Prevention and Screening for Breast Cancer: What’s New?

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Lots of Issues
- Do I need to still get mammograms if I am 75 years old?
- What does increased breast density mean?
- Are there really drugs that prevent breast cancer?
- Do I need to be followed any differently if my mom had breast cancer?
- What age do I need to begin mammogram screening?
- Who should get MRI screening?
- How can I predict my risk of getting breast cancer?

Breast Cancer Epidemiology-
Issues pertaining to Screening
- Approximately 12.3% of women will be diagnosed with breast cancer at some point during their lifetime. 1/8 at age 85
- Number of new cases of breast cancer is 124.6 per 100,000 women per year
- 14% all new cancers are breast
- 12% diagnosed in reproductive years (ages 20-44)
- More than 25,000 cases per year in California
Breast Cancer – What do Clinicians Need to Understand?

- What are the risk factors for breast cancer?
- Who should be screened?
- What type of screening should be done?
- Who should be offered preventative medications or surgeries?

Breast Cancer – Risk Factors

- **Age** – increases as we age
- **Female gender**
- **Race and ethnicity** – highest incidence in whites, but highest mortality in African Americans
- **Benign breast disease** – particularly Atypical Ductal Hyperplasia (ADH), Atypical Lobular Hyperplasia (ALH), or proliferative breast lesion

Breast Cancer – Risk Factors

- **Family history and genetic factors** – 15-20% of women with breast cancer reported to have family history in first degree relative
- **Personal history of breast cancer**
- **Exposure to ionizing radiation**

Breast Cancer – Risk Factors

- **Lifestyle and dietary factors**
  - May increase risk: obesity, smoking, high fat intake, red meat, alcohol use, soy phytoestrogens
  - May be protective: regular exercise, greatest benefit seen in adolescence
  - Vitamin D – some studies suggest low levels of Vit D associated with increased risk
Why is alcohol use associated with breast cancer?

- Increases risk primarily of hormone positive cancer
- Alcohol can affect the way estrogen is metabolized and increase blood levels
- Alcohol can reduce blood levels of folic acid which is involved in copying and repairing DNA. Low levels of folic acid may make it more likely that DNA is incorrectly copied when cells divide causing errors that may lead to cancer
- Women who have 2 - 5 drinks per day have about 1.5 x the risk of developing breast cancer compared to non-drinkers

Breast Cancer – Risk Factors

- Reproductive and hormonal factors
  - Increased risk: early menarche, late menopause, late age of first child or nulliparity, increased breast density, long-term HRT, ?endogenous hormone levels
  - No association: prior abortion
  - Decreased risk: breastfeeding, ?Estrogen Replacement Therapy (ERT)

Factors that may increase risk:
- Environment exposures: PCB’s, hair dyes, etc. - no clear data
- Night time light exposure - Exposure to light at night suppresses nocturnal production of melatonin (thought to have antioxidant effects preventing damage to cells)

Factors without association:
- Antibiotic use
- Caffeine
- Antiperspirants
- Bras
- Breast implants

Factors thought to be protective:
- Non-steroidal drugs - NSAIDs especially aspirin and COX-2 inhibitors shown in recent meta-analysis to be protective for hormone positive breast cancer (likely via anti-inflammatory effects)

Breast Cancer Risk Factors

- Bisphosphonates: meta-analysis have shown these drugs can reduce the rate of breast cancer recurrence in bone and improve survival in postmenopausal women with breast cancer - not in premenopausal women and no clear data that it reduces the risk of getting breast cancer.

Issues pertaining to Screening?

- How should screening should be done?
- Should all women be screened?
- What age to begin screening?
- Should screening stop at older ages?
- Should screening differ based on risk factors?

How Should Screening be Done?

- **Self Breast Exam (SBE)**
  - American Cancer Society no longer recommends
  - ACOG recommends teaching breast self exams
  - Many other organizations (USPSTF) do not recommend
  - WHO and NCCN talk about SBE to “raise breast awareness”
  - Not great evidence that it helps
    - Few RCT, one of largest studies 2008 looked at 400,000 women in Russia and China showed no benefit in breast cancer mortality and more biopsies done for benign disease
    - 2 case control studies showed less advanced disease if women taught appropriate SBE

How Should Screening be Done?

- **Clinical Breast Exam (CBE)**
  - Many US organizations recommend CBE every 3 years from age 20 to 39, annually thereafter
  - American Cancer Society new guidelines do not support CBE
  - US Preventive Task force and WHO says not enough evidence to support regular CBE
  - ACOG supports doing CBE
  - Evidence not clear:
    - most studies combine CBE with mammography so independent effects less clear
    - Less standardization for CBE compared to mammography
    - 2009 review found no clear benefit
**How Should Screening be Done?**

- **Mammograms**
  - Screening mammogram clearly detects early stage breast cancer
  - Controversies are whether it improves breast cancer mortality (over-diagnosis)
    - 9 RCT looking at 650,000 women have looked at mortality – mammo +/- CBE. Results show a benefit in women ages 40-69
    - Older studies looking at mortality also affected by older treatments that weren’t as effective
    - 25 yr. fu 2014 from Canadian National Breast Screening Study: randomized screening trial did not show a benefit in mortality compared to exam alone when adjuvant therapy is available
    - 22% (106/484) of screen detected invasive breast cancers were over-diagnosed. BMJ. 2014;348

**American Cancer Society changes guidelines 2015**

- Women with an average risk of breast cancer should begin yearly mammograms at age 45
- Women ages 40-44 should have the choice to start annual breast cancer screening with mammograms if they wish to do so. The risks and benefits should be considered.
- Women 55 and older should have mammogram screening every other year or have the choice to continue annual screening.
- Regular mammograms should continue for as long as a woman is in good health
- Breast exams, either from a medical provider or self-exams, are no longer recommended

**Mammogram Screening – Problem for clinicians?**

- ACOG recommends mammograms annually beginning at age 40
- USPSTF and other organizations state that in low risk women, every 2 year screening should begin at age 50
- WHO recommends every 2 years for women 50-69
- ACS recommends annually from 45-55 and every two years for women 55 and older
- Lots of confusion but highlights the need to INDIVIDUALIZE

**How Frequent Should Mammograms be done?**

- Most North American groups recommend annual screening for women under 55 because of evidence of more rapid tumor growth in younger women
- Benefits of detecting more tumors in earlier stage in younger women needs to be balanced against the increased harms associated with an increased rate of false-positives
- Every 2 year screening thought to decrease false positives, and no overall differences in survival on a population basis
Should Mammogram Screening Stop at Older Ages?

- Controversy as many cancers in women over 80 are slow growing and not likely to affect survival, as other competing causes of death
- US Preventive Task Force states no benefit for screening above age 74
- American College of Radiology says continue until life expectancy < 5-7 years on basis of age or other co-morbidities
- Other groups make no recommendations

CLINICIANS SHOULD INDIVIDUALIZE

Why isn’t the Golden Gate Bridge Golden?

- A. It originally was but construction crew didn’t like the color
- B. It is only called golden based on the Golden Gate Strait, the narrow entrance between the Pacific Ocean and the San Francisco Bay and was never going to be painted golden
- C. The U.S. Navy didn’t want it golden and wanted it painted black and yellow stripes to assure even greater visibility for passing ships.

TRIVIA TIME

And the Answer Is.....

- B
- C

The strait was named by explorer and U.S. Army officer John C. Frémont, who marveled at its beauty in 1846 - two years before the discovery of gold in California.

Consulting Architect Irving Morrow selected the distinctive orange color because it blends well with the span’s natural setting as it is a warm color consistent with the warm colors of the surrounding land and distinct from the cool colors of the sky and sea. It also provides enhanced visibility for passing ships.
Breast Screening with Newer Technologies

- Breast MRI
- Breast Tomosynthesis
- Whole Breast Ultrasound
- Thermography
- Magnetic resonance spectroscopy
- Computer aided detection (CAD)
- Contrast-enhanced digital mammography
- Stereoscopic Digital Mammography
- High field strength MRI

Need for data and subsequent guidelines

Other Screening Modalities - Breast MRI

Breast MRI for Screening

- Creates images of the breast by measuring changes in the movement of protons in fat and water with changing magnetic fields. Image is created based on differences in tissue relaxation that occur after pulses of energy applied.

- Requires IV contrast with gadolinium and use based on increased blood supply in tumors that take up and release of gadolinium quickly leading to specific pattern of rapid enhancement and washout on MRI.

Breast MRI of invasive ductal cancer kinetic color map

2014 UpToDate
Breast MRI for Screening

- Very sensitive for detecting small invasive cancers in high risk women (but less specific than mammogram) with suggestion of improved mortality
- No data showing a benefit for screening MRI in average risk women
- High false positives (nationally as high as 40%) which cause patient anxiety, painful procedures
- Substantial costs - $1000 (vs $100 for mammo)

MRI for Screening - Controversies

- MRI can detect smaller cancers and more node-negative malignancies in high risk women compared to other imaging modalities
- No clear evidence of reduced mortality or improved disease-free survival from screening with MRI

Uses of Breast MRI

- Assessment of silicone implant integrity
- Follow up for occult breast cancers (missed on mammogram) or assessing for primary breast cancer in women with axillary disease
- Assessing disease extent in newly diagnosed breast cancer patients
- Assessing response to neoadjuvant chemotherapy
- Assessing recurrence of disease
- Clarifying inconclusive clinical or mammographic findings
- Screening of high risk patients

MRI Screening Recommendations in High Risk Women – ACS, NCCN

- Annual MRI should be done in the following high-risk groups:
  - Women with a BRCA1 or BRCA2 mutation
  - Women who have a first-degree relative with a BRCA mutation (even if they have not yet been tested themselves)
  - Prior radiation therapy to the chest between the ages of 10-30
  - Known Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome, or have first-degree relatives with one of these syndromes
  - Women with an approximate lifetime risk of breast cancer from 20-25%, according to risk prediction models primarily using family history
MRI for Screening
- No clear benefits of MRI screening in low or average risk women.
- The American Cancer Society recommends against MRI screening for women whose lifetime risk of breast cancer is less than 15%.

Breast Screening – general guidelines for clinicians
- Not enough evidence to support teaching SBE.
- Evidence is mixed whether to do CBE at routine visits.
- Baseline mammograms 40-50 depending on risks.
- Frequency of mammography 1-2 years.
- Continue mammogram screening as long as patient is healthy.
- Do not use MRI screening in average risk women.
- Clinicians should INDIVIDUALIZE guidance depending on risk.

Other Screening Modalities
- Tomosynthesis “3D” Mammography:
  - Modification of digital mammography that uses a moving x-ray source and digital detector to create 3-D view.
  - Currently FDA approved for clinical use as an adjunct to mammography.
  - Thought to decrease recall rates by delineating true lesions from superimposition.
Tomosynthesis “3D” Mammography

- 2 prospective and several retrospective studies comparing digital mammogram alone vs digital mammogram plus breast tomosynthesis found improved positive predictive value for cancer, lower recall rates.
- Incremental breast cancer detection is in the range of 0.5-2.7/1000 screens.
- Recall rates in the range of 0.8-3.6%.
  - [Lancet Oncol. 2016 Jun 23](#)

Tomosynthesis “3D” Mammography

- Older techniques had twice the radiation exposure.
- Newer techniques create a 2-D image from the 3-D tomosynthesis images, lowering radiation dose to slightly above standard mammogram — upgrading to this technique is costly so many facilities don’t have and issues related to insurance reimbursement.
- Particularly useful for moderately dense breasts and high-risk women.
- Randomized controlled trials needed before recommending for all women.

Whole Breast Ultrasound

- Useful for dense breast tissue, but increased false positives.
- Ultrasound in addition to mammography slightly improves cancer detection but has not been shown to affect breast cancer mortality.
- No RCT comparing screening ultrasound plus mammogram vs. mammogram alone.
- Operator dependent.

Whole Breast Ultrasound

- Confusion for clinicians and patients as many patients have been screened in centers where ultrasound is routinely done, but no guidelines for use in screening.
- FDA approved an automated device in 2012 for as an adjunct to mammography for asymptomatic women with dense breasts and a negative mammogram — no published data from a screening trial using this device.
- Generally felt not enough evidence to support device.
Computer Aided Detection (CAD)

- Computer-based technology designed to recognize mammographic patterns and help radiologists identify suspicious areas
- FDA approved CAD in 1998 after several studies showed improved cancer detection
- Debate about usefulness and no randomized trials have been performed to determine its effect on breast cancer mortality
- Picks up more DCIS
- Studies have shown improved sensitivity but higher recall rate and potential for over-diagnosis

Thermography

- Developed based on the observation that patients have elevated breast skin temperatures over their breast cancers
- Received FDA approval in 2004 based on safety of infrared imaging technology but not based on efficacy
- Many thermography centers now exist
- Specificity is low
- No studies have shown this to be an effective screening tool

TRIVIA TIME
World Series Facts or Fiction

- The Yankees have played 153 World Series games, almost a full season, since the Cubs last played one.
- From 1994 - 2016, the Cleveland Indians have made the playoffs nine times and came within one out of winning the World Series.
- The last time the Cubs played in the World Series was 1945 and since then they’ve only finished in the top half of their league or division 13 times.
- Forty-three men have managed the Chicago Cubs since they last played in the World Series and 58 different managers since their last World Series win.

And the Answer Is.....

- All are sad, but true

Breast Density and Breast Cancer

- Increased Breast Density associated with increased risk of getting breast cancer
- Newer models used to predict risk of breast cancer taking breast density into consideration:
  - Breast Cancer Surveillance Consortium
    - 5 and 10 yr. risk calculations based on Age, Race/ethnicity, FH of breast ca in a first-degree relative, history of prior breast biopsy with results, breast density
Dense Breast Notification Legislation

- Reporting law that mandates written notification to women after screening mammography regarding their tissue density and the need to discuss screening options with their primary care MD.
- Breast density notification laws are in effect in 26 states.
- 50% of women have either heterogeneously or extremely dense breast tissue on screening mammography.
- Used to allow individualized risk-based approach for guiding decision-making.

Dense Breast Notification Legislation

- Problems – women are asking about what this means and PCP’s and ob/gyn’s should be able to answer questions with evidence-based information that offers guidance but many clinicians don’t know enough.
- Information should be easily available to all clinicians ordering screening mammograms.
- Excellent guidance on breastdensity.info - maybe this should go along with all reports?
- Should the starting conversation begin with radiology?

What about genetic profiling for risk stratification?

- Personal DNA analysis that provides insight into a person’s potential for developing certain diseases like cancer.
- Several US companies exist that offer this with costs typical of $2000.
- Thought that these tests might provide reassurance or enable people to take preventative action.
- Problems - The test results can be unreliable and difficult to interpret, may lead to further unnecessary testing, personal distress, ethical issues.
- But this is the Future – will allow for better utilization of resources, more tailored care.

Breast Screening – What about the patient perspective?

- Most women likely overestimate their risk.
- Many questions regarding screening mammograms and frequency.
- Most women feel reassured by getting mammograms.
- Many questions regarding what breast density means.
- More questions about new technologies as information hits the press/internet - clinicians should know the evidence to discuss.
Prevention of Breast Cancer: Clinical Issues

- When should we consider?
  - Drugs: Tamoxifen, Raloxifene, Aromatase Inhibitors
  - Preventative Surgeries: Prophylactic mastectomies, oophorectomies

Tamoxifen for Breast Cancer Prevention

- Complex drug with estrogen and anti-estrogen properties
- Approved by FDA in 1998 for breast cancer prevention in high risk pre and PMP women
- 2013 US Preventive Services Task Force (USPSTF) meta-analysis of 4 trials showed 30% reduction in risk of primarily hormone positive breast cancer in tamoxifen users vs. placebo (RR 0.70, 95% CI 0.59-0.82)
- Meta-analysis also found significant reduction in the incidence of non-vertebral fractures (three cases in 1000 women, RR 0.66, 95% CI 0.45-0.98)
- Treatment trials have shown a greater benefit for 10 yrs. vs 5 yrs. of use but no data in prevention setting so recommendation to take for 5 years

Raloxifene for Breast Cancer Prevention

- In the same class of drugs as Tamoxifen
  - Raloxifene - FDA approved 2007 for prevention of breast cancer in PMP women
  - 2013 US Preventive Services Task Force (USPSTF) meta-analysis of 4 trials showed 10% reduction in risk of hormone positive breast cancer in raloxifene users vs. placebo (nine cases in 1000 women, RR 0.44, 95% CI 0.27-0.71)
  - A reduction in the incidence of vertebral fractures (seven cases in 1000 women, RR 0.61, 95% CI 1.41-2.64).
  - No increased incidence of endometrial cancer
  - No difference in breast cancer-specific or all-cause mortality

Consider based on risk-
- ASCO and USPSTF have guidelines
  - High risk based on family history: particularly first degree relatives diagnosed pre-menopausal or multiple family members
  - age > 35
  - Risk Prediction Models like Gail, BCSC: > 1.7% 5 yr. risk
  - Concern for hereditary breast ovarian cancer syndrome
  - A history of lobular carcinoma in situ (LCIS) or prior biopsies showing atypical change
Tamoxifen and Raloxifene - overall data

- Overall in 7 fair/good quality studies, tamoxifen and raloxifene reduced incidence of invasive breast cancer by 7 to 9 cases in 1000 women over 5 years compared with placebo-
in 1 study tamoxifen slightly more effective than raloxifene
- Neither tamoxifen or raloxifene trials showed difference in breast cancer-specific or all cause mortality
- Fewer thromboembolic events, cataracts, and endometrial cancer with raloxifene

Aromatase Inhibitors in the Prevention Setting

- Tamoxifen competes with estrogen at receptor binding site in the breast preventing receptor activation
- Aromatase Inhibitors prevent conversion of male hormones into estrogens and decrease peripheral circulating estrogen
- Third generation AI’s used:
  - Anastrozole (Arimidex)
  - Letrozole (Femara)
  - Exemestane (Aromasin)

Aromatase Inhibitors in the Prevention Setting

- International Breast cancer Intervention Study (IBIS-II), looked at 4000 PMP women at high risk of breast cancer and randomly assigned them to treatment with anastrozole vs. placebo for 5 yrs. Found 50% percent reduction in the number of invasive breast cancers or DCIS with AI vs. placebo [HR] 0.47, 95% CI 0.32-0.68
- American Society of Clinical Oncology (ASCO) added this to updated guidelines in 2013 for prevention of hormone positive breast cancer in PMP women
- Not yet FDA approved in the prevention setting

Preventative Surgeries for Reducing Risk of Breast Cancer

- Risk Reducing Mastectomies (RRM)
  - Removes most, but not all of breast tissue
- Skin Sparing procedures
  - Recently developed procedure
  - Removes more breast tissue than subcutaneous mastectomy
  - Usually combined with immediate reconstruction
  - Provides good cosmetic result
Do Preventative Surgeries Prevent Breast Cancer?

- Significantly reduces risk of breast cancer and death
- In premenopausal women, prophylactic mastectomies decreases the risk of hormone receptor positive breast cancer by 90+%
- For women having prophylactic oophorectomy before age 40, there is an approximate 50% reduction in breast cancer risk
- Recommendation to consider in BRCA or other gene mutation carriers that carry significant increased lifetime risks for breast cancer

Who Sleeps the Most in a Day?

- Dogs
- Cats
- Monkeys
- First year medical students

And the Answer Is.....

- Cats - average 16 hours of sleep a day, more than any other mammal.
Clinical Concerns

Is breast imaging needed after bilateral mastectomies? NO

- If complete mastectomy no need for imaging
- If skin sparing, nipple sparing procedure, some centers may still recommend screening mammography
- MRI can be helpful to establish the presence of residual breast tissue after bilateral mastectomy, and routine screening not recommended if no residual breast tissue is seen
- With saline or silicone implants or autologous reconstruction procedures imaging typically not recommended

Should mammograms still be done if women get MRI for screening? YES

- Mammograms can pick up calcifications not seen on MRI that could be a sign of cancer
- High risk women should begin MRI screening annually starting at 25 and then alternate annual MRI and mammogram starting at 30

Conclusions

- Hopefully you now will now:
  - Know the risk factors for breast cancer
  - Understand issues surrounding screening from a clinician's perspective
  - Know what drugs are used for prevention
  - Understand the adverse effects of the drugs used for prevention
  - Know what the screening and prevention strategies are for women who are high risk
  - Understand that screening and prevention should be individualized
Thank You!