Breast Cancer Screening and Prevention: A Clinician’s Perspective

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Breast Cancer Epidemiology-Issues pertaining to Screening

- Approximately 12.3% of women will be diagnosed with breast cancer at some point during their lifetime
- 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- Clinical Concerns

- 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

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**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

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**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, but benefits may stop if not maintained
  - ?Vitamin D – conflicting data

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**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
- Women who have 2 - 5 drinks per day have about 1.5 x the risk of developing breast cancer compared to non-drinkers
- 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
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 like 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

Breast Cancer – Risk Factors

• Factors thought to be protective:
  
  – Non-steroidal drugs (ibuprofen) and aspirin – 2 recent studies suggesting protective effect mainly in obese women – likely via anti-inflammatory effects

• Bisphosphonates (ex. Fosomax, Actonel) - previously thought protective but based on observational studies in women with breast cancer on aromatase inhibitor therapy. New randomized controlled trial in women with osteoporosis and no breast cancer showed no reduction in risk or breast cancer

  – Trisha F. Hue, PhD, MPH, Jama online Aug 11, 2014
Clinical Issues pertaining to Screening?

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

General Screening for Breast Cancer

General Screening for Breast Cancer

- Self Breast Exam (SBE)
  - American Cancer Society and ACOG recommend teaching breast self exams
  - Many other organizations (USPSTF) do not recommend women doing SBE
  - Not great evidence that it helps
    - Few RCT, largest Cochrane review from 2003 showed no benefit in breast ca mortality and more biopsies done for benign disease
    - 2 case control studies showed less advanced disease if women taught appropriate SBE

Mammogram Screening for Breast Cancer – Controversies

- Screening mammogram clearly detects early stage breast cancer

- Controversies are whether it improves breast cancer mortality (over diagnosis)
  - 2009 review showed decreased mortality in all age groups
  - 2012 review of RCT showed decreased mortality but based on older trials where less effective treatments
  - Most international trials have shown reduced mortality
  - American Cancer Society reviewing literature and expected to make new recommendations

- Clinical Breast Exam (CBE)
  - American Cancer Society and most US organizations recommend CBE every 3 years from age 20 to 39, annually thereafter
  - US Preventive Task force and WHO says not enough evidence to support regular 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
Mammogram Screening for Breast Cancer – What Should Clinicians do?

- ACS, ACOG and many other organizations recommend mammograms every 1-2 years beginning at age 40
- USPSTF and other organizations state that in low risk women, screening should begin at age 50
- WHO recommends every 2 years for women 50-69
- 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

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

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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 mammogram)

Recommendations for Breast MRI for Screening

- American Cancer Society Recommendations for annual MRI 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 when they were between the ages of 10 and 30 years
  - 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

Breast Screening - no standard guidelines for clinicians

- Individual variation regarding recommendations for self breast exam
- Clinical breast exams typically done as part of well woman exam
- Baseline mammograms 40-50 depending on risks
- Frequency of mammography in 40’s varies greatly
- Yearly or biannually varies greatly
- More clinicians ordering screening MRI for high risk women

Breast Screening with Newer Technologies

Need for data and subsequent guidelines

- High field strength MRI
- Breast Tomosynthesis
- Breast MRI
- Whole Breast Ultrasound
- Thermography
- Computer aided detection (CAD)
- Contrast-enhanced dual energy digital mammography
- Magnetic resonance spectroscopy
Breast Screening - 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 as an adjunct to mammography
- Thought to decrease recall rates by delineating true lesions from superimposition

Breast Screening - Tomosynthesis “3D” Mammography

- Studies to date comparing digital mammogram alone vs digital mammogram plus breast tomosynthesis found improved positive predictive value for cancer, lower recall rates
- Thought to be useful for dense breasts and high risk women

Breast Screening - Tomosynthesis “3D” Mammography

- Older techniques had twice the radiation exposure
- Newer techniques create a 2-D image from the 3-D tomo images, lowering radiation dose to slightly above standard mammogram - upgrading to this technique is costly so most facilities don’t have and issues related to insurance reimbursement
- No prospective data looking at patient outcomes yet

Breast Screening – 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
### Breast Screening – Whole Breast Ultrasound

- 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
- 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

### Thermography – What to do when patients ask about this

- 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

### Thermography – What to do when patients ask about this

- No major organization makes screening recommendations for thermography
- FDA issued a safety communication in June 2011 saying thermography is not a replacement for screening mammography and on its own is not an effective screening tool - difficult when abnormal thermogram and normal mammogram

### California Dense Breast Notification Legislation

- Reporting law took effect in April 2013, mandates written notification to women after screening mammography, regarding their tissue density and the need to discuss screening options with their primary care physicians
- About 50 % of women who undergo screening mammography are classified as having either heterogeneously or extremely dense breast tissue
- Individualized risk-based approach for guiding decision-making
California 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?

Clinical Issues Surrounding Screening with Newer Technologies

- Most clinicians don’t necessarily know about newer imaging modalities.

- Quick questionnaire to faculty in gynecology division:
  1. Do you know what breast tomosynthesis is?
  2. Do you know when you might order breast tomo?
  3. Do you know when to order breast MRI for screening?
  4. Have you ever heard of the California Dense Breast Notification Legislation? Do you know what it is?

Clinical Issues Surrounding Screening with Newer Technologies

- Questionnaire results:
  - Only 1 faculty member had heard of breast tomosynthesis.
  - No one knew when you would order breast tomo.
  - 50% knew when to get screening breast MRI.
  - Most had heard of dense breast legislation.
  - Comments were would be helpful to get guidelines.

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 from patients regarding mammograms and frequency
- Many questions regarding what should be done based on breast density
- Most women still believe in mammogram screening
- More questions about new technologies as information hits the press/internet

**Prevention of Breast Cancer: Clinical Issues**

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

**Prevention of Breast Cancer: Clinical Issues**

- Consider based on risk
  - High risk based on family history: particularly first degree relatives diagnosed pre-menopausal or multiple family members
  - Models like Gail Risk to calculate risk
  - Concern for hereditary breast ovarian cancer syndrome
  - Prior biopsies showing atypical change

**How Much Breast and Ovarian Cancer Is Hereditary?**

- 75% Sporadic
- 10-15% Familial
- 5-10% Hereditary

5-10% of hereditary breast cancer thought due to BRCA
10-15% of hereditary ovarian cancer thought due to BRCA
Other gene mutations make up a small percent of hereditary cancers – p53, PTEN, CHEK2, newer genes
When to think about Hereditary Breast and Ovarian Cancer (HBOC) Syndrome

- If breast cancer is diagnosed before age 50
- If there are 2 or more relatives who've had breast cancer
- If there is a male relative who's had breast cancer
- With bilateral breast cancer or breast cancer twice in the same breast
- With breast cancer and Ashkenazi, or Eastern European Jewish ancestry
- If ovarian cancer at any age

Risks and Recommendations with BRCA Carriers

- Current reported lifetime risk of invasive breast cancer:
  - 57% for BRCA 1 and 49% for BRCA 2 by age 70
- Consensus that increased surveillance should be performed for BRCA carriers 25-30 years of age or older
- Breast surveillance - clinical breast examinations every 6 months, and annual imaging including alternating mammograms and breast MRI
- Chemoprevention with Tamoxifen or Raloxifene
- Consideration for prophylactic bilateral mastectomy

Drugs for Prevention - Tamoxifen

- Complex drug with estrogen and anti-estrogen properties
- Originally made as contraceptive then found to suppress mammary tumors in rats
- By 1992 shown to increase disease free interval and decrease contralateral breast cancer in pre and postmenopausal women

Tamoxifen for Breast Cancer Prevention

- Breast Cancer Prevention Trial showed 5 years of Tamoxifen in high risk women reduced risk of hormone receptor positive breast cancer by 45%
- Approved by FDA in 1998 for breast cancer prevention
- 2013 US Preventive Services Task Force (USPSTF) meta-analysis of 4 trials showed 30% reduction in risk of primarily hormone positive breast ca in tamoxifen users vs. placebo (RR 0.70, 95% CI 0.59-0.82)
Tamoxifen for Breast Cancer Prevention

- Currently recommended for use in pre and postmenopausal women at higher risk for breast cancer

- Non-cancer benefits: In USPSTF meta-analysis found significant reduction in the incidence of non-vertebral fractures (three cases in 1000 women, RR 0.66, 95% CI 0.45-0.98)

Tamoxifen – Why Don’t More Women Use for Prevention?

- Fear of side effects and uterine cancer

- Reports of hot flashes, vaginal discharge, vaginal dryness, weight gain

- Older reports suggested up to 60% of women experience negative side effects and 20-40% discontinuation rate

- 2 studies looking at QOL in placebo controlled prevention trials showed tamoxifen use was not associated with any significant differences compared to placebo in depression, anxiety, major psychosocial outcomes, or overall QOL

Tamoxifen – Adverse Events

- 2-3 fold increased rate of blood clots (deep vein thrombosis and pulmonary embolus) particularly in first two years

- In studies, non-significant increased risks for stroke - most recommendations are to discontinue tamoxifen for few days before surgery or long travel

Tamoxifen - Biologic Effects

- Agonist and Antagonist effects

- Effects of vary depending on hormonal environment

- Acts differently in pre vs. postmenopausal women
**Tamoxifen and Premenopausal Women**

- Induces estrogen production and ovulation - has been used for ovulation induction for IVF
- Reports of ovarian cysts in upwards of 30% women
- Menstrual irregularities
- Growth of endometrial polyps, fibroids, endometriomas
- Not thought to increase the risk of endometrial cancer

**Tamoxifen and Postmenopausal Women**

- Increased endometrial proliferation, cystic changes, polyp formation, adenocarcinoma and uterine sarcoma
- The reported risks of endometrial cancer in Tamoxifen users have ranged from 1.3-7.5 in RCT, and increase with longer use
- Meta-analysis of 32 RCT trials showed RR 2.7, primarily in women > 50

**Tamoxifen and Endometrial Cancer**

- Absolute risks - about 4 cases of endometrial cancer per 1000 women taking Tamoxifen each year
- 95% of Endometrial Cancers present with Vaginal Bleeding
- Risks are thought to decrease as soon as tamoxifen is stopped
- Most women get a much greater benefit to their breast than risk to their uterus

**Should women on tamoxifen have ultrasounds to evaluate endometrial thickness?**

- Increased endometrial thickness, irregular echoes, cystic changes ("Swiss-cheese appearance"), polyps and hyperplasia
- Findings do not correlate with malignant histology
- Tamoxifen causes enlargement of subendometrial glands so the endometrial thickness tends to be overestimated
- No prospective data on what is normal endometrial thickness for women on tamoxifen
What are the problems with routine surveillance?

- Absence of a defined endometrial thickness cut-off for the tamoxifen patients reduces ultrasound accuracy and increases the number of patients referred for unnecessary biopsies and surgeries like hysteroscopy.
- Overtreatment with unnecessary surgeries.

Raloxifene for Prevention

- Also a SERM, in the same class of drugs as Tamoxifen.
- Raloxifene - FDA approved for treatment of osteoporosis since 1997.
- In the trials that led to the FDA approval for bone loss found lower incidence of hormone positive breast cancers which led to the design of the STAR prevention trial.

Ultrasound of Patient on Tamoxifen

Tamoxifen vs. Raloxifene for Breast Cancer Prevention – STAR Trial

- STAR trial: 5 years, one of largest breast cancer prevention studies, took place at 500 centers in US, Canada, and Puerto Rico.
- Tamoxifen reduced risk of invasive breast cancer and DCIS by 50%.
- Final data: Raloxifene 75% as effective as Tamoxifen in preventing invasive breast cancer and had significantly fewer endometrial cancers, significantly fewer blood clots.
- Raloxifene was 78% as effective as Tamoxifen in preventing DCIS.
**SERMS - Tamoxifen and Raloxifene for prevention**

- 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.

- Neither tamoxifen or raloxifene trials showed difference in breast cancer-specific or all cause mortality.

**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)

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**Aromatase Inhibitors in the Prevention Setting**

- Clinical trial showed 70% reduction in ER-positive invasive breast cancer with exemestane compared to placebo over a 3-year period.

- 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.

**Clinical Concerns: Aromatase Inhibitors Adverse Effects**

- Arthralgia, myalgia, and bone loss.

- Increased cardiovascular risks with aromatase inhibitors, but no difference in MI, or MI related death.

- Increase risks of fracture in aromatase inhibitors during treatment studies but not seen after completion of treatment.

- Marked vaginal dryness, painful sex and decreased libido.
Clinical Concerns: Aromatase Inhibitors Beneficial Effects

• Fewer strokes in treatment studies but did not persist after treatment
• Lower thromboembolic events (blood clots) with AI
• Fewer endometrial cancers - Aromatase Inhibitors may PREVENT endometrial cancer

Breast Cancer Drugs for Prevention – Clinical Recommendations

• Clinicians should review family and personal history and assess risk for breast cancer
• Consider Tamoxifen in high risk premenopausal women
• Consider Raloxifene in high risk postmenopausal women
• If postmenopausal and contraindications for SERM consider AI
• Side effects and risks should be discussed
• Should not get routine ultrasounds for women on Tamoxifen

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
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

Conclusions

- Hopefully you now will now:
  - Know the risk factors for breast cancer
  - Understand issues surrounding screening from a clinicians 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!