Bile Duct</td>
<td>20,020</td>
<td>10,140</td>
</tr>
<tr>
<td>Prostate</td>
<td>33,330</td>
<td>N/A</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,420</td>
<td>9,680</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>11,460</td>
<td>8,480</td>
</tr>
</tbody>
</table>

*Source: Cancer Facts & Figures 2020, American Cancer Society (ACS), Atlanta, Georgia, 2020.*
BREAST CANCER: NATIONAL TRENDS IN INCIDENCE AND DEATH RATES

Trends in incidence rates, 1975-2016
by sex, for breast (female)
Per 100,000, age-adjusted to the 2000 US standard population.

Trends in Death rates from breast cancer (female), 1930-2017
PERCENT OF CASES & 5-YEAR RELATIVE SURVIVAL BY STAGE AT DIAGNOSIS: FEMALE BREAST CANCER

Percent of Cases by Stage

- Localized (63%)
  Confined to Primary Site
- Regional (30%)
  Spread to Regional Lymph Nodes
- Distant (6%)
  Cancer Has Metastasized
- Unknown (2%)
  Unstaged

5-Year Relative Survival

- Localized: 98.9%
- Regional: 85.7%
- Distant: 28.1%
- Unknown: 55.1%

SEER 18 2010–2016, All Races, Females by SEER Summary Stage 2000
Incidences of breast cancer by race and ethnicity, 2012-2016

Incidence rates are given per 100,000, age adjusted to the 2000 US standard population.

- Non-Hispanic white: 130.8
- Non-Hispanic black: 126.7
- American Indian and Alaska Native: 94.7
- Hispanic: 93.8
- Asian and Pacific Islander: 93.2

Data Sources: North American Association of Central Cancer Registries (NAACCR), 2019
© 2020 American Cancer Society
FEMALE BREAST CANCER:
AGE ADJUSTED DEATH RATE PER 100,000 WOMEN
BY RACE/ETHNICITY

Source: U.S. Mortality, Age-Adjusted Rate per 100,000; Surveillance Epidemiology and End Results Program
Incidence rates, 2012-2016
by state, for breast (female)
Average annual rate per 100,000, age adjusted to the 2000 US standard population.

Data Sources: North American Association of Central Cancer Registries (NAACCR), 2019
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CancerStatisticsCenter.cancer.org
RISK ASSESSMENT AND SCREENING
Effectiveness of Breast Cancer Screening: Systematic Review and Meta-analysis to Update the 2009 U.S. Preventive Services Task Force Recommendation

Heidi D. Nelson, MD, MPH; Rochelle Fu, PhD; Amy Cantor, MD, MPH; Miranda Pappas, MA; Monica Daeges, BA; and Linda Humphrey, MD, MPH

The target population for the USPSTF recommendation includes women aged 40 years or older, and excludes women with known physical signs or symptoms of breast abnormalities and those at high-risk for breast cancer whose surveillance and management are beyond the scope of the USPSTF’s recommendations for prevention services (i.e., preexisting breast cancer or high-risk breast lesions, hereditary genetic syndromes associated with breast cancer, or previous large doses of chest radiation before age 30 years).

Clinical Review & Education

Special Communication

Breast Cancer Screening for Women at Average Risk

2015 Guideline Update From the American Cancer Society

RECOMMENDATIONS The ACS recommends that women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years (strong recommendation). Women aged 45 to 54 years should be screened annually (qualified recommendation). Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually (qualified recommendation). Women should have the opportunity to begin annual screening between the ages of 40 and 44 years (qualified recommendation). Women should continue screening mammography as long as they remain asymptomatic and there is no contraindication.
Medication Use to Reduce Risk of Breast Cancer
US Preventive Services Task Force
Recommendation Statement

**Recommendation Summary**

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women at increased risk for breast cancer</td>
<td>The USPSTF recommends that clinicians offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, to women who are at increased risk for breast cancer and at low risk for adverse medication effects.</td>
<td>B</td>
</tr>
<tr>
<td>Women not at increased risk for breast cancer</td>
<td>The USPSTF recommends against the routine use of risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, in women who are not at increased risk for breast cancer.</td>
<td>D</td>
</tr>
</tbody>
</table>

**Clinician Summary**

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women aged ≥35 years at increased risk for breast cancer</td>
<td>Offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors</td>
<td>Grade: B</td>
</tr>
<tr>
<td>Women aged ≥35 years not at increased risk for breast cancer</td>
<td>Do not routinely use risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors</td>
<td>Grade: D</td>
</tr>
</tbody>
</table>

Risk Assessment: Various methods are available to identify women at increased risk for breast cancer, including formal clinical risk assessment tools or assessing breast cancer risk factors without using a formal...
Causes and Risk Factors of Breast Cancer

- Previous breast biopsies
- Lobular carcinoma in situ
- Atypical ductal hyperplasia
- Atypical lobular hyperplasia

- Increased breast density
- Prior chest irradiation
- Prolonged use of oral contraceptives
- Hormone replacement therapy after menopause
- Alcohol intake/tobacco
- Early Menstruation & Late Menopause / Obesity
- Late childbearing
- Family history
- Gene mutation
- Prior breast cancer

Previous breast biopsies
Lobular carcinoma in situ
Atypical ductal hyperplasia
Atypical lobular hyperplasia

Prior chest irradiation
MODIFIED GAIL MODEL RISK ASSESSMENT TOOL
HTTP://BRCA.NCI.NIH.GOV/BRC

6 breast cancer risk factors

• Age

• hormonal or reproductive history (age at menarche and age at first live birth)

• previous history of breast disease (number of breast biopsies and history of atypical hyperplasia)

• family history (number of first-degree relatives with breast cancer).

High risk ≥ 20% lifetime risk or ≥ 1.7% 5 yr risk
TYRER-CUZICK MODEL
HTTPS://IBIS.IKONOPEDIA.COM/
NCCN Guidelines Version 1.2020
Breast Cancer Screening and Diagnosis

SCREENING OR SYMPTOM CATEGORY

Increased Risk:

Prior history of breast cancer

See NCCN Guidelines for Breast Cancer - Surveillance Section

OR

Women who have a lifetime risk ≥20% as defined by models that are largely dependent on family history

- Recommend annual breast MR
- To begin 10 years prior to when the youngest family member was diagnosed with breast cancer, but not prior to age 25 yr or age 40 y (whichever comes first)
- Consider whole breast ultrasound or contrast-enhanced mammography for those who qualify for but cannot undergo MRI

OR

- Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction)
- Breast awareness

Patient who receives thoracic RT between the ages of 10 and 30 y

Current age <25 y

- Annual clinical encounter
- Beginning 8 y after RT
- Breast awareness

Current age ≥25 y

- Clinical encounter every 6–12 mo
- Begin 8 y after RT
- Annual screening mammogram
- Begin 8 y after RT but not prior to age 30 y
- Consider tomosynthesis
- Recommend annual breast MR
- Begin 8 y after RT but not prior to age 25 y
- Consider whole breast ultrasound or contrast-enhanced mammography for those who qualify for but cannot undergo MRI
- Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction)
- Breast awareness

Note: All recommendations are category 3A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Testing is clinically indicated in the following scenarios:

1. Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
2. Individuals meeting the criteria below but tested negative with previous limited testing (e.g., single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing
3. Personal history of cancer
   - Breast cancer with at least one of the following:
     - Diagnosed at age ≤45 y; or
     - Diagnosed at age 46-59 y with:
       - Unknown or limited family history;
       - A second breast cancer diagnosed at any age; or
       - ≥1 close blood relative with breast, ovarian, pancreatic, or prostate cancer at any age
     - Diagnosed at age ≤50 y with triple-negative breast cancer;
     - Diagnosed at any age with:
       - Ashkenazi Jewish ancestry; or
       - ≥1 close blood relative with breast cancer at age ≤50 y or ovarian, pancreatic, metastatic, intraductal/cribiliiform histology, or high- or very-high-risk group (see NCCN Guidelines for Prostate Cancer) prostate cancer at any age; or
     - ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
     - Diagnosed at any age with male breast cancer
     - Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
     - Exocrine pancreatic cancer at any age (See CRIT-3)
     - Prostate cancer at any age with:
       - Metastatic, intraductal/cribiliiform histology, or high- or very-high-risk group (see NCCN Guidelines for Prostate Cancer); or
     - Any NCCN risk group (see NCCN Guidelines for Prostate Cancer) with the following family history:
       - Ashkenazi Jewish ancestry; or
   - If testing criteria not met, consider testing for other hereditary syndromes
4. Family history of cancer
   - An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except individuals who meet criteria only for systemic therapy decision-making).
   - If the affected relative has pancreatic cancer or prostate cancer (metastatic, intraductal/cribiliiform, or NCCN Guidelines for Prostate Cancer - High- or Very-High-Risk Group), only first-degree relatives should be offered testing unless indicated for other relatives based on additional family history.
   - An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a BRCA1/2 pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk)
# CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
</table>
| ATM  | Increased risk of female breast cancer<sup>1</sup>  
  • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y<sup>6</sup>  
  • RRM: Evidence insufficient, manage based on family history | Potential increased risk of ovarian cancer  
  • RRSO: Evidence insufficient; manage based on family history | Pancreatic  
  • See PANCA  
  • Unknown or insufficient evidence for prostate cancer |
| BARD1| Limited emerging evidence to suggest increased risk of breast cancer, particularly ER, PR and HER-2 negative (triple negative disease)  
  • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y<sup>6</sup>  
  • RRM: Evidence insufficient, manage based on family history | Unknown or insufficient evidence for ovarian cancer risk | Unknown or insufficient evidence for other cancers |
| BRCA1| Increased risk of breast cancer (with predisposition to triple negative disease)  
  • See BRCA Pathogenic Variant-Positive Management | Increased risk of ovarian cancer  
  • See BRCA Pathogenic Variant-Positive Management | Pancreatic (See PANCA), Prostate  
  • See BRCA Pathogenic Variant-Positive Management |
| BRCA2| Increased risk of breast cancer (with predisposition to ER+ disease)  
  • See BRCA Pathogenic Variant-Positive Management | Increased risk of ovarian cancer  
  • See BRCA Pathogenic Variant-Positive Management | Pancreatic (See PANCA), Prostate, Melanoma  
  • See BRCA Pathogenic Variant-Positive Management |

Comments: Counsel for risk of autosomal recessive condition in offspring. Heterozygous ATM mutation should not lead to a recommendation to avoid radiation therapy at this time. See Discussion for information regarding the c.7271T>G variant.

Comment: There have been few case reports of Fanconi-like conditions in individuals with two BRCA1 pathogenic variants.<sup>1</sup>

RRM: Risk-reducing mastectomy  
RRSO: Risk-reducing salpingo-oophorectomy

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Note: All recommendations are category 2A unless otherwise indicated.  
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
NEW SCREENING MODALITIES

Abbreviated breast MRI

- Shorter protocol, fewer images and faster turnover than standard MRI

Contrast enhanced mammography

- Mostly for diagnostic purposes
- Beneficial for screening in women with dense breasts who do not qualify for MRI
BREAST CANCER MANAGEMENT
TREATMENT ALGORITHM CIRCA 2007

Breast cancer diagnosis

- Surgery
  - Breast: Mastectomy vs Lumpectomy
  - Lymph nodes
    - Clinically node negative
      - Sentinel lymph node biopsy
      - Positive SLN
        - Axillary dissection
    - Clinically node positive
      - Chemotherapy based on clinicopath factors
      - +/- Radiation
        - Endocrine Therapy if ER+
  - Chemotherapy if inoperable
BREAST CANCER – IT’S NOT ONE DISEASE

Worse Prognosis

Intrinsic subtypes

Basal
HER2 over-expression
BRCA1 mutation

Better Prognosis

Luminal B
Luminal A
ER/PR positivity

Molecular subtypes

ER-PR-HER2-
ER-PR-HER2+
[ER+|PR+]HER2+
[ER+|PR+]HER2-
Overall and relapse-free survival analysis of the 49 breast cancer patients, uniformly treated in a prospective study, based on gene expression classification.
PERCENT OF FEMALE BREAST CASES BY CANCER SUBTYPE

- **HR+/HER2-**: 68%
- **HR-/HER2-**: 10%
- **HR+/HER2+**: 10%
- **HR-/HER2+**: 4%
- **Unknown**: 8%
TREATMENT ALGORITHM CIRCA 2020

Breast cancer diagnosis

Surgery

Breast: Mastectomy vs Lumpectomy +/- reconstruction

Chemotherapy based on genomic testing

 +/- Radiation

Endocrine Therapy if ER+

Lymph nodes

Clinically node negative or node positive low burden of disease

Sentinel lymph node biopsy

Positive SLN, high burden

Axillary dissection

Chemotherapy if ER- or HER2+ or node positive or high genomic risk

Endocrine therapy
MULTIDISCIPLINARY CANCER CARE
TREATMENT TRENDS FOR STAGE 1-3 BREAST CANCER

**Surgery**
- Oncoplastic surgery
- Image guided surgery
- Better breast reconstruction
- Less lymph node surgery
- Surgery to correct lymphedema

**Medical Oncology**
- Increased use of neoadjuvant chemotherapy (NAC)
- Increased tailoring of therapy using genomic testing and response to NAC

**Radiation oncology**
- Omission of radiation in low-risk subgroups
- Hypofractionation
- Partial breast radiation
- Increased post mastectomy radiation
DUCTAL CARCINOMA IN SITU
COMET (Comparison of Operative to Monitoring and Endocrine Therapy) trial for low risk DCIS

Eligibility criteria:
- Age ≥ 40
- Grade I/II DCIS without invasive cancer
- Diagnosed confirmed by core or surgical biopsy
- ER(+) and/or PR(+) and HER2(-) if tested
- No mass on PE or imaging

Endpoints:
- 2, 5, 7-year invasive cancer dx
- 2, 5, 7-year OS, DSS
- PRO endpoints (QOL, fear of cancer recurrence, body image)

Registered and randomized (n=900)

GROUP 1: Usual Treatment (n=450)
- Surgery, Radiation or both choice for endocrine therapy
- Mammogram every 12 months for 5 years

GROUP 2: Close Monitoring (n=450)
- choice for endocrine therapy
- Mammogram every 6 months for 5 years

Courtesy of Shelley Hwang, MD
STAGE 4 BREAST CANCER
IMPROVED SURVIVAL IN STAGE 4 BREAST CANCER
SURVIVORSHIP
“Primary care clinicians should counsel patients about the importance of maintaining a healthy lifestyle, monitor for post treatment symptoms that can adversely affect quality of life, and monitor for adherence to endocrine therapy…..

Recommendations on surveillance for breast cancer recurrence, screening for second primary cancers, assessment and management of physical and psychosocial long-term and late effects of breast cancer and its treatment, health promotion, and care coordination/practice implications are made.
GUIDELINES

- F/u q 3-6 months until 2 years, then annual
- Annual mammography, but no routine labs
- Monitor compliance with antiestrogen therapy
- Update family history and refer for genetic testing as appropriate
- Promote healthy behavior
  - Weight control – obesity associated with increase risk of recurrence
  - Smoking cessation – higher risk of complications from breast radiation
- Monitor bone health
  - postmenopausal breast cancer survivors need a baseline DEXA scan + repeat DEXA scans every 2 y for women taking an aromatase inhibitor, premenopausal women taking tamoxifen and/or a GnRH agonist, and women who have chemotherapy-induced premature menopause
GUIDELINES

Monitor for sequelae of treatment:

- Lymphedema
- Neuropathy – after chemotherapy most commonly
- Cardiac disease – from chemotherapy (adriamycin) and radiation
- Shoulder morbidity
- Cognitive impairment – ‘chemobrain’
- Depression, anxiety
- Body image issues
IOM: SURVIVORSHIP CARE PLAN

• Summarize critical information needed for the survivor’s long-term care:
  • Cancer type, treatments received, and their potential consequences;
  • Specific information about the timing and content of recommended follow-up;
  • Recommendations regarding preventative practices and how to maintain health and well-being;
  • Information on legal protections regarding employment and access to health insurance;
  • The availability of psychosocial services in the community
BREAST IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL)

• Rare form of lymphoma associated with texture implants
• Common symptoms include breast enlargement, pain, asymmetry, breast or axillary mass, skin changes, hardening of the breast, or a large fluid collection typically developing at least more than one year after receiving an implant, and on average after 8 to 10 years
• Work up includes breast MRI and aspiration of peri-implant fluid
THANK YOU AND QUESTIONS?
APPENDIX
CHANGES IN SYSTEMIC THERAPY
INCREASED USE OF NEOADJUVANT CHEMOTHERAPY

Associations between pathological complete response and event-free survival and overall survival

Response to neoadjuvant chemotherapy is predictive of outcome

Cortazar, Lancet 2016
Genomic tumor testing to predict benefit of chemotherapy in ER positive patients

- Oncotype
- Mammaprint

Tools often used to decide chemotherapy or not for node negative and early node positive ER+ cancer
CHANGES IN RADIATION THERAPY
BREAST RADIATION

Decreases risk of local recurrence from 26% to 7% at 5 yrs.

WHOLE BREAST RADIATION
- Standard (6 weeks)
- Hypofractionated (3 weeks)

PARTIAL BREAST RADIATION
- Catheter based
- External beam
- Intraoperative radiation
CHANGES IN SURGICAL THERAPY
Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stage I and II Invasive Breast Cancer: American Society of Clinical Oncology Endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology Consensus Guideline

Fig. 1. Immediate breast reconstruction rate and reconstructive method in the United States from 1998 to 2008.
MASTECTOMY AND RECONSTRUCTION

Before

After
Removal of all axillary lymph nodes (in patients with cancer in nodes)

20% or higher risk of lymphedema

Recent clinical trials support omission of ALND in several clinical scenarios

Model estimates in trends of ALND from 2012 to 2015 by facility type

Srour et al Ann Surg Onc, 2019
TECHNIQUES TO DECREASE RISK OF LYMPHEDEMA

• Surgical technique
• Axillary reverse mapping (ARM)
• Lymphatic Microsurgical Preventing Healing Approach (LYMPHA) in high risk patients
Don’t routinely use sentinel node biopsy in clinically node negative women $\geq 70$ years of age with early stage hormone receptor positive, HER2 negative invasive breast cancer.
Lumpectomy Plus Tamoxifen With or Without Irradiation in Women Age 70 Years or Older With Early Breast Cancer: Long-Term Follow-Up of CALGB 9343

Hughes et al, JCO 2013