High Risk or High Reward: Breast Cancer Prevention and Screening in Primary Care:
New Challenges and Opportunities

Section 1 Jamie Stern, MD, MPH: Mammography in the 40s and 50s: the Data and the Controversy

Case: A 43 year old woman wants to discuss breast cancer screening. She is asymptomatic with respect to her breasts. She had menarche at age 13, gave birth to her first child at age 29, is of normal body weight and drinks wine “socially”. She has no FH of breast or ovarian cancer. She has never had a mammogram before, but has heard from her friends that they are “very painful”. What would you recommend?

1) Which statement is true regarding this patient?
   A. USPSTF guidelines recommend routine screening in her age group
   B. The NNS to prevent death in 40-49 year olds is 1904
   C. It is rare for women in their 40’s to have a false positive mammography
   D. Biopsies rarely occur as a result of false positive mammography

2) If our patient opts to have a mammogram at age 43 (her current age), she should be screened again:
   A. in 5 years
   B. in 1-2 years
   C. At age 50
   D. At age 60

Section 2 Jennifer Corbelli, MD: Routine Screening: Considerations Outside the Controversy

1) A 38 year old woman with no significant PMHx or FHx presents to your office and asks if she should be doing self-breast exams (SBE). You advise her:

   A. Most guidelines continue to recommend that women be instructed to perform a structured monthly self-breast exam
   B. Some guidelines now recommend against instructing women to perform the SBE
   C. Although the SBE has not been shown to decrease breast cancer mortality, these studies were observational, and therefore it is unclear if the findings are valid

2) A 51 year old premenopausal woman presents for her first mammogram. She requests a digital mammogram because she read in a magazine that it is superior to traditional (film) mammography. How would you counsel her about the difference between these options?

   A. Breast cancer detection rates are overall superior with digital mammography vs. film
   B. Digital mammography has no indications for screening mammography but can be a useful modality for diagnostic mammography
   C. Digital mammography is more sensitive than film in pre- and peri-menopausal women
3) A 45 woman undergoes screening mammography. Her mammogram report reads: “No evidence of malignancy. Breasts are heterogeneously very dense.” How should this finding impact your plan for screening?

A. This finding has no impact on her cancer risk and therefore does not impact her screening
B. This finding has no impact on her cancer risk, but it means film mammography will be less sensitive. Digital mammography is the test of choice for screening
C. She is at increased cancer risk, and per guidelines should be screened more aggressively than women without dense breasts
D. She is at increased cancer risk but no guidelines state that she should be screened differently than women without dense breasts

Section 3  Rachel Bonnema, MD, MS: Identification of High-Risk Women

1) A 43 year old Caucasian patient who has not been seen since her last child was born presents for a “check-up” because both her mother and sister were diagnosed with breast cancer in the last 2 years. You determine her Gail score to be 2.7%. You tell her this is:

A. Lower than average risk
B. Average risk
C. Higher than average risk

2) You discuss with this patient that the best management at this point is:

A. Continuing with usual screening patterns as she is average risk for breast cancer.
B. Referral for genetic counseling for further delineation of risks, including possible genetic evaluation, as she is high risk for breast cancer.
C. Referral to a breast surgeon for evaluation of possible mastectomy as she is high risk for breast cancer.
D. Managing her increased risks for breast cancer, but no need for genetic evaluation as it will not add further information to her already known high risk for breast cancer.
Section 4 Annie Im, MD: Breast Cancer Primary Prevention

For the following patients, choose one of the following options for prevention:

A. Tamoxifen
B. Raloxifene
C. Neither
D. Either tamoxifen or raloxifene

Patient #1:

- 42 year old Caucasian female, mother with breast cancer age 50, personal history of breast biopsy with atypical hyperplasia, Gail 5-year risk score = 4.6%

Patient #2:

- 66 year old female, sister with breast cancer age 60, Gail 5-year risk score = 3.3%, personal history of DVT 2 years ago

Patient #3:

- 64 year old female, Gail 5-year risk 1.8%, history of osteoporosis, no history of thrombotic events or other comordities

Patient #4:

- 47 year old female, premenopausal, paternal grandmother and 2 paternal aunts with breast cancer, Gail 5-year risk 1%
Case: 37 yo female presents to your office for a routine visit. Her PMH is significant for NHL s/p chemo and mediastinal radiation at age 22, currently in remission. She is nulliparous, menarche at age 11 and underwent early menopause due to primary gonadal failure. FHX is significant for a paternal aunt with breast CA at age 35, paternal GM with “belly cancer” deceased at age 40, and a maternal aunt with breast CA at age 60.

1. Which factors make this woman high risk for developing breast CA?
   - ☐ History of mediastinal radiation
   - ☐ History of early menarche
   - ☐ History of nulliparity
   - ☐ Early menopause
   - ☐ Family history of paternal aunt with breast CA age 35
   - ☐ Family history of paternal GM with “belly cancer” deceased age 40
   - ☐ Family history of maternal aunt with breast CA age 60

2. Should she be tested for BRCA?
   A. Yes
   B. No

3. How should our patient be screened for breast cancer?
   A. Yearly mammography
   B. Yearly MRI
   C. Yearly mammography + MRI
   D. Alternating mammography and MRI q6m

4. When should screening start in this patient?
   A. Should have started at age 25
   B. Should have started at age 30
   C. Should have started at age 35
   D. Start at age 40
High-Risk or High-Reward? Breast Cancer Prevention and Screening in Primary Care: New Challenges and Opportunities

Rachel Bonnema, MD, MS
Jennifer Corbelli, MD
Annie Im, MD
Jamie Stern, MD MPH
Sarah Tilstra, MD
Workshop Format

• Introductions and Brainstorm (10 minutes)

• 5 Content Subsections (15 minutes each)
  – 5 Minutes Questions/Answers in Small Groups
  – 10 Minutes Content

• Discussion (10 minutes)
Workshop Objectives: By the end of this workshop, participants will be able to

- Counsel patients on risks and benefits of:
  - Starting breast cancer screening at age 40 vs. 50
  - Continuing screening after age 70
  - Chemoprevention

- Recognize:
  - Indications for genetic counseling
  - Implications of breast density on cancer risk
  - Patients at high risk for breast cancer
  - Indications for breast MRI

- Incorporate Gail model into clinical practice
Brainstorm

What challenges do you face when deciding how and when to screen your patients for breast cancer?

What do you see as the barriers to using breast cancer preventive therapy?
Mammography in the 40s and 50s:
The Data and the Controversy

Jamie Stern, MD, MPH
University of Pittsburgh Medical Center
Case

• A 43 year old woman wants to discuss breast cancer screening. She is asymptomatic with respect to her breasts. She had menarche at age 13, gave birth to her first child at age 29, is of normal body weight and drinks wine “socially”. She has no FH of breast or ovarian cancer. She has never had a mammogram before, but has heard from her friends that they are “very painful”. What would you recommend?
Question #1

Which statement is true regarding this patient?:

A. USPSTF guidelines recommend routine screening in her age group
B. The NNS to prevent death in 40-49 year olds is 1904
C. It is rare for women in their 40’s to have a false positive mammography
D. Biopsies rarely occur as a result of false positive mammography
Question #2

If our patient opts to have a mammogram at age 43 (her current age), she should be screened again:

A. in 5 years
B. in 1-2 years
C. at age 50
D. At age 60
2009 USPSTF Mammography Guidelines

• Age 40-49 – recommends against routine screening (C), net benefit is small, **NNS to prevent death 1904**

• Age 50-74 – recommends biennial screening (B), net benefit is moderate, **NNS to prevent death is 1339 for women in their 50’s and 377 for women in their 60’s**

• Age >75 – insufficient evidence (I), net benefit unknown, **NNS unknown**

USPSTF guidelines

• 2 major changes in guidelines from 2002-2009
  – Reclassification of screening women in their 40’s from a B to a C recommendation
  – Frequency of screening of women changed from 1-2 years to every 2 years

Other Organizations

- The American Cancer Society, American College of Radiology, AMA, NCI, ACOG, National Comprehensive Cancer Network, American Academy of Family Physicians all recommend starting routine screening at 40
- ACP and the Canadian Task Force on the Periodic Health Examination recommend starting routine screening at 50

Warner, Ellen. Breast-cancer screening. NEJM 365;1025-32
Harms of Screening

• Unnecessary imaging tests and biopsies
• Breast discomfort
• Radiation exposure
• Inconvenience
• Overdiagnosis-harms associated with treatment of cancer that would not become clinically apparent during a women’s lifetime
• Harms of unnecessary earlier treatment of breast cancer that would have become clinically apparent, but would not have shortened a women’s life
Overdiagnosis

• Recent study in the Annals of Internal Medicine estimated the percentage of overdiagnosis of breast cancer attributable to screening mammography in 50-69 year old women in Norway
• Results show that the estimated rate of overdiagnosis was 15-25%, p <0.001
• This translates to 6-10 women overdiagnosed for every 2,500 women invited to screen

Kalager, M, Overdiagnosis of invasive breast cancer due to mammography screening:results from the Norwegian screening program. Ann int med 2012;156:491-99
Data: Women 50-69

• Screening for women in this age group is universally recommended
• A USPSTF meta-analysis (2009) showed significant reductions in the number of deaths due to breast cancer in this age group
  – 14% for women in their 50’s
  – 32% for women in their 60’s
• The greater reduction in the older age group is due to
  – Increased sensitivity of mammography with age
  – Decreased breast density
  – Slower tumor growth

Data: Women 40-49

- No single RCT has clearly shown a reduction in mortality from mammography in this age group
- Several meta-analyses have shown a 15-20% reduction in breast cancer mortality, though
- USPSTF conducted its own meta-analysis published in 2002 which showed that mammography decreased death from breast cancer with a RR 0.85, 95% CI 0.79-0.99
- Therefore, the USPSTF previously recommended routine screening mammography in this age group (2002 recommendations)

Data: Women 40-49 Age Trial

- Randomized trial that assessed the effects of screening among 161,000 women aged 39-41, mean follow-up was 10.7 years
- Those assigned to annual mammography had a nonsignificant decreased risk of death from breast cancer RR 0.83, 95% CI 0.66-1.04. RR of death from any cause was 0.97, 95% CI 0.89-1.04, NNS to prevent one death from breast cancer was 2512

Moss SM. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years’ follow-up: a randomised controlled trial. Lancet 2006;368:2053-60.
Data: Women 40-49

• An updated USPSTF meta-analysis (2009) which included results from the Age Trial provided results similar to the first meta-analysis. RR of death from breast cancer 0.85, 95% CI 0.75-0.96, NNS 1904

• The USPSTF guideline included the following statement, “The USPSTF recommends against routine screening mammography in women aged 40-49 years”

Data: Women 40-49

- The decision to change the USPSTF recommendations was based on:
  - Negative results of the Age Trial (the only trial that specifically focused on women in their 40’s)
  - Lower breast cancer risk
  - Lower mammographic sensitivity (greater breast density)
  - Higher rate of false positives

Frequency of Screenings

- Another controversial change from the 2002 USPSTF guidelines was a switch from 1-2 year screening to 2 year screening.
- Supporting this change was the observation that there was little difference in the likelihood of detecting advanced breast cancer with annual versus biennial screening.

Frequency of Screening

• In statistical models, screening of women 50-69 every 2 years maintained 81% of the benefit associated with annual screening and decreased the number of false positive results by almost half.

• As compared with screening every 2 years, annual screening prevented about 2 additional deaths from breast cancer per 1000 women screened.

The Bottom Line

• Age 40-49
  – Shared decision making
  – Still recommend mammography if the patient is willing
  – Would recommend screening every 1-2 years due to rapid tumor growth in young women

• Age 50-69
  – Strongly recommend mammography
  – Based on my review of the literature, I have changed my recommendation from yearly to biennial
Routine Screening: Considerations Outside the Controversy

Jennifer Corbelli, MD
University of Pittsburgh Medical Center
Question #1

A 38 year old woman with no significant PMHx or FHx presents to your office and asks if she should be doing self-breast exams (SBE). You advise her:

A. Most guidelines continue to recommend that women be instructed to perform a structured monthly self-breast exam
B. Some guidelines now recommend against instructing women to perform the SBE
C. Although the SBE has not been shown to decrease breast cancer mortality, these studies were observational, and therefore it is unclear if the findings are valid
A 51 year old premenopausal woman presents for her first mammogram. She requests a digital mammogram because she read in a magazine that it is superior to traditional (film) mammography. How would you counsel her about the difference between these options?

A. Breast cancer detection rates are overall superior with digital mammography vs. film
B. Digital mammography has no indications for screening mammography but can be a useful modality for diagnostic mammography
C. Digital mammography is more sensitive than film in pre- and peri-menopausal women
A 45 woman undergoes screening mammography. Her mammogram report reads: “No evidence of malignancy. Breasts are heterogeneously dense (>75%).” How should this finding impact your plan for screening?

A. This finding has no impact on her cancer risk and therefore does not impact her screening

B. This finding has no impact on her cancer risk, but it means film mammography will be less sensitive. Digital mammography is the test of choice for screening.

C. She is at increased cancer risk, & per guidelines should be screened more aggressively than women without dense breasts

D. She is at increased cancer risk but no guidelines state that she should be screened differently than women w/o dense breasts
Clinical Breast Exam (CBE): Guidelines

- USPSTF: Insufficient evidence to assess additional benefits of CBE beyond screening mammography (Nelson Annals 2009)

- ACOG: CBE yearly after age 40 (Smith Cancer Journal 2010)

Clinical Breast Exam

• Sensitivity 54%, Specificity 94%
• Limitations in data:
  – No trials compare CBE alone to no screening (unethical)
  – Studies did not specify/standardize exam techniques
• Bottom Line for CBE:
  – Unable to quantify CBE benefit in addition to mammogram
  – Most studies show independent contribution of CBE to cancer detection (offset by harms?)
• UPMC algorithm:
  – Housestaff need to learn (normal vs. abnormal)
  – Generally done every 1-2 years

Barton JAMA 1999
Key Points, *JAMA* Rational Clinical Exam

- The vertical strip method ("lawnmower") is more thorough than the circular method

- Nipple should NOT be squeezed
  - Spontaneous discharge associated with increased cancer risk
  - Expressed discharge is not

- Increased time per breast increases sensitivity
  - Recommended 3 min/breast (average size, i.e. B cup)
  - Based on expert consensus
  - Average clinician spends 1.8 minutes for both breasts
Self-Breast Exam (SBE)

- USPSTF: Recommends *against* advising regular SBE
- ACOG: Encourage breast self-awareness, which may include SBE
- ACS: SBE an option for women starting age 20, emphasis on breast awareness
- 2 large RCTs (11 year follow up) showed no mortality benefit to monthly SBE
- Associated with higher biopsy rates for benign findings
- Bottom Line: Breast awareness should be emphasized over a structured, monthly SBE

Thomas *JNCI* 2002
Semiglazov *Vopr Onkol* 1999
Hackshaw *BJCa* 2003
Digital vs. Film Mammography

- Film is traditional method, many centers have now moved to all digital
- Digital: increased contrast between tumor & breast

- Digital mammography (DMIST trial):
  - 50,000 asymptomatic women ≥ 40, screened with digital and film
  - Overall no significant difference in sensitivity
  - Digital significantly more sensitive than film if:
    - Pre- and peri- menopausal
    - Dense breasts
    - Age <50
  - No difference in specificity (both 92%)

Pisano *Radiology* 2008
## Digital vs. Film Mammography

<table>
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<tr>
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<th>Total Sensitivity</th>
<th>Sensitivity: Women &lt;50, premenopause, dense breasts</th>
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<tbody>
<tr>
<td>Digital</td>
<td>70%</td>
<td>78%</td>
</tr>
<tr>
<td>Film</td>
<td>66%</td>
<td>51%</td>
</tr>
</tbody>
</table>

  - Women being screened in their 40s
  - Women of any age with dense breasts
  - Premenopausal women >50

Pisano *Radiology* 2008
Warner, NEJM 2011
Breast Density

• Dense breast tissue (mammographic, not Pex finding) increases cancer risk (not included in Gail)

• Nested case-control ➔ vs <10% density:  (Boyd NEJM 2007)
  – 10-25% density = RR 1.8
  – >75% density = RR 4.7
  – Increased risk both for cancers detected both by mammogram and within 12 months of negative test
  – Attributable risk of >50% density:
    • 16% all breast cancers
    • 40% found within 12 mos. of negative mammogram

• No recommendations for different screening
Breast Density and Screening

• Two *Annals* papers (May 2012)
  – Modeling study: women in 40s with cancer risk 2x average have harm to benefit ratio comparable to women 50-74
  – Meta-analysis, 2x inc breast cancer risk with either:
    • Extremely dense breasts (>50%)
    • One first degree relative with breast cancer

• Conclusion (?): Women with dense breasts should start mammography at age 40
  • But won’t know until first mammogram
Stopping Mammograms

- USPSTF: Insufficient evidence to recommend for or against screening after 75
- ACS: continue mammograms “while in good health”
- ACOG: “consider life expectancy” in patients >75

Issues:
- Data limited
- Shorter life expectancy decreases benefit of screening
- Not all women want to know/treat
- Cost: Benefit Ratio (as always)
Data: Stopping Mammograms

• Only one RCT
  – Swedish study, included women up to 75
  – RR of death from Br CA: 1.12, 95% CI 0.73-1.72
  – No NNS calculated (total # deaths not reported)

• National Cancer Institute: 2 additional cancer deaths prevented per 1000 women screened ages 70-74

• Expert opinion: screening may be indicated if estimated >10 years life expectancy (if patient would desire and be candidate for treatment)

Nystrom *Lancet* 2002
Nelson *Annals* 2009
Take-Home Points

• Benefit of clinical breast exam remains unclear (sensitivity 54%): use vertical-strip method if you do it

• Advise breast self-awareness rather than monthly SBE

• Generally opt for digital over film mammogram in women <50, with dense breasts, and/or pre- or peri-menopausal

• Breast density increases cancer risk, independently of decreased mammography sensitivity

• Hot off the press: Women <50 with dense breasts should potentially begin mammography starting at age 40 (but you won’t know until you screen)
Identification of High-Risk Women

Rachel Bonnema, MD, MS
University of Nebraska Medical Center
A 43 year old Caucasian patient who has not been seen since her last child was born presents for a “check-up” because both her mother and sister were diagnosed with breast cancer in the last 2 years. You determine her Gail score to be 2.7%. You tell her this is:

A. Lower than average risk
B. Average risk
C. Higher than average risk
You discuss with this patient that the best management at this point is:

A. Continuing with usual screening patterns as she is average risk for breast cancer.
B. Referral for genetic counseling for further delineation of risks, including possible genetic evaluation, as she is high risk for breast cancer.
C. Referral to a breast surgeon for evaluation of possible mastectomy as she is high risk for breast cancer.
D. Managing her increased risks for breast cancer, but no need for genetic evaluation as it will not add further information to her already known high risk for breast cancer.
Importance of Appropriate Risk Assessment

• Appropriately managing women with BRCA1/2 mutations decrease breast cancer incidence by 80-95%

• Adherence to recommendations for genetic testing and counseling for high risk women is low
  – 41% in recent vignette-based survey
  – Average-risk women often mislabeled as high risk
  – Important barrier is lack of knowledge in genetic risk and risk reduction skills

Quantitative Risk Assessment

The Gail Model:

• Projects the absolute risk of invasive breast cancer over five years for women >35 years

• Factors included in calculating risk:
  • Age
  • Age at menarche
  • Number of first-degree female relatives with breast cancer
  • Number of previous breast biopsies
  • Age at first live birth (or nulliparity)
  • Race
  • Personal history of atypical hyperplasia

Gail Model

• We recommend using the computer program available at: http://www.cancer.gov/bcrisktool

  – Most commonly used breast cancer prediction tool

Risk Calculator

(Click a question number for a brief explanation, or read all explanations.)

1. Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)?
   Select

2. What is the woman's age?  
   This tool only calculates risk for women 35 years of age or older.
   Select

3. What was the woman's age at the time of her first menstrual period?
   Select

4. What was the woman's age at the time of her first live birth of a child?
   Select

5. How many of the woman's first-degree relatives - mother, sisters, daughters - have had breast cancer?
   Select

6. Has the woman ever had a breast biopsy?
   Select

   6a. How many breast biopsies (positive or negative) has the woman had?
   Select

   6b. Has the woman had at least one breast biopsy with atypical hyperplasia?
   Select

7. What is the woman's race/ethnicity?
   Select

Calculate Risk >
Gail Model

• An increased risk of developing breast cancer is defined as a Gail Score of 1.66% or greater
Gail Model

Is the Gail Model valid?
• Breast Cancer Prevention Trial
• Nurses Health Study

In the above studies, the Gail Model’s expected number of breast cancer cases closely approximated the actual number of breast cancer cases

• Has been validated in white, African American, Asian and Pacific Islander women

Gail Model

Shortcomings of the Gail Model:

• Does not incorporate family history outside of first degree relatives or presence in paternal lineage
  – BRCAPRO model, CLAUS model
  – PAT (Pedigree Assessment Tool)

• Does not account for young age of breast cancer onset

• Does not incorporate estrogen use, alcohol use

• Does not account for breast density

• Does not account for risks due to previous thoracic radiation

• Not valid in women under age 35
Gail Score

• Not static throughout patient’s life
• Should be reassessed periodically
  – No recommendations on interval

• Our practice → calculate Gail score:
  – Anyone > age 35 with any FHx of breast cancer
  – Anytime a patient’s family member is newly diagnosed with breast cancer
  – New diagnosis of atypical hyperplasia, DCIS, LCIS
  – In general: ~age 50 if not done prior, repeat ~q 5 years especially if prior 5-year risk close to 1.66% (depending on comorbidities, life expectancy, etc)
Other Risks

• Genetic disorder
  – Li-Fraumeni, Cowden, Bannayan-Riley-Ruvalcada Syndromes
• Previous thoracic radiation treatment
• Dense breasts
Hereditary Breast Cancer

• A positive family history is reported in up to 20% of women with breast cancer

• Only 5-6% of all breast cancers are associated with an inherited mutation

• Two major susceptibility genes for breast cancer are BRCA1 and BRCA2
  – General population prevalence 0.1-0.25%
  – Ashkenazi Jewish prevalence 2.5%

Tung N. JAMA, 2011.
BRCA1 and BRCA2

- BRCA genes encode for proteins which function to repair breaks in double stranded DNA
- Mutations in these genes account for the majority of inherited breast cancers
- Mutations are inherited in an autosomal dominant fashion
- Lifetime estimate of breast cancer in BRCA ½ is 36-90%

Referring for Genetic Counseling

Indications for referral:

• Known BRCA ½ mutation in family
• ≥2 breast cancers from same side of family
• Breast + ovarian cancer from same side of family
• ≥1 ovarian cancer from same side of family

• Breast cancer occurring before age 50
• Male relatives with breast cancer
• Ashkenazi Jewish heritage and a family history of breast or ovarian cancer

NCCN Guidelines, Version 1.2011
Referral for Genetic Counseling

- Genetic Counselor may or may not say patient is appropriate for genetic testing
- Does not change Gail score or risk of developing breast cancer
  - Patient may not be tested, still remain high risk
  - Patient tested and negative for BRCA, still remains high risk
Breast Cancer Primary Prevention

Annie Im, MD
Hematology/Oncology Fellow
University of Pittsburgh Cancer Institute
High risk or High reward?

For the following patients, choose one of the following options for prevention:

A) Tamoxifen
B) Raloxifene
C) Neither
D) Either tamoxifen or raloxifene
Patient #1

• 42 year old Caucasian female, mother with breast cancer age 50, personal history of breast biopsy with atypical hyperplasia, Gail 5-year risk score = 4.6%

A) Tamoxifen  
B) Raloxifene  
C) Neither  
D) Either tamoxifen or raloxifene
Patient #2

• 66 year old female, sister with breast cancer age 60, Gail 5-year risk score = 3.3%, personal history of DVT 2 years ago

A) Tamoxifen
B) Raloxifene
C) Neither
D) Either tamoxifen or raloxifene
Patient #3

- 64 year old female, Gail 5-year risk 1.8%, history of osteoporosis, no history of thrombotic events or comorbidities

A) Tamoxifen
B) Raloxifene
C) Neither
D) Either tamoxifen or raloxifene
Patient #4

• 47 year old female, premenopausal, paternal grandmother and 2 paternal aunts with breast cancer, Gail 5-year risk 1%

A) Tamoxifen
B) Raloxifene
C) Neither
D) Either tamoxifen or raloxifene
Risk Reduction Strategies

• Risk reduction mastectomy*
• Preventive therapy
  – Tamoxifen
  – Raloxifene
  – Aromatase Inhibitors
• Lifestyle modifications
  – Weight loss
  – Exercise
  – Alcohol intake
Tamoxifen

- Selective Estrogen Receptor Modulator (SERM)
- Role in prevention developed after shown to decrease contralateral breast cancer incidence when used as adjuvant hormonal therapy for early stage breast cancer
- Anti-estrogenic properties in breast tissue
- Estrogenic properties in uterus, bone, coagulation
Prevention Guideline #1:
Tamoxifen 20mg daily x 5 years reduces risk of ER-positive breast cancer by 50% for 10 years

Recommended:
- Premenopausal or postmenopausal women age >35 with Gail 5-year breast cancer risk \( \geq 1.7\% \)
- History of LCIS

Contraindicated:
- History of DVT/PE, TIA, or stroke

Not recommended:
- Postmenopausal women with uterus
- History of cataracts
Tamoxifen: Adverse effects

- Increased risk of uterine cancer
- Increased risk of DVT/PE and stroke, especially in postmenopausal women
- Increased risk of cataracts
- Hot flashes, sexual side effects, gynecologic symptoms
Tamoxifen: Tips

• Benefit of 5 years therapy lasts up to 10 years, with decreasing risk of toxicities and side effects
• NNT to prevent 1 cancer over 5 years = 95, over 10 years = 56
• Only chemoprevention option for premenopausal women, and benefit/risk ratio more favorable
Raloxifene

- Second generation SERM, initially studied as an osteoporotic agent
- Anti-estrogenic properties in breast and uterus
- Estrogenic properties in bone and coagulation
Prevention Guideline #2: Raloxifene 60mg daily x 5 years reduces risk of ER-positive breast cancer by 40%

Recommended:
- Postmenopausal women age >35 with Gail 5-year breast cancer risk \( \geq 1.7\% \)
- History of LCIS

Contraindicated:
- History of DVT/PE, TIA, or stroke
Raloxifene: Adverse effects

Compared to tamoxifen:
• Does not increase risk of uterine cancer
• Does not increase risk of cataracts
• Less risk of DVT and PE (30%), but similar risk of stroke
• Hot flashes, musculoskeletal complaints, weight gain
Raloxifene: Tips

- Toxicity profile is better for postmenopausal
- NNT to prevent 1 cancer over 4 years = 96, over 8 years = 52
- Decreases risk of vertebral fractures and increases bone density, and may be used longer for osteoporosis
The Future of Preventive Therapy: Aromatase Inhibitors

• AIs (anastrozole, exemestane, letrozole) block estrogen production in peripheral tissue in postmenopausal women
• Currently used in early stage breast cancer for adjuvant hormonal therapy
• Benefits – no increased risk of thromboembolic events, stroke, uterine malignancies, cataracts
• Risks – no estrogenic effect on bone
• Recent phase III study shows risk reduction of 65% for ER-positive cancers in high risk women...
Prevention Guideline #3: Lifestyle Modifications

Evidence for risk reduction:
• Weight loss and avoiding postmenopausal weight gain
• Exercise
  – >5hrs vigorous exercise or >10 hours brisk walking per week, >10 hours per week, regular strenuous activity
• Alcohol consumption
  – <1 drink/day

Evidence unclear:
• Low fat diet/nutrition – but in general a good thing!
• HRT – recommend to limit long term use
Risk Reduction Strategies

Gail score > 1.7% or LCIS?

Postmenopausal?

N
  History of DVT/PE or stroke?
  N
   Tamoxifen
  Y
   Lifestyle modifications

Y
  History of DVT/PE or stroke?
  N
   Uterus?
   N
    Raloxifene or Tamoxifen
   Y
    Raloxifene
  Y
   Lifestyle modifications
Risk Reduction Strategies

Strong family history

Gail score >1.7%
Indications for genetic screening?
Refer to genetic counseling

Gail score <1.7%
Indications for genetic screening?
Lifestyle modifications
Refer to genetic counseling

Use previous algorithm

YN
Risk/benefit Counseling

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<th>5-Year Projected Risk of IBC (%)</th>
<th>Tamoxifen v Placebo (without uterus)</th>
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</tr>
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<tr>
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<td>27  2  -4</td>
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<td>49  23  18</td>
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<td>57 2  -39</td>
<td>71  45  40</td>
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<tr>
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<td>84 29 -12</td>
<td>92  67  62</td>
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<td>3.5</td>
<td>111 56  15</td>
<td>114 88  82</td>
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<td>270 215 175</td>
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</tr>
<tr>
<td>7.0</td>
<td>297 242 201</td>
<td>262 237 232</td>
</tr>
</tbody>
</table>

- Strong evidence of benefits outweighing risks
- Moderate evidence of benefits outweighing risks
- Benefits do not outweigh risks

5-year projected risk of IBC is ≥ 1.67%.

Using BCPT data and WHI baseline rates

Combining RR from BCPT and STAR using WHI baseline rates
Take Home Message

• Recommendations for prevention strategies should be individualized based on patient’s baseline breast cancer risk, comorbidities, and personal preference

• Preventive therapy is safe and effective, and plays an essential role in the primary care setting
References


Screening for Breast Cancer in High-Risk Women

Sarah Tilstra, MD
University of Pittsburgh Medical Center
Case

37 yo female presents to your office for a routine visit. Her PMH is significant for NHL s/p chemo and mediastinal radiation at age 22, currently in remission. She is nulliparous, menarche at age 11 and underwent early menopause due to primary gonadal failure. FHX is significant for a paternal aunt with breast CA at age 35, paternal GM with “belly cancer” deceased at age 40, and a maternal aunt with breast CA at age 60.
Questions

1. What makes this women at high risk for breast cancer? Will get to this...
2. Should she be tested for BRCA?
   A = Yes, B = No
3. How should she be screened?
   A. Yearly mammography
   B. Yearly MRI
   C. Yearly mammography + MRI
   D. Alternating mammography and MRI q6m
4. At what age should screening start?
   A = 25, B = 30, C = 35, D = 40
“High Risk”

1. BRCA1 or BRCA2 carrier (RR 5-30)
2. BRCA1 or BRCA2 carrier in first-degree relative, unknown patient carrier status
3. Strong family history of breast/ovarian CA (RR 3-4)
   - Mother/sister diagnosed <40
   - 2+ first-degree relatives with breast or ovarian cancers
4. Radiation treatment to chest area ages 10-30 (RR 4-11)
5. Known genetic syndrome predisposing pt to breast CA (Li-Fraumeni, Cowden, Bannayan-Riley-Ruvalcada Syndromes)

Or ... >20% lifetime risk of breast CA

American Cancer Society
ww5.komen.org
Question 1: Which factors make this woman high risk for developing breast CA?

- Hx of mediastinal radiation
- Hx of early menarche
- Hx of nulliparity
- Early menopause
- FHx of paternal aunt with breast CA age 35
- FHx of paternal GM with “belly cancer” deceased age 40
- FHx of maternal aunt with breast CA age 60
“Moderate Risk”

• Lifetime breast CA risk 15-20% according to risk-assessment tools
• Personal hx of breast CA, ductal CA in situ (DCIS), lobular CA in situ (LCIS), atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH)
• Extremely dense breasts
• Unevenly dense breasts on mammography
Question 2: Test for BRCA?

• Yes!
  – Paternal aunt with breast CA at age 35
  – Paternal GM with “belly cancer” deceased age 40
  – Suspicious for BRCA

• Maternal aunt with breast CA at age 60 → not an indication
BRCA1/BRC2A

- If inherited, 50-85% lifetime risk of breast CA
- Harder to detect in families with no female members >45

Who Should *Definitely* Be Tested

- Known BRCA ½ mutation in family
- ≥2 breast cancers from same side of family
- Breast + ovarian cancer from same side of family
- ≥ 1 ovarian cancer from same side of family
- Breast cancer occurring before age 50
- Male relatives with breast cancer
- Ashkenazi Jewish heritage *and* a family history of breast or ovarian cancer

NCCN Guidelines, Version 1.2011
Who Should You Consider for Testing...

Patients with Cancer

- Breast CA <40
- Ovarian CA
- Bilateral breast CA
- Breast CA <50 with close relative breast CA <50
- Breast CA any age with 2+ relatives breast CA

ACOG Routine Screening for Hereditary Breast and Ovarian Cancer, 2009
Who Should You *Consider* for Testing... Patients Without Cancer

- Two first-degree relatives with breast CA, one diagnosed <50
- First-degree relative with bilateral CA or male breast CA
- First/second degree relative with both breast and ovarian CA
- 3+ first/second degree relative with breast CA
- 2+ first/second degree relatives with ovarian CA
Question 3: How Should Our Patient Be Screened?

A. Yearly mammography
B. Yearly MRI
C. Yearly mammography + MRI
D. Alternating mammography and MRI q6m
Screening MRI + Mammography

• Complementary, sensitivity MRI + mammogram > MRI alone
• Q6m vs. yearly → no evidence to support one over the other. All trials obtained imaging at the same time
• Sensitivity in high risk women:
  – 71-100% MRI
  – 16-40% Mammography/Ultrasound
• MRI: more false+, more call-backs, more biopsies (3-15%)

MRI

• Evidence:
  – BRCA mutation, first-degree BRCA carrier, but untested, lifetime risk >20%

• Expert consensus:
  – Chest radiation, genetic syndromes

• Insufficient evidence for/against:
  – Hx CA (mammo occult..), lifetime risk 15-20%, dense breasts, DCIS, LCIS, ALH, ADH

• Against MRI: <15% lifetime risk

Question 4: When Should Screening Start?

A. Should have started at age 25
B. Should have started at age 30
C. Should have started at age 35
D. Start at age 40
When to Start Screening High Risk Women

• BRCA: age 25, yearly MRI + mammography
• Strong family history: 5-10 years before earliest breast CA in the family
• Radiation: 8-10 years after radiation or age 25, whatever comes last
• OR.....
• Age 30

Breast Cancer Survivors

• Caveat: requires a workshop in itself
• SBE: Survivors should perform monthly
• Physical exam (CBE implied but not specified)
  – q3-6 months for first three years
  – q6-12 months years 4-5
  – Annually thereafter
• Mammography:
  – Breast-conserving tx: q6-12 months
  – s/p mastectomy: yearly if stable mammography findings
• MRI: not recommended for routine surveillance
  – No evidence of improved outcomes

2006 ASCO guidelines
Discussion
## Risk/benefit Counseling

### Table 1: 5-Year Projected Risk of IBC

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### Table 2: 5-Year Projected Risk of IBC

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### References:


Top Ten Clinical Pearls for Breast Cancer Screening and Prevention in Primary Care

1. For average risk women aged 40-49, USPSTF recommends against routine screening with mammography (class C). The number needed to screen to prevent 1 death is 1904. Harms include overdiagnosis and false positive mammograms.

2. For average risk women aged 50-74, USPSTF recommends biennial screening with mammography (class B). The number needed to screen to prevent one death is 1339 for women in their 50’s and 377 for women in their 60’s. Patients should be counseled regarding reasons for this controversy, and engaged in shared-decision making when discussing screening.

3. There is no overall difference in sensitivity between digital and film mammography. However, digital mammography is significantly more sensitive (78% vs 51%) than film in women under age 50, who have dense breasts, and who are premenopausal.

4. Women with dense breasts are at an independently increased risk for breast cancer. There are no clear recommendations to guide screening in this population. However, recently published data shows that women in their 40s with extremely dense breasts may have a screening harm:benefit ratio that is comparable to women over 50. These data suggest that these women may benefit from initiating mammography at age 40 more so than age-matched women without dense breasts.


5. Women with a Gail score >1.7% should be considered at increased risk for breast cancer, whether or not they meet criteria for genetic counseling. Although there are no recommendations on when to first calculate the Gail score or how often to repeat it, it should be reassessed periodically throughout a woman’s life.

6. Absolute indications for genetic counseling include:
   - Known BRCA mutation in family
   - ≥2 breast cancers on same side of the family
   - ≥1 ovarian cancers in family
   - Breast cancer <age 50 in close relative
   - Ashkenazi Jewish heritage and a family history of breast or ovarian cancer
   - Male relatives with breast cancer
7. Women who fit into one of more of the following categories should be considered at very high risk for breast cancer:

- Known BRCA carrier
- Mother/sister diagnosed <40
- 2+ first-degree relatives with breast or ovarian cancers
- Known genetic syndrome predisposing to breast cancer
- Radiation treatment to chest area ages 10-30
- >20% average lifetime risk of breast cancer per risk-analysis tools

8. High-risk women should be screened for breast cancer with yearly mammography and MRI. Alternating mammography and MRI every 6 months is also acceptable. Breast cancers survivors are not considered part of this high-risk group, and should not undergo MRI for routine surveillance.

9. Recommendations for breast cancer prevention strategies should be individualized based on a patient's baseline breast cancer risk, comorbidities, and personal preference.

10. Preventive therapy is safe and effective, and counseling of the benefits and risks plays an essential role in the primary care setting. It should be considered in all women with a 5-year risk of invasive breast cancer >1.7% based on the Gail score, and in women with LCIS.

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