

COUNSELING WOMEN ABOUT SCREENING MAMMOGRAMS

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Learning Objectives

- Describe current epidemiology of breast cancer and screening methods for early detection
- Describe rationale behind current recommendations for breast cancer screening
- Assess individual breast cancer risk in patients in order to:
 - Effectively counsel a patient about her risk for breast cancer to achieve shared decision making about breast cancer screening and
 - Identify women at increased risk of breast cancer who would benefit from modified screening and other interventions.

Case History

A.S. is a 44 year old pre-menopausal g3 p3 with no breast complaints who comes in to discuss breast cancer screening.

She read on the internet that women who are under 50 should see their doctor before getting a mammogram.

Her friend told her that “You don’t need a mammogram until you’re 50.”

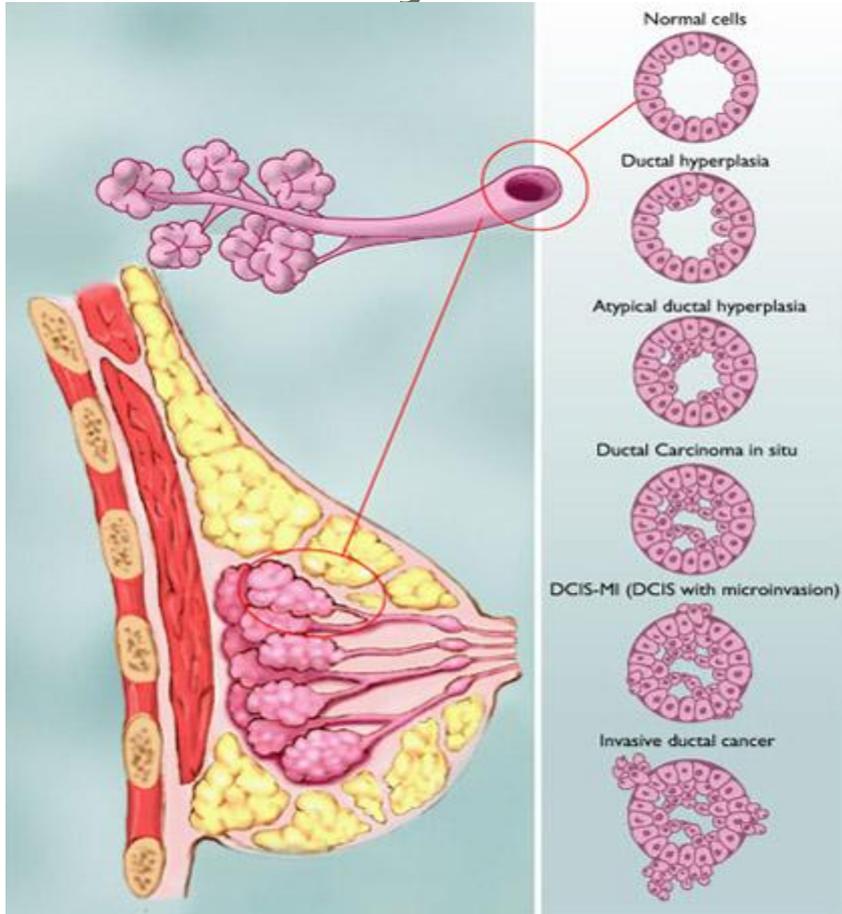
Her period began at age 13, her first child was born age 21, her BMI is 31, she does not smoke or drink alcohol and gets less than 2 hours of exercise per week. She has a typical diet and eats fast food twice per week. Her paternal grandmother had breast cancer, onset age 64, and no other family history of cancer, but her mother has diabetes.

Questions

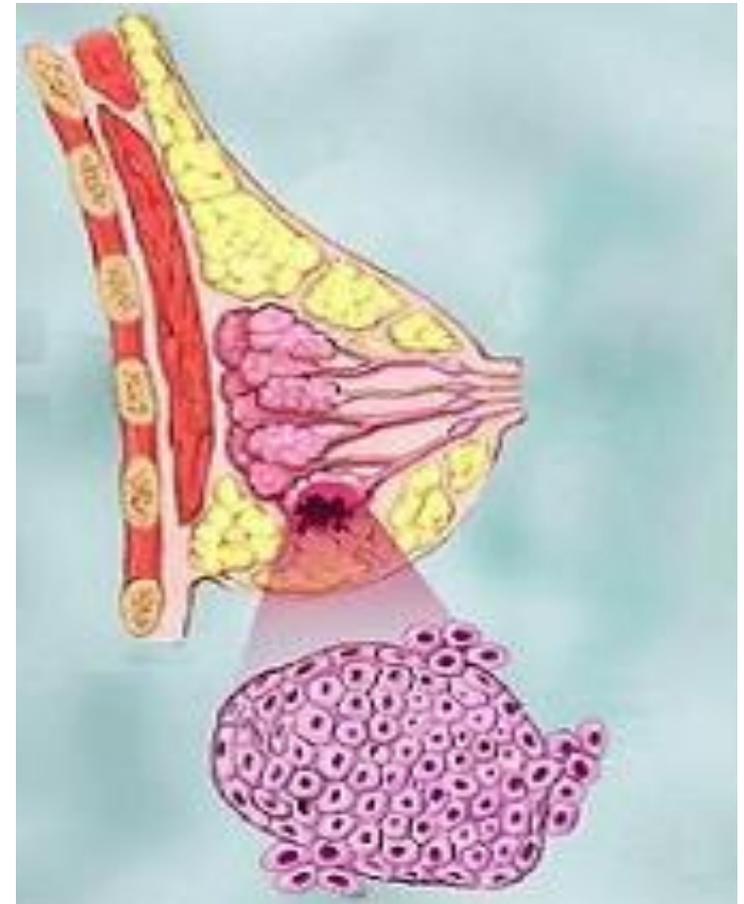
- What is the breast cancer screening recommendation for this woman?
- What risks and benefits will breast cancer screening give her?
- What is her individual risk for breast cancer?
- How can you best help her decide when to start getting breast cancer screening?

CURRENT EPIDEMIOLOGY OF BREAST CANCER AND SCREENING METHODS

Anatomy: Ductal vs. Lobular Cancer



Invasive Ductal and DCIS are both considered breast cancer



Invasive Lobular is considered breast cancer, but LCIS is not.

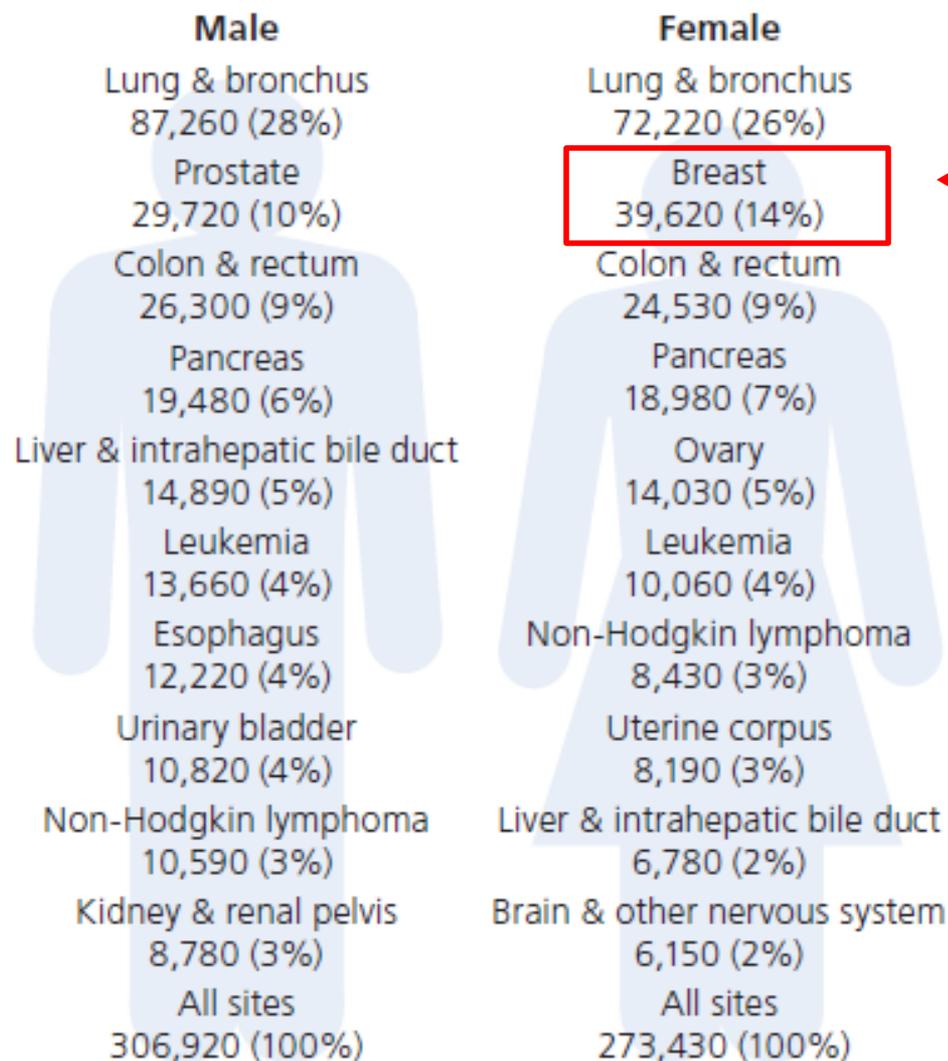
Breast Cancer risk, incidence, prevalence*

- 12.2% of women born today will be diagnosed with breast cancer, based on 2008-2010 rates, or 1 in 8.
- 123/100'000 women diagnosed and 22 women/100'000 women died from breast cancer in 2010.
- 2,829,041 women living with breast cancer in 2010.

Howlander N, et al. *SEER Cancer Statistics Review, 1975-2010*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, 2013.

2013 CANCER MORTALITY

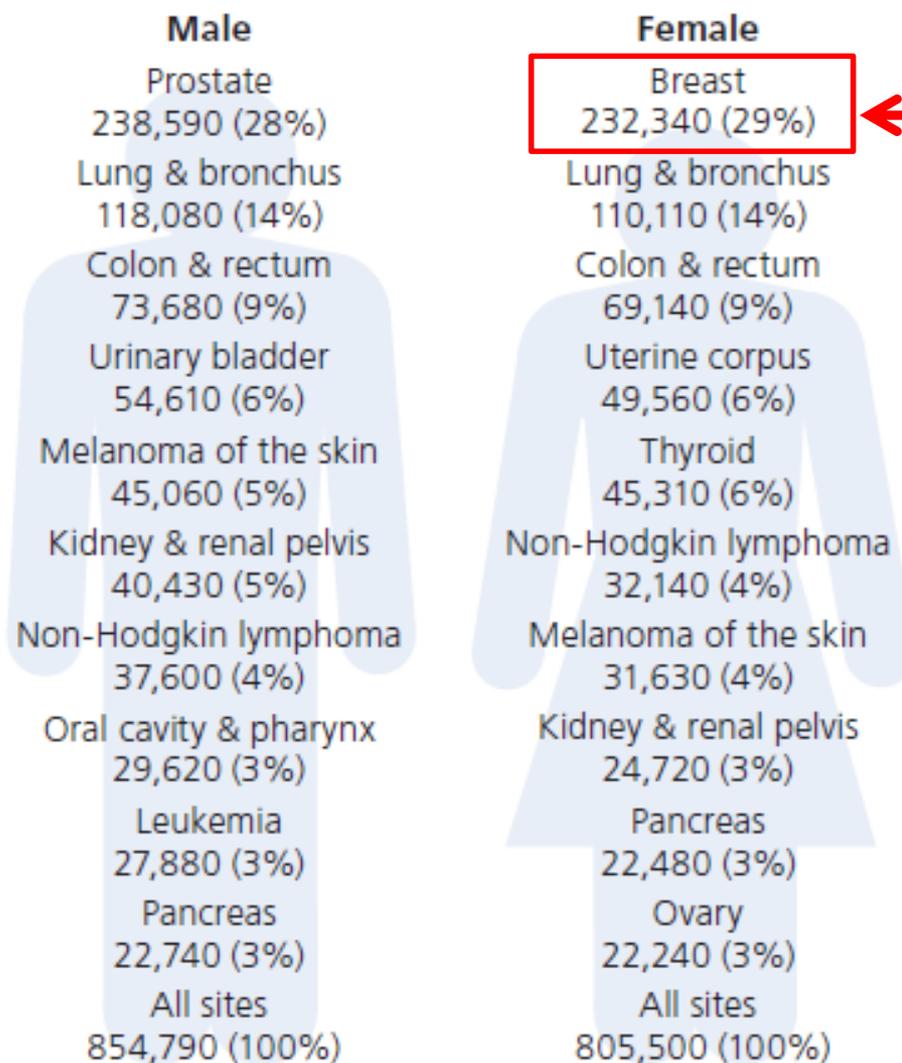
Estimated Deaths



Breast cancer is 2nd leading cause of cancer death in US women

2013 CANCER INCIDENCE

Estimated New Cases*

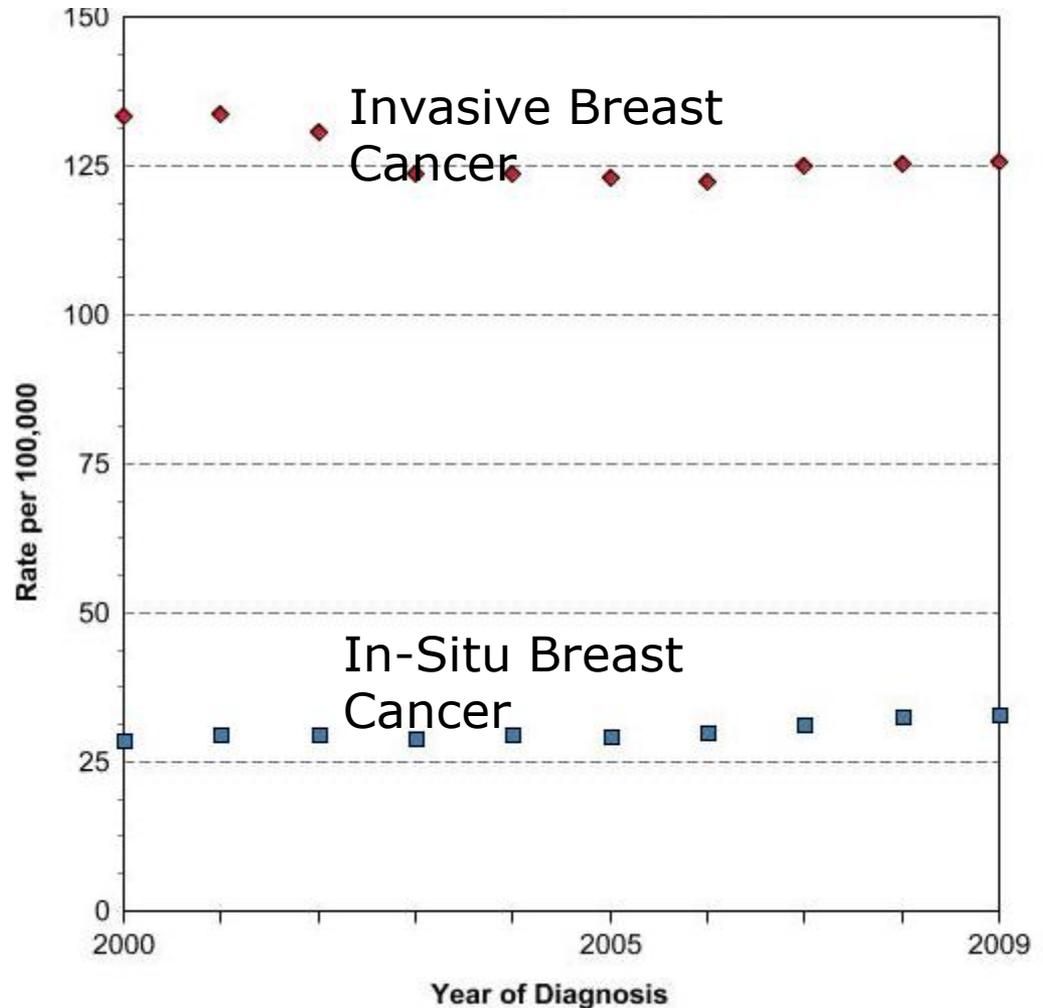


Breast cancer is leading cause of cancer in US women

American Cancer Society
2013

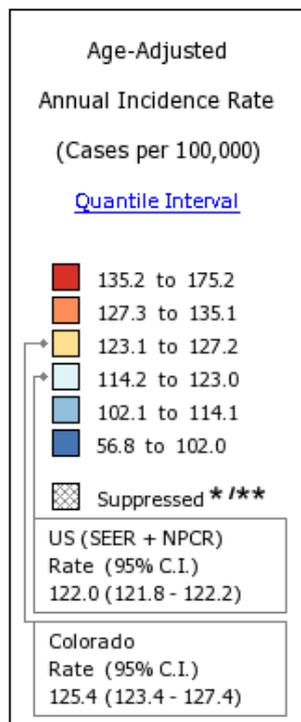
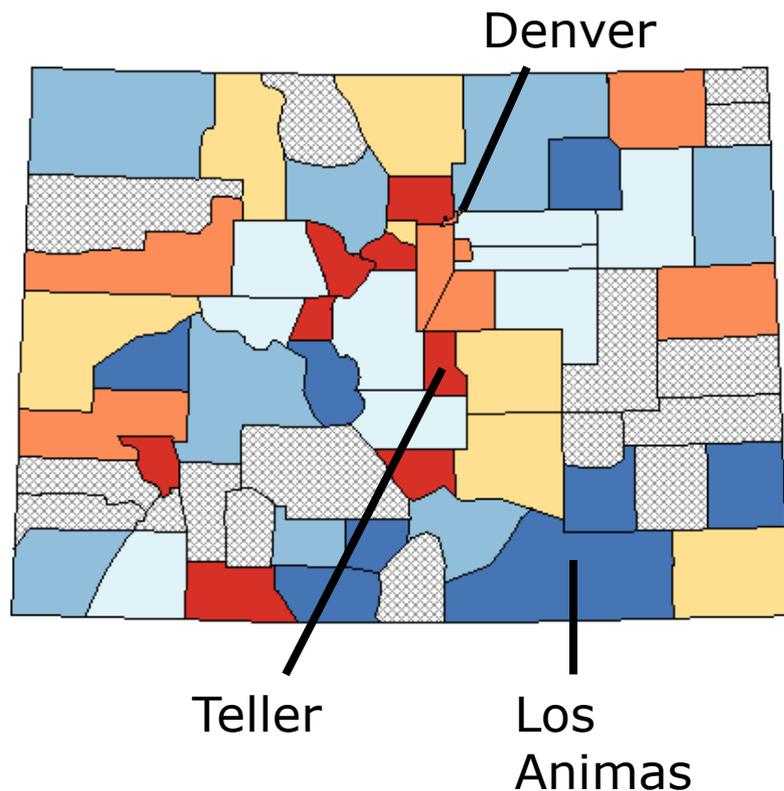
2000-2009 SEER Incidence

- In US, incidence of invasive breast cancer, level at 125 per 100,000
- Incidence of In-Situ Breast Cancer, slight increase trend, from 28 to 33 per 100,000.



US vs. Colorado Incidence

Incidence Rates[†] for Colorado, 2005 - 2009
Breast
All Races (includes Hispanic), Female, All Ages



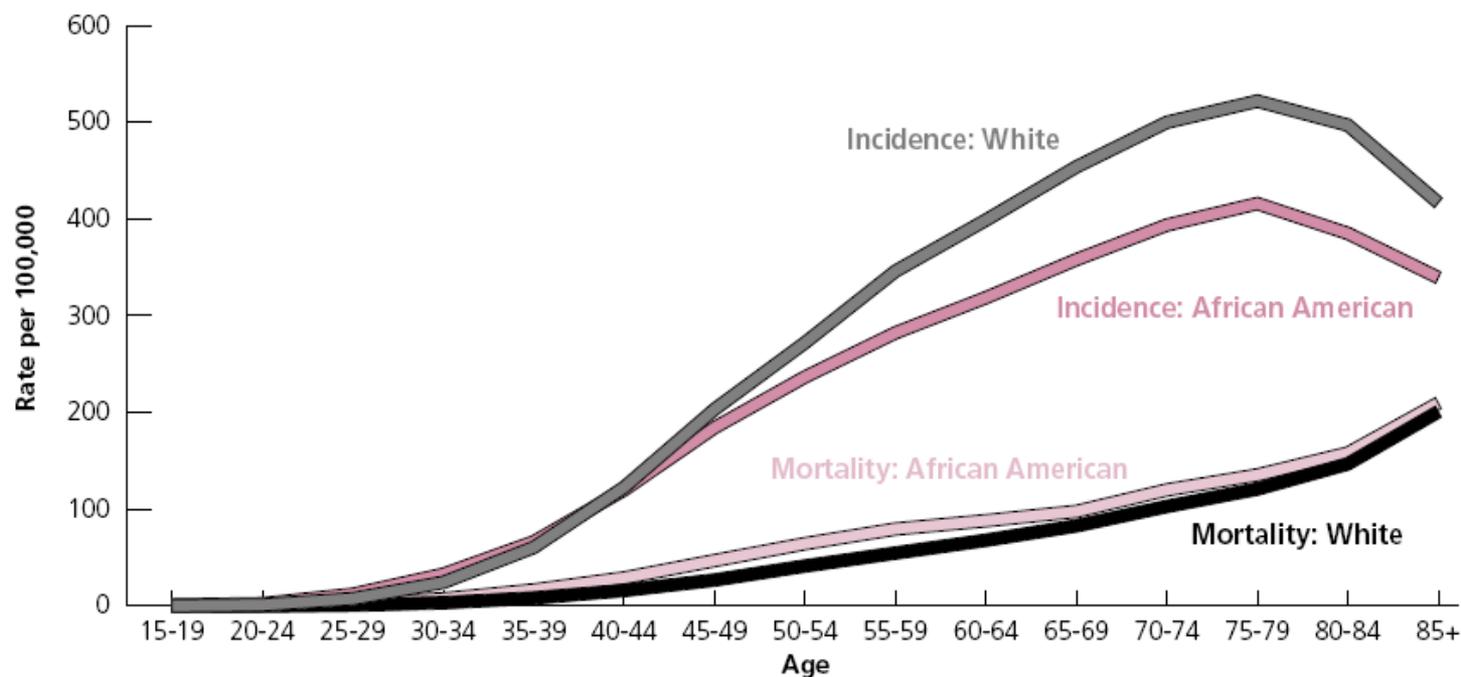
From '05-'09
Per 100,000

Colorado: 125.4
 US: 122.0

Colorado Counties
 Lowest: Los Animas
 56.8
 Highest: Teller 175
 Denver: 131.2

Breast cancer by age and race

Figure 1. Female Breast Cancer – Age-Specific Incidence and Death Rates, by Race, United States, 1996-2000



Data sources: *Incidence* – Surveillance, Epidemiology, and End Results Program, 1973-2000, Division of Cancer Control and Population Science, National Cancer Institute, 2003. *Deaths* – National Center for Health Statistics, Centers for Disease Control and Prevention, 2003.

American Cancer Society, Surveillance Research, 2003

Invasive breast cancer

Incidence

- 60/100'000 women in 1940
- 90/100'000 women in 1980
- 123/100'000 women in 2009

Causes: obesity, longer life expectancy, ?.

Mortality:

- 33/100'000 in 1940-1990
- 21.5/100'000 in 2005

Causes: widespread screening in 1980, better knowledge and treatment for invasive breast cancer.

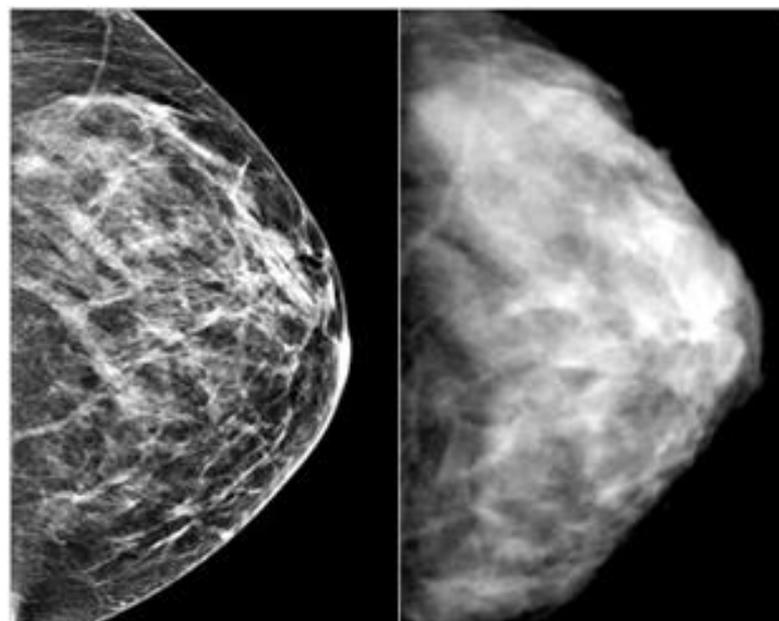
Screening methods

Screening mammography

- Cranio-caudal and medio-lateral-oblique view
- Compress breast tissue to reduce overlying tissue distortion, reduce radiation exposure, decrease movement.
- 15-20 pounds of pressure.
- Breasts become fattier/more radiolucent with age:
Women <40 – density reduces sensitivity of mammography and disease less prevalent.

Mammography

- Digital mammography FDA approved in 2000
- By 2006, only 8% of mammography units in US were digital ¹



Digital

Film

Changes in Diagnostic Imaging

- Digital Mammography Imaging Screening Trial (DMIST)
 - 33 US/ Canadian centers
 - 49, 528 women with both film and digital imaging
 - Results: Digital mammography was statistically significantly better for pre- or peri-menopausal women < 50 y.o. with dense breasts

¹ Pisano ED, NEJM 2005: 353; 1773-83

² Pisano ED, Radiology 2008: 246(2); 376-383.

Mammography

- Specificity: 94-97% (3-6% false positive)
 - 18% of women receiving mammograms yearly for 10 years receive a biopsy
- Sensitivity:
 - 77-95% of cancers diagnosed in next year
 - 56-86% of cancers diagnosed in subsequent two years
 - Less in younger women, women with dense breasts, and women on HRT

Screening Mammography

- PPV: increases with age and risks:
 - 40-49: 2-4%
 - 50-59: 5-9%
 - 60 +: 7-19%
 - +FH: 5-12%

MRI Accepted Uses

- Screening (in addition to mammography) in women with a lifetime risk of breast cancer greater than 20%, including carriers of BRCA1/2. Rating: B recommendation*
 - Evaluate breast implant integrity
 - Evaluation of known breast cancer
 - Screen contralateral breast
 - Response to neoadjuvant chemotherapy
 - Post-lumpectomy change
 - Evaluate for recurrent cancer
 - Troubleshooting when mammo/US and PE cannot accurately determine extent of disease (e.g. dense breast tissue).

**Ann Intern Med* 2005 Sep 6;143(5):355-61.

MRI screening

- Sensitivity 95-100%
- Specificity 30-70%
- Patient gets an IV
- Exam takes 45 minutes

Automated whole breast ultrasound (AWBU)

- Can detect 2 to 7 cases of breast cancer/1000 women screened with dense breasts

Screening Imaging Summary

- ▶ Digital Mammography is now standard
- ▶ Breast MRI (in addition to mammography) is widely accepted for...
 - high risk women (>20% lifetime risk)
- ▶ AWBU being offered to women with dense breasts to improve sensitivity of screening mammography but evidence not strong
- ▶ Clinical Breast exam does not add benefit to mammography (average risk women)
- ▶ Self-breast exam not recommended

RECOMMENDATIONS FOR SCREENING

Rationale behind USPSTF guidelines

USPSTF Guidelines:

Summary of Recommendations

- **The USPSTF recommends biennial screening mammography for women aged 50 to 74 years.**
Grade: B recommendation.
- **The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms.**
Grade: C recommendation.

USPSTF Guidelines (cont).

- **The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of screening mammography in women 75 years or older.**
Grade: I Statement.
- **The USPSTF recommends against teaching breast self-examination (BSE).**
Grade: D recommendation.
- **The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of clinical breast examination (CBE) beyond screening mammography in women 40 years or older.**
Grade: I Statement.

Controversy: Screening Recommendations for ages 40-49

▶ Ages 40-49, annually:

- American College of Radiology
- American Cancer Society
- American College of Surgeons and Surgical Oncologists
- American College of Obstetrics and Gynecology (as of 2011)

▶ Ages 40-49: only with PCP discussion of risks/benefits

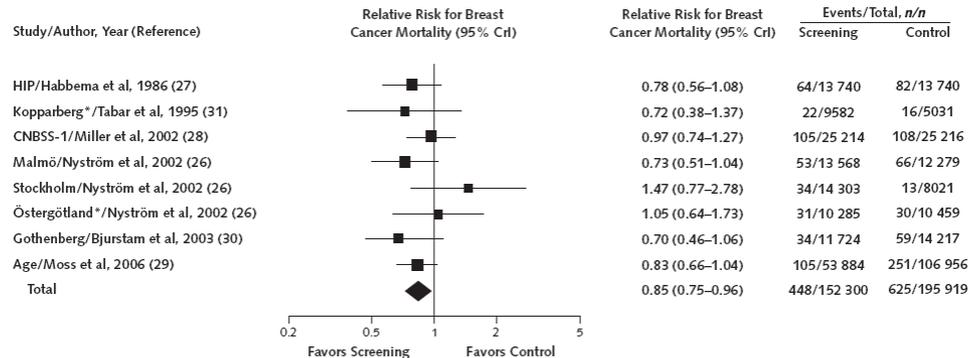
- USPSTF 2009
- AAFP: “The AAFP *recommends* that the decision to conduct screening mammography before age 50 should be individualized and take into account patient context including her risks as well as her values regarding specific benefits and harms.”

Update on summary of the evidence: November, 2009

- Key questions regarding:
 - Population for screening
 - Outcomes and harm associated with screening
 - Optimal screening interval

Key Question: Does screening mammography reduce breast cancer mortality in women aged 39-49:

Figure. Pooled relative risk for breast cancer mortality from mammography screening trials compared with control for women aged 39 to 49 years.



CNBSS-1 = Canadian National Breast Screening Study-1; CrI = credible interval; HIP = Health Insurance Plan of Greater New York.
* Swedish Two-County trial.

not reveal serious heterogeneity among the studies (16). Results are consistent with the 2002 meta-analysis (RR, 0.85 [CrI, 0.73 to 0.99]; 7 trials) (2, 3).

Sensitivity analysis excluded the HIP trial (27) because it was conducted more than 30 years ago and used outdated technology and the CNBSS-1 trial (28) because it

(28) resulted in a lower RR (0.81 [CrI, 0.68 to 0.95]). For women aged 60 to 69 years, 2 trials (Malmö [26] and Swedish Two-County [Östergötland] [26]) provided a pooled RR of 0.68 (CrI, 0.54 to 0.87) for breast cancer mortality for women randomly assigned to mammography screening. The number needed to invite was 377 (CrI, 230

Nelson, H et al. Screening for Breast Cancer: An Update for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151:727-737.

Key Question: Harms Associated with Breast Cancer Screening

- Radiation exposure:
 - Most x-rays are considered low-dose, low-energy radiation, with the mean glandular dose of bilateral, 2-view mammography averaging 4 -7 mGy. (equivalent of eating 40 bananas). (High dose exposure: 300-43000 mGy RR 1.33-11.39).
 - Women aged 40 to 49 years, yearly mammography screening for 1 decade with potential additional imaging would expose an individual to approximately 60 mGy.
 - High levels of radiation exposure (4000 mGy to 40'000 mGy) in childhood/early adulthood associated with increased risk for breast cancer.*

Exposure is low-dose. Inconsistent association with increased risk for breast cancer.

**Henderson, TO et al. Systemic Review: Surveillance for Breast Cancer in Women treated with chest radiation for childhood adolescent or young adult cancer. Ann Intern Med. 2010 Apr 6;152(7):444-55; W144-54.*

Key Question:Harms and Outcomes Associated with Screening

- Pain associated with mammography screening (does not affect screening behavior)
- Anxiety and distress: False-positive mammography results had no consistent effect on most women's general anxiety and depression but increased breast cancer-specific distress, anxiety, apprehension, and **perceived breast cancer risk** for some.
- Overdiagnosis: Best estimate 0.07 to 0.073/1000 women screened.

False positive and negative results and additional procedures

False-positive mammography results are common in all age groups but are most common among women aged 40 to 49 years (97.8 per 1000 women per screening round).

False-negative mammography results occur least among women aged 40 to 49 years (1.0 per 1000 women per screening round).

Rates of additional imaging are highest among women aged 40 to 49 years (84.3 per 1000 women per screening round) and decrease with age, whereas biopsy rates are lowest among women aged 40 to 49 years (9.3 per 1000 women per screening round) and increase with age.

For every case of invasive breast cancer detected by mammography screening in women aged 40 to 49 years, 556 women have mammography, 47 have additional imaging, and 5 have biopsies.

Summary

Mammography screening reduces breast cancer mortality by 15% for women aged 39 to 49 years (relative risk, 0.85 [95% CI, 0.75 to 0.96]; 8 trials).

Data are lacking for women aged 75 years or older.

Radiation exposure from mammography is low.

Patient adverse experiences are common and transient and do not affect screening practices.

Overdiagnosis ranges from 0.7-1%.

Younger women have more false-positive mammography results and additional imaging, but less biopsies than older groups.

Nelson, H et al. Screening for Breast Cancer: An Update for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151:727-737.

Clinical Breast Exam

- No clear additional benefit to doing clinical breast exam with mammography compared to clinical breast exam alone

Self Breast Exam

- Relative risk of all cause mortality in women doing self-breast exam diagnosed with breast cancer: 1.07 (CI 0.88 to 1.29)

USPSTF Guidelines: Genetic Testing

- **The USPSTF recommends against** routine referral for genetic counseling or routine breast cancer susceptibility gene (BRCA) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*).

Grade: D Recommendation.

- **The USPSTF recommends that** women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for BRCA testing.

Grade: B Recommendation

Recommendations from the United States Preventive Services Task Force on who should be offered genetic testing for BRCA mutations

- A family history of breast or ovarian cancer that includes a relative with a known deleterious BRCA mutation

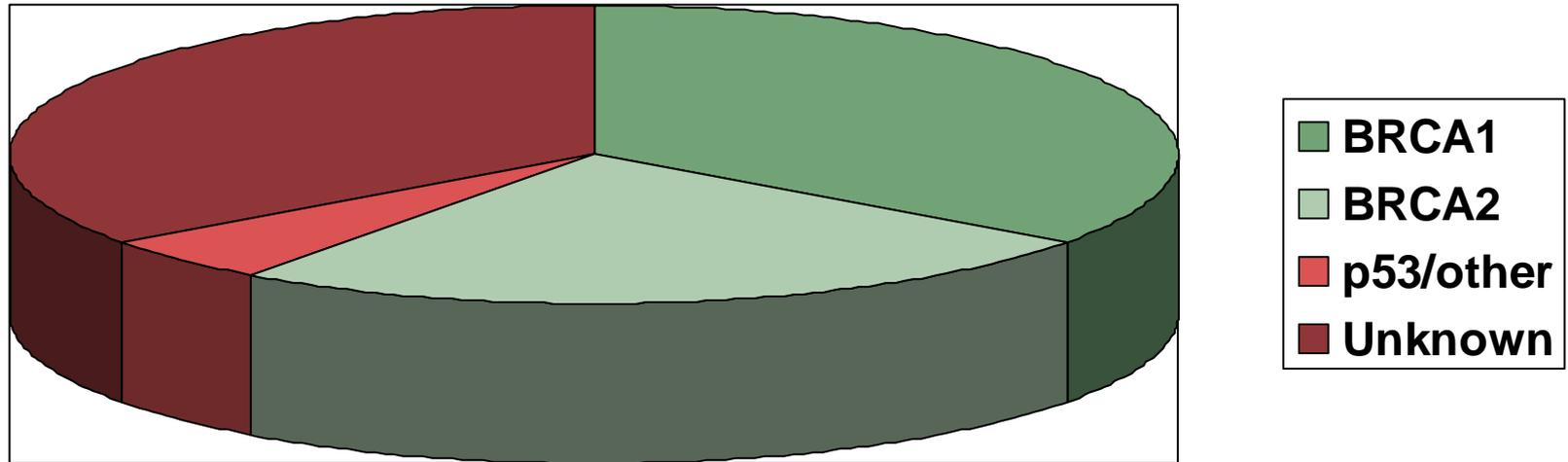
For non-Ashkenazi Jewish women:

- Two first-degree relatives with breast cancer, one of whom was diagnosed at age 50 or younger
- A combination of three or more first or second-degree relatives with breast cancer regardless of age at diagnosis
- A combination of both breast and ovarian cancer among first and second-degree relatives
- A first-degree relative with bilateral breast cancer
- A combination of two or more first or second degree relatives with ovarian cancer, regardless of age at diagnosis
- A first or second-degree relative with both breast and ovarian cancer at any age
- History of breast cancer in a male relative

For women of Ashkenazi Jewish descent:

- Any first-degree relative (or two second degree relatives on the same side of the family) with breast or ovarian cancer

Genetic Mutations Causing Breast Cancer



Key Clinical Question: Screening interval for screening mammography

- Evaluate U.S. Breast Cancer Screening Strategies (6 mathematical models using common data elements)

<http://www.uspreventiveservicestaskforce.org/uspstf09/breastcancer/brcanart.htm>

Interval for screening mammography

Table 2. Percentage of Reduction in Breast Cancer Mortality Maintained When Moving From an Annual Screening Interval to a Biennial Interval, by Screening Strategy and Model

| Model* | Maintained Reduction In Breast Cancer Mortality, by Screening Strategy, %† | | | | | | | | | |
|--------|--|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | Ages 50–69 y | Ages 40–69 y | Ages 45–69 y | Ages 40–79 y | Ages 40–84 y | Ages 55–69 y | Ages 60–69 y | Ages 50–74 y | Ages 50–79 y | Ages 50–84 y |
| D | 76 | 75 | 78 | 79 | 82 | 83 | 79 | 81 | 78 | 83 |
| E | 75 | 73 | 74 | 75 | 75 | 75 | 73 | 76 | 75 | 76 |
| G | 85 | 86 | 91 | 87 | 88 | 91 | 86 | 89 | 88 | 89 |
| M | 90 | 96 | 97 | 97 | 99 | 92 | 84 | 95 | 93 | 95 |
| S | 74 | 73 | 78 | 76 | 77 | 80 | 74 | 79 | 85 | 79 |
| W | 68 | 67 | 70 | 70 | 71 | 71 | 70 | 72 | 70 | 73 |

* Model group abbreviations: D = Dana-Farber Cancer Institute; E = Erasmus Medical Center; G = Georgetown University; M = M.D. Anderson Cancer Center; S = Stanford University; W = University of Wisconsin/Harvard.

† Differences in the range of results reflect differences in modeling approaches. For example, the benefit of screening in model M is modeled through stage shift, as with most other models, but also includes a “beyond stage shift” factor based on a cure fraction for small tumors. However, because many of these “cures” occur among women with invasive cancer that is not fatal, finding such cancer 1 year earlier confers very little mortality advantage to annual (vs. biennial) screening.

Interval for screening mammography

Table 3. Incremental Changes in Percentage of Reduction in Breast Cancer Mortality and Life-Years Gained per 1000 Women, by Age of Screening Initiation and Cessation

| Model* | Start at Age 40 y vs. 50 y† | | | | | | Stop at Age 79 y vs. 69 y‡ | | | | | |
|----------------------|--|----------|---|----------|--|----------|--|----------|---|----------|--|----------|
| | Difference In Percentage of Reduction In Breast Cancer Mortality | | Difference In Breast Cancer Deaths Averted per 1000 Women | | Difference In Life-Years Gained per 1000 Women | | Difference In Percentage of Reduction In Breast Cancer Mortality | | Difference In Breast Cancer Deaths Averted per 1000 Women | | Difference In Life-Years Gained per 1000 Women | |
| | Annual | Biennial | Annual | Biennial | Annual | Biennial | Annual | Biennial | Annual | Biennial | Annual | Biennial |
| D | 3 | 2 | 1 | 1 | 25 | 20 | 11 | 9 | 3 | 3 | 28 | 26 |
| E | 8 | 5 | 2 | 1 | 58 | 40 | 8 | 6 | 2 | 2 | 18 | 15 |
| G | 3 | 3 | 1 | 1 | 34 | 29 | 7 | 7 | 2 | 2 | 27 | 25 |
| M | 2 | 3 | 1 | 1 | 11 | 18 | 7 | 7 | 2 | 2 | 21 | 21 |
| S | 2 | 1 | 1 | 1 | 32 | 21 | 10 | 10 | 4 | 4 | 38 | 31 |
| W | 10 | 6 | 2 | 1 | 57 | 37 | 8 | 6 | 2 | 1 | 19 | 15 |
| Median across models | 3 | 3 | 1 | 1 | 33 | 25 | 8 | 7 | 2 | 2 | 24 | 23.5 |

* Model group abbreviations: D = Dana-Farber Cancer Institute; E = Erasmus Medical Center; G = Georgetown University; M = M.D. Anderson Cancer Center; S = Stanford University; W = University of Wisconsin/Harvard.

† Incremental difference between screening from 40 to 69 y versus 50 to 69 y.

‡ Incremental difference between screening from 50 to 79 y versus 50 to 69 y.

Interval for screening mammography

Table 4. Benefits and Harms Comparison of Different Starting and Stopping Ages Using the Exemplar Model*

| Strategy | Average Screenings per 1000 Women | Potential Benefits (vs. No Screening) | | | Potential Harms (vs. No Screening)† | |
|--|-----------------------------------|---------------------------------------|--------------------------------------|----------------------------------|---------------------------------------|-------------------------------------|
| | | Percentage of Mortality Reduction | Cancer Deaths Averted per 1000 Women | Life-Years Gained per 1000 Women | False-Positive Results per 1000 Women | Unnecessary Biopsies per 1000 Women |
| Comparison of different starting ages | | | | | | |
| Biennial screening | | | | | | |
| 40–69 y | 13 865 | 16‡ | 6.1 | 120‡ | 1250 | 88 |
| 45–69 y | 11 771 | 17‡ | 6.2 | 116‡ | 1050 | 74 |
| 50–69 y | 8944 | 15 | 5.4 | 99 | 780 | 55 |
| 55–69 y | 6941 | 13 | 4.9 | 80 | 590 | 41 |
| 60–69 y | 4246 | 9 | 3.4 | 52 | 340 | 24 |
| Annual screening | | | | | | |
| 40–69 y | 27 583 | 22‡ | 8.3 | 164‡ | 2250 | 158 |
| 45–69 y | 22 623 | 22‡ | 8.0 | 152‡ | 1800 | 126 |
| 50–69 y | 17 759 | 20‡ | 7.3 | 132‡ | 1350 | 95 |
| 55–69 y | 13 003 | 16‡ | 6.1 | 102‡ | 950 | 67 |
| 60–69 y | 8406 | 12‡ | 4.6 | 69‡ | 600 | 42 |
| Comparison of different stopping ages | | | | | | |
| Biennial | | | | | | |
| 50–69 y | 8944 | 15 | 5.4 | 99 | 780 | 55 |
| 50–74 y | 11 109 | 20 | 7.5 | 121 | 940 | 66 |
| 50–79 y | 12 347 | 25 | 9.4 | 130 | 1020 | 71 |
| 50–84 y | 13 836 | 26 | 9.6 | 138 | 1130 | 79 |
| Annual | | | | | | |
| 50–69 y | 17 759 | 20‡ | 7.3 | 132‡ | 1350 | 95 |
| 50–74 y | 21 357 | 26‡ | 9.5 | 156‡ | 1570 | 110 |
| 50–79 y | 24 439 | 30 | 11.1 | 170 | 1740 | 122 |
| 50–84 y | 26 913 | 33 | 12.2 | 178 | 1880 | 132 |

* Results are from model S (Stanford University). Model S was chosen as an exemplar model to summarize the balance of benefits and harms associated with screening 1000 women under a particular screening strategy.

† Overdiagnosis is another significant harm associated with screening. However, given the uncertainty in the knowledge base about ductal carcinoma in situ and small invasive tumors, we felt that the absolute estimates are not reliable. In general, overdiagnosis increases with age across all age groups but increases more sharply for women who are screened in their 70s and 80s.

‡ Strategy is dominated by other strategies; the strategy that dominates may not be in this table.

Summary of Screening Interval

- Biennial screening achieves most of the benefit of annual screening with less harm. Decisions about the best strategy depend on program and individual objectives and the weight placed on benefits, harms, and resource considerations.
- 19% loss of benefit in screening women aged 40-49 biennially versus annually.
- Breast Cancer screening in older (>65) women: \$34k/yr of life saved
 - *Ann Intern Med* 2003;139(10):835-42.

Current USPSTF Guidelines:

"So, what does this mean if you are a woman in your 40s?
You should talk to your doctor and make an informed decision about whether mammography is right for you based on your family history, general health, and personal values."

Diana Petitti, MD, MPH

Vice Chair, U.S. Preventive Services Task Force

November 19, 2009

CNBSS February, 2014.

- **Canadian National Breast Screening Study: Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: Randomised screening trial**

- Poor quality mammography missed numbers of cancer
- Poor randomization: Women with abnormal CBE assigned to “screening” group: assuring more cancer in screened versus unscreened women.

American College of Radiology: <http://www.acr.org/News-Publications/News/News-Articles/2014/Quality-Care/BMJ-Article-on-Breast-Cancer-Screening-Effectiveness-Incredibly-Flawed-and-Misleading>

ASSESSING BREAST CANCER RISK IN INDIVIDUAL PATIENTS

American College of Physicians Guidelines

- **Recommendation 1:** *In women 40 to 49 years of age, clinicians should periodically perform individualized assessment of risk for breast cancer to help guide decisions about screening mammography.*

The 5-year breast cancer risk can vary from 0.4% for a woman age 40 years with no risk factors to 11.0% for a woman age 49 years with several risk factors.

American College of Physicians Guidelines

- **Recommendation 2: *Clinicians should inform women 40 to 49 years of age about the potential benefits and harms of screening mammography.***

American College of Physicians Guidelines

- **Recommendation 3: *For women 40 to 49 years of age, clinicians should base screening mammography decisions on benefits and harms of screening, as well as on a woman's preferences and breast cancer risk profile.***

American College of Physicians Guidelines

- **Recommendation 4: *We recommend further research on the net benefits and harms of breast cancer screening modalities for women 40 to 49 years of age.***

http://www.acponline.org/pressroom/mam_guideline.htm

Individual patient assessment

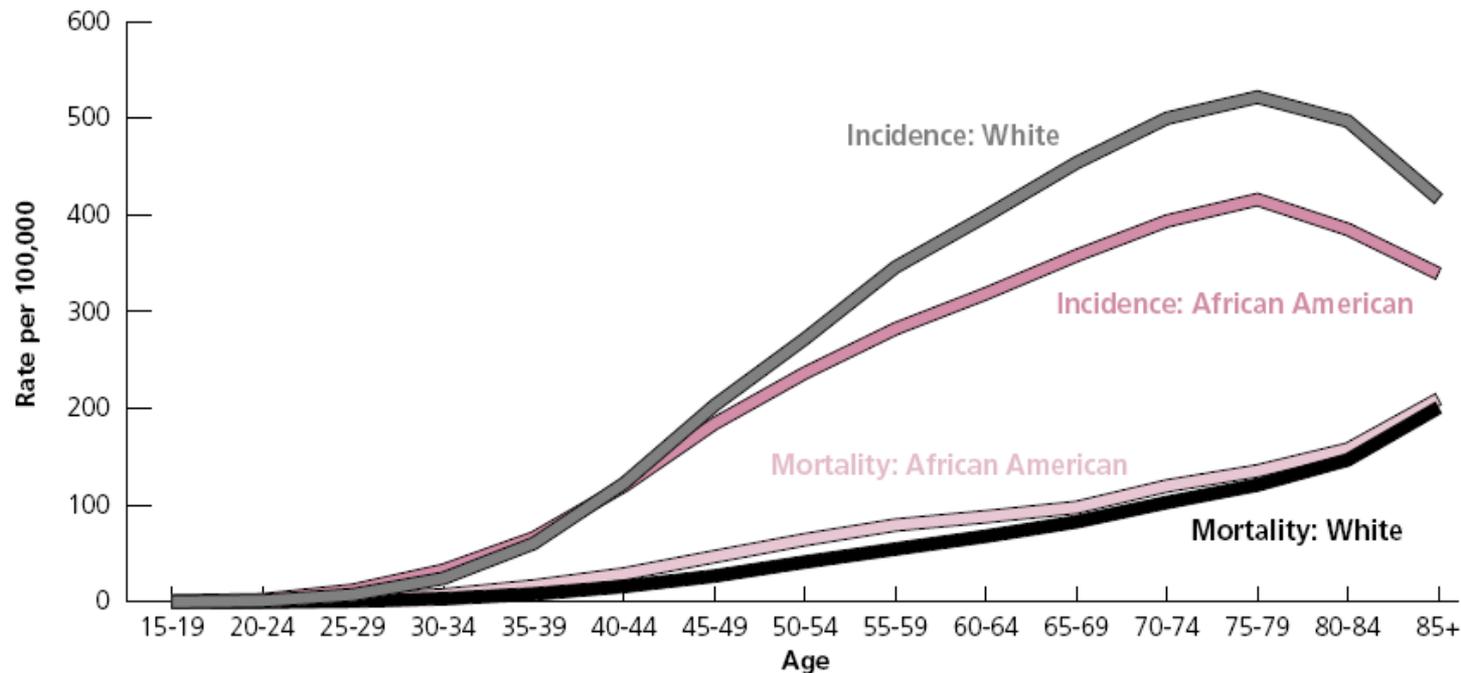
- Personal History
- Breast complaints (pain, discharge, mass, skin changes)
- **Risk Factors**, including family history
- Life expectancy

Risk Factors

- **Female**
- **Age >40**
- Family History (Maternal and Paternal)
- Previous malignancy, esp. Breast/ovarian
- Exposure to endogenous hormonal cycling (parity, onset of menarche/menopause, breast feeding, nulliparity or 1st child after age 30)
- Exposure to supradiaphragmatic radiation (RR 4.1*)
- Proliferative histology on previous biopsy
- Obesity/alcohol use/hormone replacement
- Mammographic density

Age as a risk factor for breast cancer

Figure 1. Female Breast Cancer – Age-Specific Incidence and Death Rates, by Race, United States, 1996-2000



Data sources: *Incidence* – Surveillance, Epidemiology, and End Results Program, 1973-2000, Division of Cancer Control and Population Science, National Cancer Institute, 2003. *Deaths* – National Center for Health Statistics, Centers for Disease Control and Prevention, 2003.

American Cancer Society, Surveillance Research, 2003

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- Proliferative histology on previous biopsy
- Obesity/alcohol use/hormone replacement
- Mammographic density

Assessing High vs. Average Risk

- Women with multiple relatives with breast/ovarian cancer, or personal history suggestive of risk:
 - Young age at diagnosis
 - Bilateral breast cancers
 - Male breast cancer
 - Both ovarian and breast cancer
 - Multiple family cases of cancer (breast and ovarian)
 - Ashkenazi Jewish heritage (prevalence of BRCA1/2 1 in 50).
 - San Luis Valley



For some people in the region (Chapel of All Saints, San Luis, Colorado), the DNA results have been a revelation. (Scott S. Warren)

The 'Secret Jews' of San Luis Valley

In Colorado, the gene linked to a virulent form of breast cancer found mainly in Jewish women is discovered in Hispanic Catholics

By Jeff Wheelwright
Smithsonian Magazine |
October 2008

Family History

Table 4

Standardised incidence ratios (SIRs) of breast cancer by the number of first-degree relatives diagnosed with breast cancer of ≤ 50 years

| | Observed (rate per 10^5) | Expected (rate per 10^5) | SIRs | 95% CI | P-value |
|--|-----------------------------|-----------------------------|------|-----------|---------|
| No first-degree relative with breast cancer of ≤ 50 years (N=607) | 25 (678.2) | 7.11 (192.9) | 3.52 | 2.38–5.19 | <0.0001 |
| One first-degree relative with breast cancer of ≤ 50 years (N=677) | 27 (646.9) | 6.29 (150.7) | 4.29 | 2.95–6.25 | <0.0001 |
| Two or more first-degree relatives with breast cancer of ≤ 50 years (N=207) | 12 (965.4) | 3.08 (247.8) | 3.90 | 2.23–6.81 | 0.0006 |

Br J Cancer. 2009 January 27; 100(2): 421–425.

Published online 2008 December 16. doi: 10.1038/sj.bjc.6604830.

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Risk Factors

- Female
- Age >40
- Family History (Maternal and Paternal)
- Previous malignancy, esp. Breast/ovarian
- ***Exposure to endogenous hormonal cycling (parity, onset of menarche/menopause, breast feeding, nulliparity or 1st child after age 30)***
- Exposure to supradiaphragmatic radiation (RR 4.1*)
- Proliferative histology on previous biopsy
- ***Obesity/alcohol use/hormone replacement***
- Mammographic density

Modifiable Risk Factors

- Exercise 1.5 to 4 hours weekly
- BMI below 25
- Low alcohol consumption
- Having children before age 30
- Breastfeeding more than 7 months
- Not using hormone replacement therapy
- Healthy diet low in refined carbohydrates, processed food, rich in “colorful” anti-oxidant foods.

Risk Factors

- Female
- Age >40
- Family History (Maternal and Paternal)
- Previous malignancy, esp. Breast/ovarian
- Exposure to endogenous hormonal cycling (parity, onset of menarche/menopause, breast feeding, nulliparity or 1st child after age 30)
- Exposure to supradiaphragmatic radiation (RR 4.1*)
- ***Proliferative histology on previous biopsy***
- Obesity/alcohol use/hormone replacement
- Mammographic density

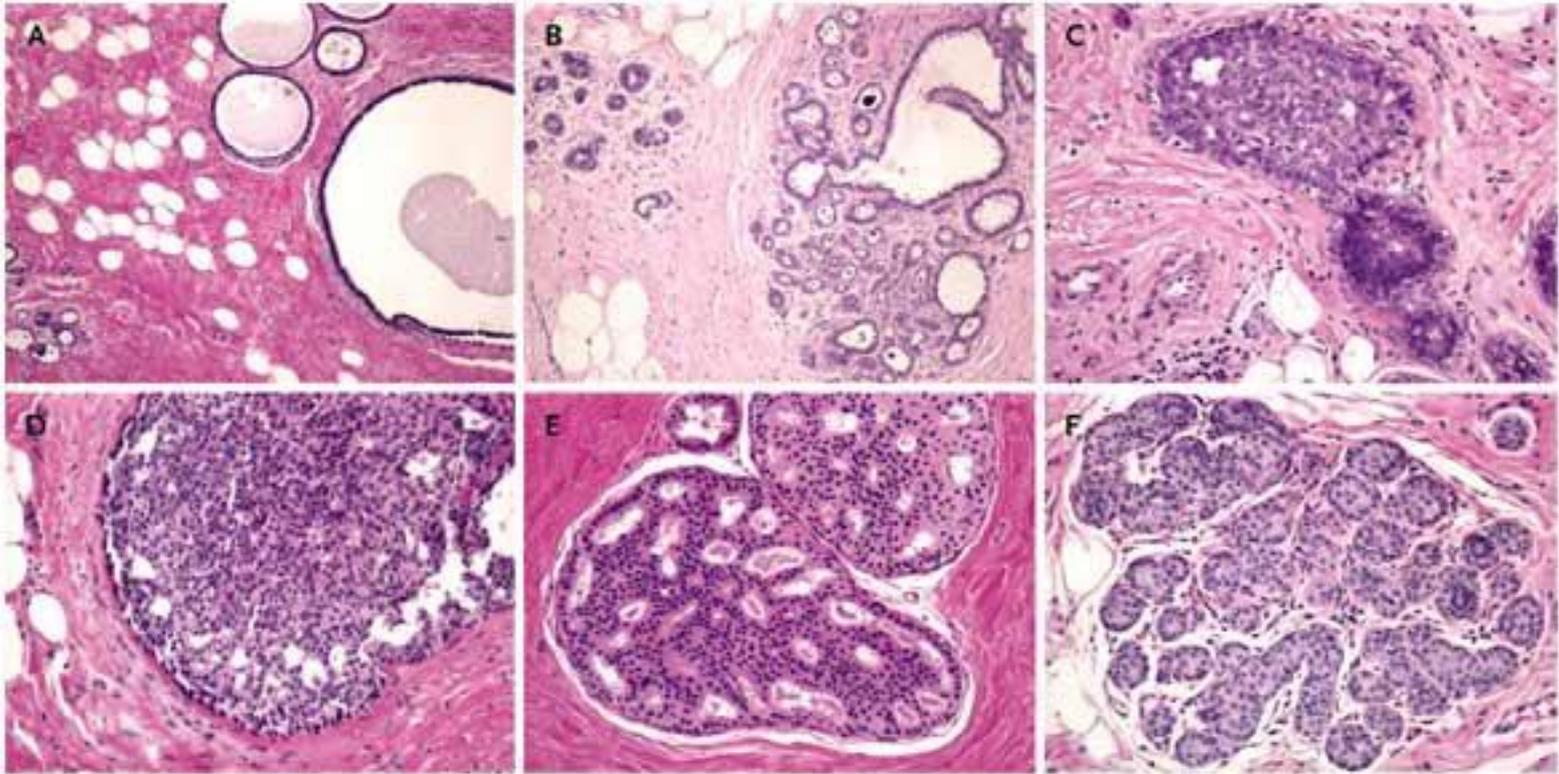
Benign Breast Disease and Breast Cancer Risk

- Non-proliferative
 - Breast cysts
 - Mastodynia
 - Epithelial related calcifications (seen on mammography)
 - Non proliferative lesions (on biopsy)
 - Other lesions not associated with increased cancer
- Proliferative
- Proliferative with atypia

Histology of Benign Breast Disease and Risk for Breast Cancer*

9087 women followed for mean 15 years, primary outcome observed versus expected breast cancers

- RR 1.56 (95% CI, 1.45 to 1.68) in entire cohort
- RR 1.27 (95% CI, 1.15 to 1.41) for non proliferative histology (67%)
- RR 1.88 (95% CI, 1.66 to 2.12) proliferative changes without atypia (30%)
- RR 4.24 (95% CI, 3.26 to 5.41), proliferative changes with atypia (4%)
- Family history was an independent risk factor



Non-proliferative lesions: RR 1.0 to 1.2

- Simple breast cysts (can be diagnosed with ultrasound)
- Simple fibroadenomas
- Papillary apocrine change*, epithelial related calcifications, mild ductal hyperplasia of the usual type (histologic diagnosis)

[*Cancer Epidemiol Biomarkers Prev.](#) 1996 Jan;5(1):29-32.

Papillary apocrine change of the breast: associations with atypical hyperplasia and risk of breast cancer.

[Page DL,](#) [Dupont WD,](#) [Jensen RA](#)

Other breast lesions not affecting breast cancer risk

- Lipomas
- Fat necrosis
- Galactocele
- Diabetic mastopathy (seen in Type 1 DM)
- Hamartomas (require excision)
- Idiopathic granulomatous mastitis
- Pseudoangiomatous stromal hyperplasia
- Sarcoidosis
- Galactorrhea

Proliferative breast lesions without atypia (RR 1.5-2.0)

- Usual ductal hyperplasia
- Intraductal papillomas
- Sclerosing adenosis
- Complex sclerosing lesions (radial scars)
- Fibroadenomas (with complex features or adjacent proliferative change)

Proliferative lesions with atypia RR 2.0-4.25

- Atypical ductal hyperplasia
- Atypical lobular hyperplasia (some features of ductal carcinoma in situ)

Risk Factors

- Female
- Age >40
- Family History (Maternal and Paternal)
- Previous malignancy, esp. Breast/ovarian
- Exposure to endogenous hormonal cycling (parity, onset of menarche/menopause, breast feeding, nulliparity or 1st child after age 30)
- Exposure to supradiaphragmatic radiation (RR 4.1*)
- Proliferative histology on previous biopsy
- Obesity/alcohol use/hormone replacement
- ***Mammographic density***

Automated Whole Breast Ultrasound*

- Detects 2-7 cases of breast cancer per 1000 women screened with mammographic density – Mammography alone misses one in two cancers in women with mammographically dense breasts: AWBU primary detects occult invasive cancers <1 cm, mammography still method of choice for DCIS.
- 40% of women have mammographic density but 70% of cancers are diagnosed in women with mammographic density

*Kelly, K and Richwald, G. Automated whole-breast ultrasound: advancing the performance of breast cancer screening. [Semin Ultrasound CT MR](#). 2011 Aug;32(4):273-80. doi: 10.1053/j.sult.2011.02.004.

Counseling your patient

- Risk assessment and perception of risk
- Personal values and self-efficacy in decision making

Tools to assist with breast cancer risk assessment

- Gail
 - Pro: Fast, easily accessible (link on LCR)
 - Con: Does not evaluate 2DR, overestimates risk if h/o biopsy, in goodness of fit model, can underestimate risk
- Tyrer-Cuzick*
 - Pro: Most accurate
 - Con: Takes longer
- BRCAPRO/Claus/BOADICEA
 - Pro: Most predictive of ovarian cancer and other familial cancer syndromes
 - Con: Must be downloaded, recommend additional training, takes time (not user-friendly)

[Amir E](#), [Evans DG](#), [Shenton A](#), [Lalloo F](#), [Moran A](#), [Boggis C](#), [Wilson M](#), [Howell A](#). **Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme.** [J Med Genet.](#) 2003 Nov;40(11):807-14.

Gail Model

www.cancer.gov/bcrisktool



National Cancer Institute

U.S. National Institutes of Health | www.cancer.gov

Breast Cancer Risk Assessment Tool

An interactive tool to help estimate a woman's risk of developing breast cancer

Last modified date: 04/28/200

- > **Risk Calculator**
- About the Tool
- Breast Cancer Risk
- Mobile Access
- Download Source Code

Page Options

- Print Page
- Email Page

Quick Links

- [Breast Cancer Home Page](#)
- [Breast Cancer: Prevention, Genetics, Causes](#)
- [Initial Results of STAR Released](#)
- [Current Clinical Trials: Breast Cancer In Situ Treatment](#)
- [Current Clinical Trials: Breast Cancer Prevention](#)
- [Current Clinical Trials: Breast Cancer Screening](#)
- [Estimating Breast Cancer: Q&A](#)
- [Understanding Cancer Risk](#)
- [National Cancer Institute](#)

The Breast Cancer Risk Assessment Tool is an interactive tool designed by scientists at the National Cancer Institute (NCI) and the [National Surgical Adjuvant Breast and Bowel Project \(NSABP\)](#) to estimate a woman's risk of developing [invasive breast cancer](#). The tool has been updated for African American women based on the Contraceptive and Reproductive Experiences (CARE) Study. See [About the Tool](#) for more information.

Results (Breast Cancer Risk) [New Risk Calculation](#)

Reminder: The Breast Cancer Risk Assessment Tool was designed for use by health professionals. If you are not a health professional, you are encouraged to discuss these results and your personal risk of breast cancer with your doctor.

Race/Ethnicity:
White

5 Year Risk

- > This woman (age 44): 0.7%
- > Average woman (age 44): 0.9%

Explanation

Based on the information provided (see below), the woman's estimated risk for developing invasive breast cancer over the next 5 years is 0.7% compared to a risk of 0.9% for a woman of the same age and race/ethnicity from the general U.S. population. This calculation also means that the woman's risk of NOT getting breast cancer over the next 5 years is 99.3%.

Lifetime Risk

- > This woman (to age 90): 8.7%
- > Average woman (to age 90): 12%

Tyrer-Cuzick model

<http://www.ems-trials.org/riskevaluator/>

Untitled - IBIS Risk Evaluator

File Edit View Help

Add Del Risk Sort Find

Personal factors

Woman's age: 44 Menarche: 12

Nulliparous: Parous: Age First Child: 30 Unknown:

Hyperplasia (without atypia): Atypical hyperplasia: LCIS: Ovarian cancer:

Measurements

Metric: Imperial:

Height: 5 ft 4 in Weight: ? stone 173 lb

Premenopausal: Perimenopausal: Postmenopausal: No information: Age at menopause: ?

Ashtkenazi inheritance:

Half Sisters: Affected cousins: Affected Nieces: Genetic Testing:

Calculate Risk

View Family History

HRT use

Never: Length of use (years): 0

5 or more years ago: Less than 5 years ago: Current user:

Ovarian: Bilateral: Breast cancer: Age: 49

Sisters: Number: 2 Breast cancer: Age: 38 40 ?

Ovarian: Bilateral: Breast cancer: Age: 85

Maternal Gran: Ovarian: Bilateral: Breast cancer: Age: 75

Paternal aunts: Ovarian: Bilateral: Breast cancer: Age: ? ?

Maternal aunts: Ovarian: Bilateral: Breast cancer: Age: ? ?

Daughters: Ovarian: Bilateral: Breast cancer: Age: 8 ?

Family History Diagram:

```
graph TD
    G1[85] --- G2[75]
    G1 --- P1[ ]
    G2 --- P2[ ]
    P1 --- D1[38]
    P1 --- D2[40]
    P1 --- D3[44]
    P2 --- D4[?]
```

Ready

NUM

start Women's Health Elect... Counseling_About_5... Counseling_Mammogr... Risk Evaluator Softw... Untitled - IBIS Risk Ev... 12:06 PM

Tyrer-Cuzick Final Output

Personal factors

Woman's age: Menarche:

Nulliparous: Parous: Age First Child:

Unknown:

Hyperplasia (without atypia): Atypical hyperplasia: LCIS: Ovarian cancer:

Ovarian: Bilateral:

Mother: Breast cancer: Age:

Ovarian: Breast cancer: Age:

Paternal Gran: Breast cancer: Age:

Maternal Gran: Breast cancer: Age:

Measurements

ft: in: stone: lb: Metric:

Height:

Weight:

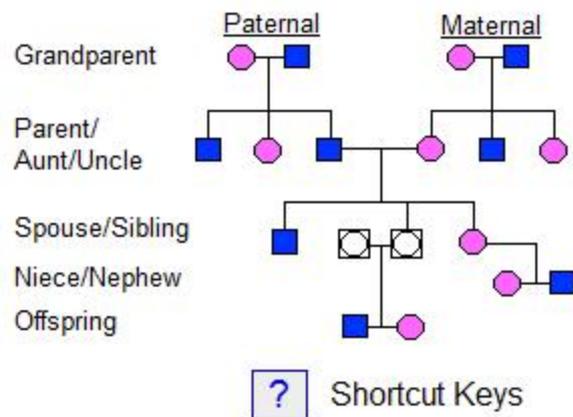
Patient id: Patient no.:

Print Preview

Woman's age is 44 years.
 Age at menarche was 12 years.
 Age at first birth was 30 years.
 Person is premenopausal.
 Height is 5 ft 4 ins.
 Weight is unknown.
 Woman has never used HRT.

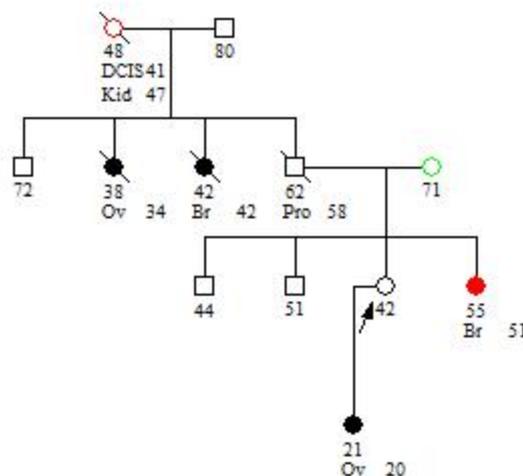
Risk after 10 years is 6.097%.
 10 year population risk is 2.145%.
 Lifetime risk is 24.78%.
 Lifetime population risk is 9.325%.
 Probability of a BRCA1 gene is 0.36%.
 Probability of a BRCA2 gene is 0.27%.

| Age | Personal Risk (%) | Population Risk (%) |
|-----|-------------------|---------------------|
| 44 | 0.0 | 0.0 |
| 54 | ~5.0 | ~1.0 |
| 64 | ~10.0 | ~2.0 |
| 74 | ~15.0 | ~3.0 |
| 84 | 24.78 | 9.325 |



DOE
11123
Ashkenazi: NO

| | |
|----------------|-----------|
| Done | New Pedit |
| Change Proband | Print |
| Notation | Exit |



○ BRCA Positive
○ BRCA Negative

8/30/2008

DOE
11123

Claus Family History Model

Print

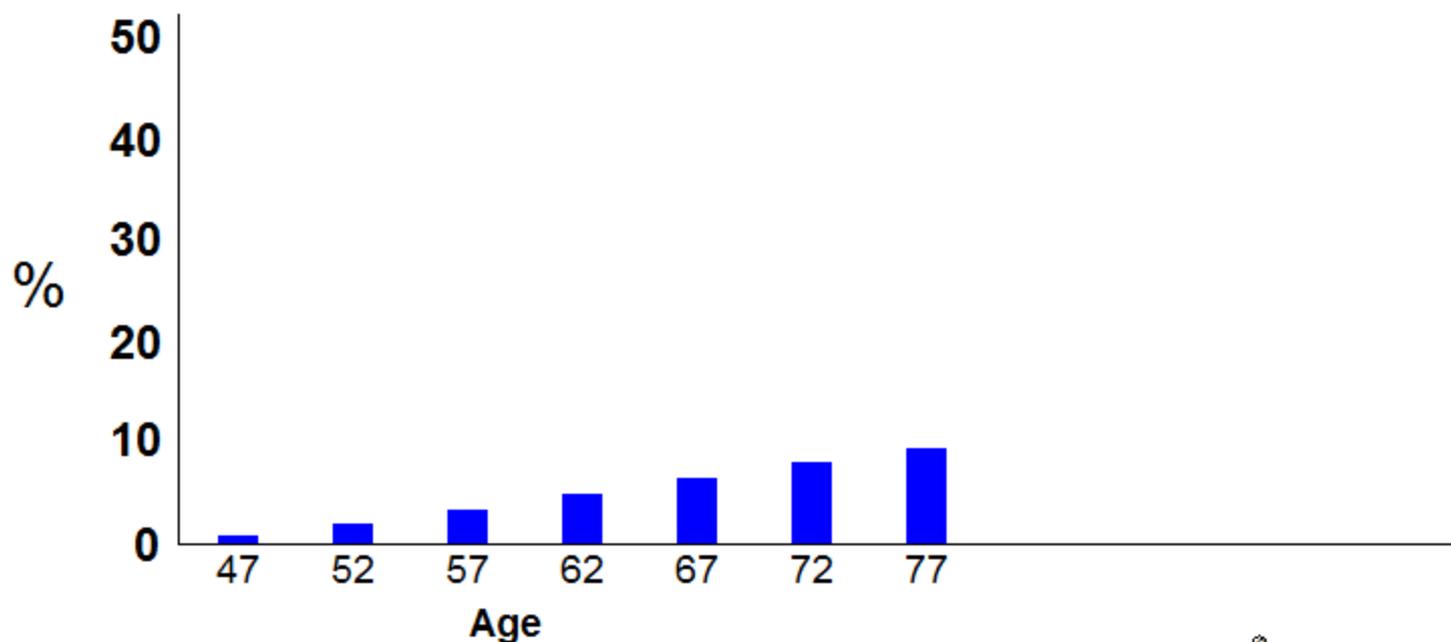
Quit

The Claus table used in this calculation is:

One first-degree relative

| | | | | | |
|-----|-----|-----|-----|-----|------|
| 29 | 39 | 49 | 59 | 69 | 79 |
| 0.2 | 0.8 | 2.3 | 4.9 | 8.2 | 11.0 |

Probability of Developing Breast Cancer by Age



Remaining Risk

| Age | % |
|-----|------|
| 47 | .76 |
| 52 | 1.85 |
| 57 | 3.17 |
| 62 | 4.7 |
| 67 | 6.37 |
| 72 | 7.89 |
| 77 | 9.31 |

To Age 79: 9.9

8/30/2008

DOE
11123

BRCAPRO: BayesMendel

BRCApenet.metaDSL.2006

Carrier Probabilities

BRCA1: 0.021

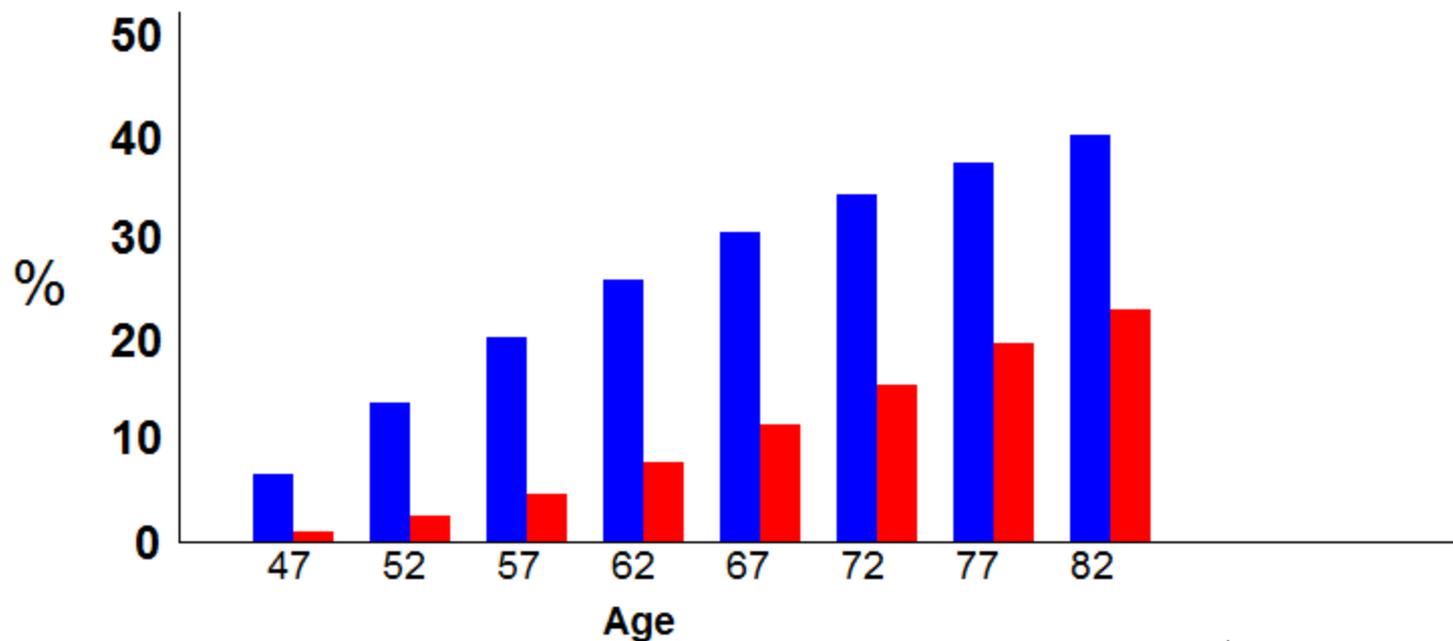
BRCA2: 0.806

BRCA 1 or 2: 0.817

Print

Quit

| Probabilities | | |
|---------------|---------|---------|
| Age | Breast | Ovarian |
| [47, | [0.066, | [0.009, |
| 52, | 0.135, | 0.024, |
| 57, | 0.199, | 0.046, |
| 62, | 0.257, | 0.077, |
| 67, | 0.304, | 0.113, |
| 72, | 0.340, | 0.154, |
| 77, | 0.372, | 0.193, |
| 82] | 0.399] | 0.226] |

Probability of Breast ■ or Ovarian ■ Cancer by Age

How can you help guide her decision?

- Personal values: Risk of false positive versus risk of failure to diagnose
 - Understanding of risks/benefits of screening mammography
 - Clarify understanding of personal risk
 - Assess personal values

Now versus later?

1 (wait) to 10 (screen now)

Per 1000 women screened every 2 years from age 40 to age 50:

- 740 correctly reassured
- 240 have “false alarms” with extra tests
- 9 women get cancer in between screenings found by symptoms
- 7 women have cancer detected by screening
- 0.5 women do not die from breast cancer

Screening Mammography Decision Guides

- **Patient Handouts**
- **Australian Screening Mammography Decision Aid:**
<http://www.mammogram.med.usyd.edu.au/>
- **Risk Assessment Algorithms**
www.QAP.sdsu.edu

Summaries for Patients are a service provided by *Annals* to help patients better understand the complicated and often mystifying language of modern medicine.

The full reports are titled "Screening Mammography in Women 40 to 49 Years of Age: A Clinical Practice Guideline from the American College of Physicians" and "Screening Mammography in Women 40 to 49 Years of Age: A Systematic Review for the American College of Physicians." They are in the 3 April 2007 issue of *Annals of Internal Medicine* (volume 146, pages 511-515 and 516-526). The first report was written by A. Qaseem, V. Snow, K. Sherif, M. Aronson, K.B. Weiss, and D.K. Owens, for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians; the second report was written by K. Armstrong, E. Moye, S. Williams, J.A. Berlin, and E.E. Reynolds.

Screening Mammography in Women Age 40 to 49 Years

Who developed these guidelines?

The American College of Physicians (ACP) developed these recommendations. Members of the ACP are internists, specialists in the care of adults.

What is the problem and what is known about it so far?

A mammogram is an x-ray test that screens for breast cancer. "Screen" means to look for cancer at early stages before a woman feels a lump or has other symptoms that might suggest breast cancer. Most health care organizations agree that women 50 years of age or older should get mammograms; however, they do not agree on whether the benefits outweigh the risks for women 40 to 49 years of age because most studies involved women older than 50.

How did the ACP develop these recommendations?

The authors reviewed studies about the benefits and harms of mammograms for women between 40 and 49 years of age. They also reviewed studies on estimating a woman's chances of developing breast cancer, given her personal characteristics.

What did the authors find?

Screening mammograms for women 40 to 49 years of age decrease the risk for breast cancer deaths compared with women who do not get screened. However, the benefit for these women is smaller than it is for women 50 years of age or older.

The harmful effects of mammograms include false-positive results, radiation exposure, false reassurance, and pain during the mammogram. False-positive results are when the mammogram suggests breast cancer but further tests find no breast cancer. Mammograms frequently find a type of cancer called DCIS (ductal carcinoma in situ), and women end up getting treated for it. However, good information is lacking about how often DCIS would progress to more serious types of cancer without treatment.

For a woman in her 40s, the risk for breast cancer within the next 5 years can vary substantially, depending on whether she has any risk factors for the disease. Factors that increase the risk for breast cancer include older age, family history of breast cancer, older age at the time of first pregnancy, younger age of first period, history of a breast abnormality that required a biopsy (removal of a sample of breast tissue for laboratory examination), or a history of being exposed to chest radiation (such as in the treatment of another disease). Unfortunately, a mathematical model called the Gail model that predicts the risk for breast cancer among groups is imprecise in predicting an individual woman's risk for the disease.

What does the ACP suggest that patients and doctors do?

A woman age 40 to 49 years and her doctor should periodically evaluate her personal risk for breast cancer to help guide decisions about screening mammography.

Doctors should inform women age 40 to 49 years of the potential benefits and harms of screening mammography.

Women age 40 to 49 years and their doctors should base decisions about screening mammography on benefits and harms of screening and on the woman's personal risks for breast cancer.

If a woman age 40 to 49 years decides not to have a mammogram, she and her doctor should readdress the issue every 1 to 2 years.

We need more research on the benefits and harms of breast cancer screening for women in their 40s.

What are the cautions related to these recommendations?

Recommendations may change as new studies become available.



IS Getting a Screening Mammogram Right for Me? Information for Women Aged 40-49

What is a Screening Mammogram?

A mammogram is an x-ray to check for breast cancer. Breast cancer can be found with screening mammograms and can improve the chance of a cure. *Screening for breast cancer is done in women who do NOT have any breast problems. If you have a breast lump, pain, or nipple discharge, you should see a healthcare provider right away to be checked!*

Who should be screened?

Getting a mammogram starting at age 50 is advised. Women 50 to 74 years of age who have an average risk for breast cancer should get a mammogram every 1 to 2 years. There is less breast cancer in women under 50 years of age and more risk of having a “false alarm”. There may be a decrease in deaths from breast cancer in women 40-49 years of age who have the x-ray.

Some women who are 40-49 years of age may want to start getting mammograms sooner than age 50.

Women 40-49 years of age who:

- Have a mother, sister, or grandmother who had breast cancer at the age of 50 years or older
- Are overweight
- Drink more than 2 drinks of alcohol daily
- Have no children or had their first child after 30 years of age may have a little more risk for breast cancer

There is no right or wrong answer about when to start getting the exam. Talk with your healthcare provider and make the decision that is right for you.

Pros and Cons of getting screening exam:

Pros

- 1 death from breast cancer avoided per 2000 women aged 40-49 years screened
- More life years are gained per case of breast cancer detected
- 740 women correctly reassured that they do not have breast cancer per 1000 women aged 40-49 years screened

Cons

- False Reassurance
- “False Alarms” that result in extra tests
- Exposure to radiation
- Finding a condition that isn’t dangerous
- Pain during the mammogram
- Anxiety related to “false alarms”

Who do I call if I have questions or problems?

If you have questions call the clinic at (303) _____. You can also call the Denver Health NurseLine at (303) 739-1211 any time day or night.



Special instructions: _____

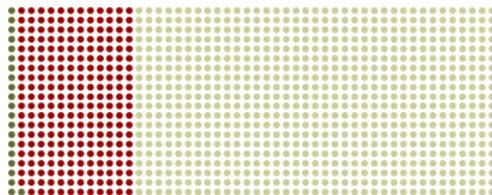


AUSTRALIAN SCREENING MAMMOGRAPHY DECISION AID TRIAL

A decision aid for women aged 40 thinking about starting mammography screening

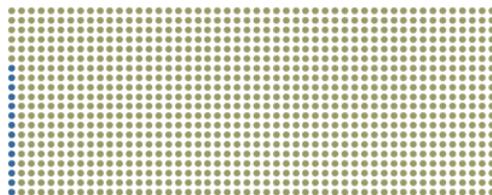


What else happens to 1000 women aged 40 who *have* screening mammograms every two years for 10 years?



- 21 women are diagnosed with breast cancer over the next 10 years
 - 12 women will have their cancer detected by screening
 - 9 women develop symptoms and are diagnosed with breast cancer between screening mammograms
- 239 women have extra tests after an abnormal mammogram. The extra tests will show these women don't have breast cancer. Aside from the inconvenience of attending for these tests, some women will worry long after they have had them⁴
- 740 women are correctly reassured they do not have breast cancer

What else happens to 1000 women aged 40 who *do not have* screening mammograms during the next 10 years?



- 14 women develop symptoms and are diagnosed with breast cancer

Australian Screening Mammography Decision Aid Trial - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Home Search Favorites Refresh Print Copy Paste

Address http://www.mammogram.med.usyd.edu.au/decision/da_01.shtml Go Links

AUSTRALIAN SCREENING MAMMOGRAPHY DECISION AID TRIAL

A decision aid for women aged 40 thinking about starting mammography screening



Should I start having mammograms to screen for breast cancer?

Many people think mammograms to detect breast cancer early are always a good thing. But there are reasons why you might choose not to start screening mammography if you are younger than 50. The following pages outline some issues you may want to consider in making your decision.

Remember there is no right or wrong answer about whether to start having screening mammograms.

It is your decision to make.

Screening is for women with no breast symptoms.
If you have any breast symptoms, you should see your doctor.

[» Next](#)

start Microsoft PowerPoint ... What Is My Cancer Ri... Australian Screening ... Internet 5:28 PM

http://www.mammogram.med.usyd.edu.au/wsheat-eg1.pdf - Microsoft Internet Explorer

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Save a Copy Print Search Select 153%

AUSTRALIAN SCREENING MAMMOGRAPHY DECISION AID TRIAL

A decision aid for women aged 40 thinking about starting mammography screening

Your personal worksheet

Tick the risk factors you have

Important risk factors:

- Personal history of breast cancer
- Family history of breast cancer
- Previous biopsies showing abnormal breast cells

If you have a strong family history this decision aid is not for you. You should seek clinical advice on managing your breast cancer risk

Risk factors that increase your risk slightly:

- Never had children
- First child after age 30
- Early age of first period (less than 12 years old)
- Currently taking the oral contraceptive pill or hormone replacement therapy
- Drink more than 2 standard drinks of alcohol per day
- Have put on a lot of weight in adulthood

Consider if each of the following points make you feel like you want to start screening now, or if you want to think about it later.

For example if one of the points makes you feel very strongly that you may want to consider screening later, select a button close to the right hand side of the list, close to the words "Consider screening later". If you are unsure or neutral, select a button close to the centre.

For 1000 women aged 40 who commence screening:
 0.5 death from breast cancer is avoided because of screening.
 This makes me feel I want to...

EXAMPLE 1: Sarah is 42 years old and had her first child after the age of 30. This is how she completed her worksheet:

She feels the 0.5 deaths/1000 women is a very small reduction – this point makes her feel quite strongly she wants to consider screening later.

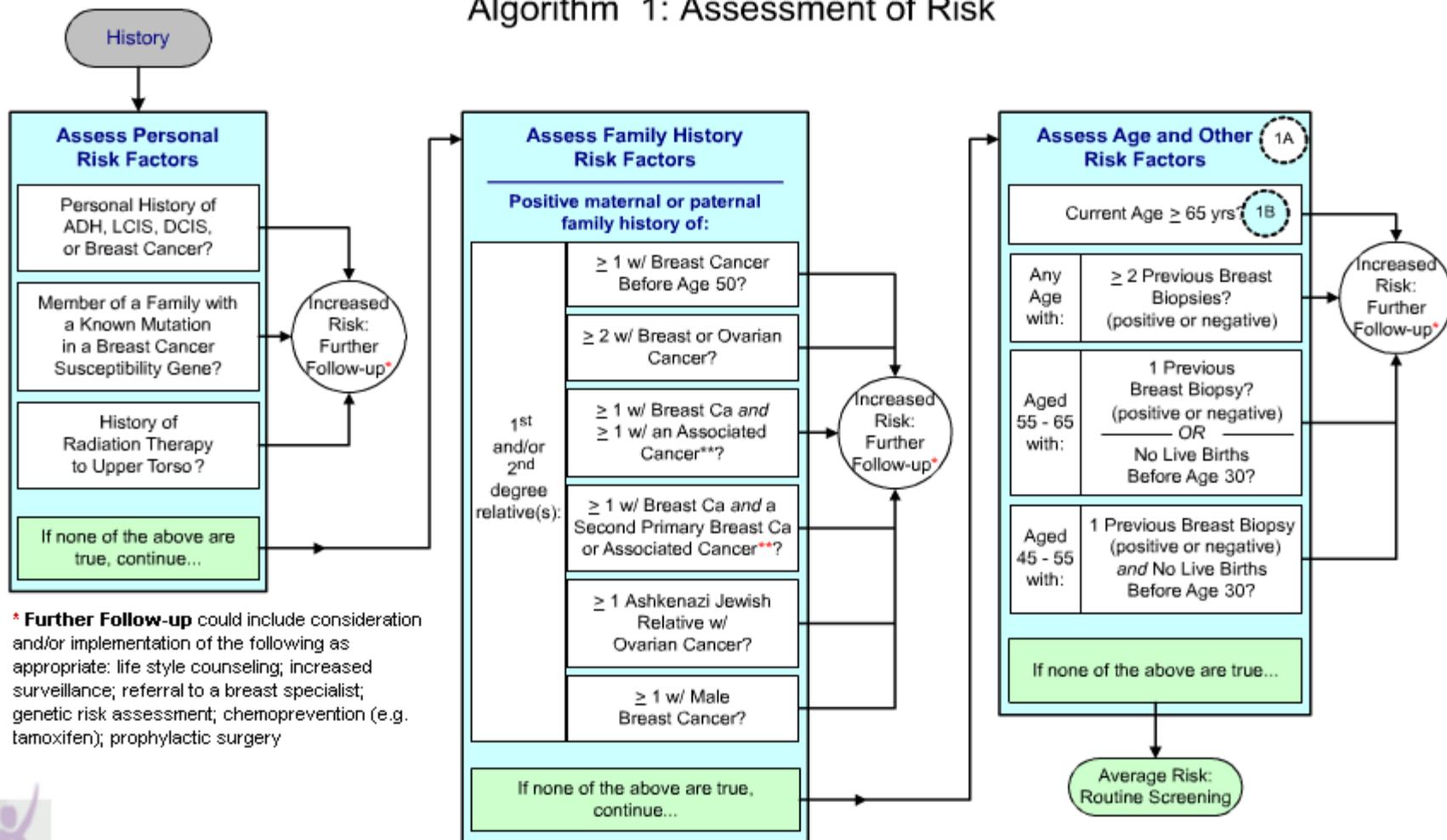
She feels very strongly about the 239 women having extra tests because of screening. This point makes her feel she wants to consider screening later.

Although the other issues (extra women diagnosed and the women reassured), make her feel like considering screening later, she doesn't feel as strongly about them.

1 of 1

Done Unknown Zone

Algorithm 1: Assessment of Risk



* **Further Follow-up** could include consideration and/or implementation of the following as appropriate: life style counseling; increased surveillance; referral to a breast specialist; genetic risk assessment; chemoprevention (e.g. tamoxifen); prophylactic surgery

** **Associated cancers:** ovarian; thyroid; colorectal; prostate; endometrial; pancreatic; adrenocortical; melanoma; childhood sarcoma; leukemia/lymphoma; brain tumor



Women at >20% lifetime risk

- Consider referral for genetic counseling/testing
- Consider MRI in addition to mammography (age 25-30)
- Chemoprophylaxis (5 year risk >1.6-3.0% using Gail model)
- Bilateral prophylactic oophorectomy/mastectomy
- Clinical breast exam

Case History

A.S. is a 44 year old pre-menopausal g3 p3 with no breast complaints who comes in to discuss breast cancer screening.

She read on the internet that women who are under 50 should see their doctor before getting a mammogram.

Her friend told her that “You don’t need a mammogram until you’re 50.”

Her period began at age 13, her first child was born age 21, her BMI is 31, she does not smoke or drink alcohol and gets less than 2 hours of exercise per week. She has a typical diet and eats fast food twice per week. Her paternal grandmother had breast cancer, onset age 64, and no other family history of cancer, but her mother has diabetes.

A.S.

- Her 5 year risk is 0.4% (average 0.6%)
- Her lifetime (to age 90) risk is 6.2% (average 7.8%)
- Not smoking or drinking improve her health and lower her risk for breast cancer.
- She would benefit from increased exercise, a healthier diet, and healthier weight.
- Screening MRI is not recommended.

Questions?



MUSH FOR THE CURE

References:

Mandelblatt, JS et al. **Effects of Mammography Screening Under Different Screening Schedules: Model Estimates of Potential Benefits and Harms.** Ann Int Med 2009;151:738-47.

SJ, Connolly JL, Schnitt SJ, Colditz GA. **A prospective study of benign breast disease and the risk of breast cancer.** JAMA. 1992;267(7):941.

Guray M, Sahin AA. **Benign breast diseases: classification, diagnosis, and management.** Oncologist. 2006;11(5):435.

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[Amir E](#), [Evans DG](#), [Shenton A](#), [Laloo F](#), [Moran A](#), [Boggis C](#), [Wilson M](#), [Howell A](#). **Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme.** [J Med Genet.](#) 2003 Nov;40(11):807-14

Kelly, K and Richwald, G. **Automated whole-breast ultrasound: advancing the performance of breast cancer screening.** [Semin Ultrasound CT MR.](#) 2011 Aug;32(4):273-80. doi: 10.1053/j.sult.2011.02.004.