Breast Cancer Screening: Making Sense of the Conflicting Guidelines

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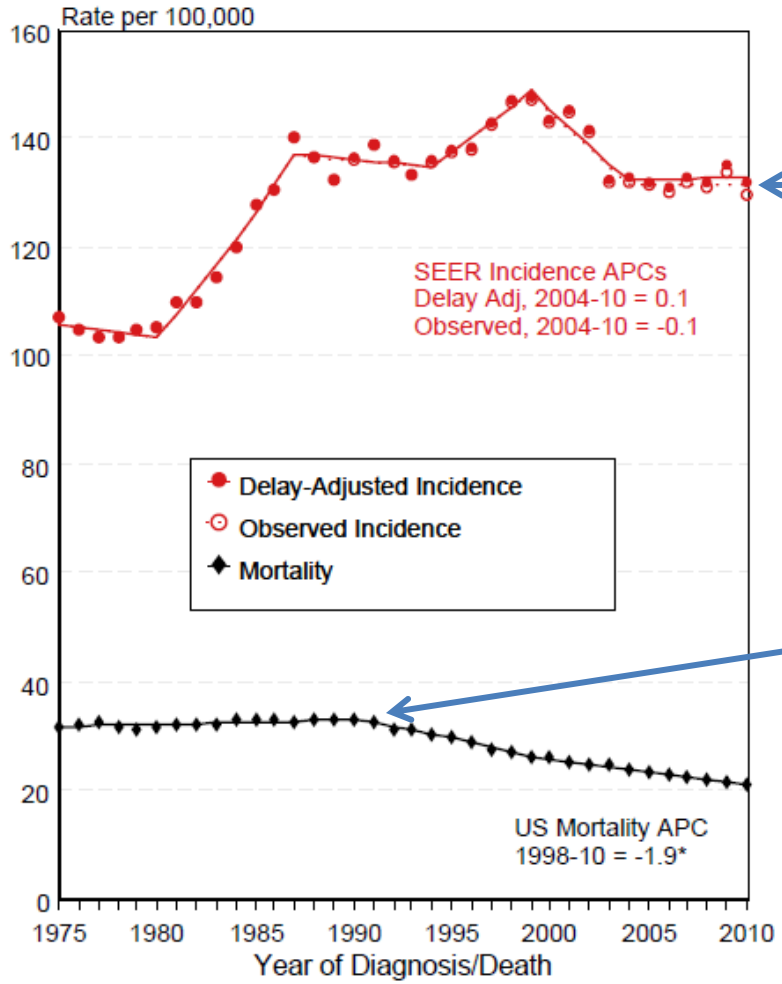
Outline

- Breast Cancer burden

http://seer.cancer.gov/csr/1975_2010/index.html

- The costs and benefits of mammography
- Screening recommendations
  - United States Preventive Services Task Force (http://www.uspreventiveservicestaskforce.org/uspstopics.htm)
  - Other National Professional Recommendations
  - Recommendations for self exams, clinical breast exams
  - Breast density

Breast Cancer Incidence and Mortality

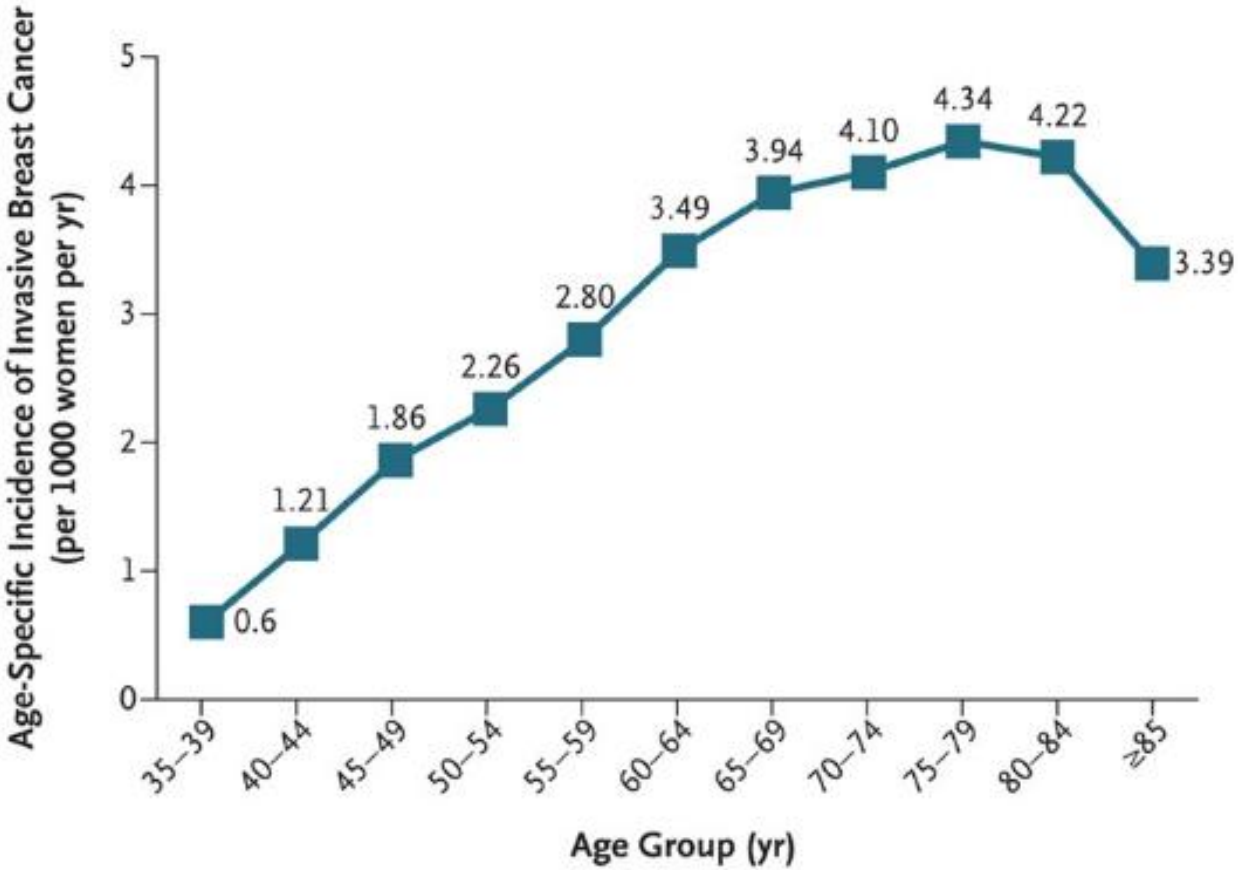


Incidence
Lifetime risk of breast cancer is 12.29% as of January 2013 = 1 in 8 US women

Mortality:
1975-1990: increased 0.4%/year
1990-1995: decreased 1.8%/year
1995-1998: decreased 3.3%/year
1999-2006: decreased 1.9%/year

[a] Source: SEER 9 areas and US Mortality Files (National Center for Health Statistics, CDC).
Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).
Regression lines and APCs are calculated using the Joinpoint Regression Program Version 4.0.3, April 2013, National Cancer Institute.
The APC is the Annual Percent Change for the regression line segments. The APC shown on the graph is for the most recent trend.
* The APC is significantly different from zero ($p < 0.05$).

Breast Cancer Incidence by Age



Risk of developing breast cancer in next 10 years:
30 yo: 1 in 250 (0.40%)
40 yo: 1 in 68 (1.47%)
50 yo: 1 in 35 (2.84%)
60 yo: 1 in 27 (3.67%)

http://seer.cancer.gov/csr/1975_2010/index.html

Screening Mammography

- Mammography is the best screening tool available
  - Good sensitivity (90+%) in fatty breasts
  - 80-90% sensitivity on average
  - Inexpensive
  - Widely available

Skaane P, Hofvind S, Skjennald A. Randomized trial of screen-film versus full-field digital mammography with soft-copy reading in population-based screening program: follow-up and final results of Oslo II study. Radiology 2007;244(3):708-17.

Breast Cancer Prognosis

- Larger cancers more likely to metastasize
  - <1 cm- 10% spread to lymph node
  - 2cm- 35%
  - 3 cm- 50%

- Median size of cancer found mammographically is 1-1.5cm
- Median size of cancer found at clinical breast exam 2-2.5 cm

Mamounas EP, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer CE Jr, Taghian A, Wickerham DL, Wolmark N. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant **Breast** and Bowel Project B-18 and B-27. J Clin Oncol. 2012;30(32):3960-6.

Benefits of Screening Mammography

- Risk of death from breast cancer reduced 14-32%
  - 8 randomized trials, over 600,000 patients.
- Detection of T1a and T1b tumors:
  - T1a and T1b are too small for manual detection
  - T1a/b tumors have better survival than T1c or greater.
- Detection of DCIS prevents development of invasive cancers
- Detection rate for digital mammography: 5.1/1000 screens
- Increased likelihood of breast conservation when screen detected.

-Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784-1792.
-Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151:727-737.
-Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784-1792

Meta-analysis of Mammogram Screening:

- Reductions in death: 14% reduction in 50's and 32% reduction in 60's
- More benefit in 60's because mammography sensitivity higher in that age group.

Table 2. Relative Risk of Death from Breast Cancer, Number Needed to Invite to Screening, and Rates of False Positive and False Negative Results, According to Age.*

Age	No. of Trials	Relative Risk of Death (95% CI)	Number Needed to Invite to Screening (95% CI)†	Rate per 1000 Women Screened				
				True Positive Rate		False Negative Rate	False Positive Rate	False Positive Rate on Biopsy
				Invasive	*DCIS*			
39–49 yr	8‡	0.85 (0.75–0.96)	1904 (929–6378)	1.8	0.8	1.0	97.8	6.7
50–59 yr	6§	0.86 (0.75–0.99)	1339 (322–7455)	3.4	1.3	1.1	86.6	6.1
60–69 yr	2¶	0.68 (0.54–0.87)	377 (230–1050)	5.0	1.5	1.4	79.0	5.1
70–79 yr	1‖	1.12 (0.73–1.72)	Not available	6.5	1.4	1.5	68.8	4.3

* Data are from a meta-analysis of randomized breast-cancer screening trials, performed by the U.S. Preventive Services Task Force,[8] and from the Breast Cancer Surveillance Consortium (for data in the five columns at the right) and are based on a single round of screening. CI denotes confidence interval, and DCIS ductal carcinoma in situ.

† Since the rate of compliance with screening was only 75 to 85% in most studies, the number needed to screen to prevent one death from breast cancer would be 15 to 25% lower but was not calculated.

‡ The results are from the Health Insurance Plan (HIP) of Greater New York,[10] Canadian National Breast Screening Study 1 (CNBSS-1),[11] Stockholm,[12] Malmö Mammographic Screening Program,[12] the Swedish Two-County trials (two),[12] the Gothenburg Breast Screening Trial,[13] and the Age trial.[14]

§ The results are from the CNBSS-2,[15] the Stockholm, Malmö, and Swedish Two-County trials (two),[12] and the Gothenburg trial.[13] The New York HIP[10] and Edinburgh[16] trials were excluded because of outdated technology and inadequate randomization, respectively.[17] Excluding the Canadian trial, which has been heavily criticized for enrolling prescreened volunteers rather than unselected samples of participants, th relative risk was 0.81 (95% CI, 0.68 to 0.95).

¶ The results are from the Malmö trial[12] and one of the Swedish Two-County trials (Östergötland).[12]

‖ The results are from one of the Swedish Two-County trials (Östergötland), which included only women 70 to 74 years of age.[12]

Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151:727-737

Mammogram Screening over age 70

- Only a single randomized trial exists (Sweden):
  - No impact on mortality from screening mammography
- Modeling using the US risk and incidence rates:
  - Uniform screening over age 70 would result in 2 lives saved per 1000 women screened.
- Consensus:
  - Too little benefit beyond age 74 to recommend routine mammogram screening for all.
  - Avoid screening mammo if life expectancy <5ys.

Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet 2002;359:909-919[Erratum, Lancet 2002;360:724.]

Screening Mammogram Guideline Variability:

Organization	Year Guidelines Issued	Mammography
USPSTF	2009	Age 50–74 yr, every 2 yr; age 40–49 yr and age ≥75 yr, individualize the decision (every 2 yr, if performed)
American Cancer Society	2010	Age ≥40 yr, annually†
National Comprehensive Cancer Network	2011	Age ≥40 yr, annually†
National Cancer Institute	2010	Age ≥40 yr, every 1–2 yr†
American College of Physicians	2007	Age 50–74 yr, every 1–2 yr‡; age 40–49 yr, individualize the decision (every 1–2 yr, if performed)
American College of Obstetricians and Gynecologists	2003	Age 40–49 yr, every 1–2 yr; age ≥50 yr, annually†
American College of Radiology	2008	Age ≥40 yr, annually†
Canadian Task Force on Preventive Health Care	1998–2001	Age 50–69 yr, every 1–2 yr; age 40–49 yr, individualize the decision (every 1–2 yr, if performed)
National Health Service, United Kingdom	2011	Age 47–73 yr, every 3 yr

Adapted from: Breast-Cancer Screening Ellen Warner, M.D. N Engl J Med 2011; 365:1025-1032.

IT TAKES 1900 MAMMOGRAMS OF WOMEN IN THEIR 40s TO SAVE ONE LIFE, BUT ONLY 1300 OF WOMEN IN THEIR 50s!
IT'S MORE COST-EFFECTIVE!
SO JUST WAIT 'TIL YOU'RE 50!
AND STOP CALLING US THE "DEATH PANEL."
NEW BREAST CANCER GUIDE-LINES
U.S. PREVENTATIVE SERVICES TASK FORCE

USPSTF

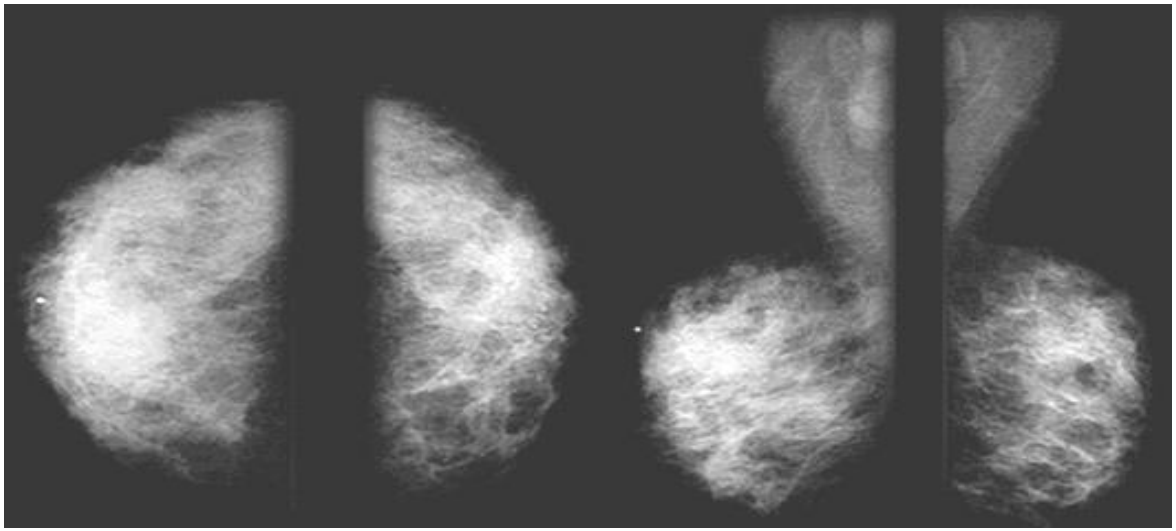
- Independent panel of nonfederal experts in prevention and evidence-based medicine
  - Volunteer members represent primary care disciplines
    - No substantial financial, intellectual, or other conflicts that would impair the scientific integrity of the work of the Task Force

USPSTF

- Rigorous review of existing peer-reviewed evidence
  - Ratings reflect the strength of the evidence on the harms and benefits of a preventive service
    - Task Force does **not** consider the costs of providing service nor make recommendations for coverage

Risks to Mammography

- False positive result leading to recall, with or without biopsy
- False negative result leading to false reassurance
- Overdiagnosis
- Radiation-induced breast cancer



USPSTF Grades

Grade	Evidence	Recommendation
A	High certainty of substantial net benefit	Provide
B	High certainty of moderate net benefit Moderate certainty of moderate/substantial net benefit	Provide
C	Moderate certainty that net benefit is small	Selectively offer/provide
D	No net benefit or harms outweigh benefits	Do not provide
I	Insufficient evidence regarding balance of benefits and harms	

Adapted from: Breast-Cancer Screening Ellen Warner, M.D. N Engl J Med 2011; 365:1025-1032.

Summary of USPSTF 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.

- **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.

Released November 2009

Summary of USPSTF Recommendations

- **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.

- **The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of either digital mammography or magnetic resonance imaging (MRI) instead of film mammography as screening modalities for breast cancer.** Grade: I Statement.

USPSTF Analysis

- Screening mammography mortality reductions in 8 randomized trials are:
  - 15% for women in their 40s
  - 14% for women in their 50s
  - 32% for women in their 60s

Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151:727-737.

Criticisms of 8 screening trials:

Benefits of screening may be underestimated

- Only 61-89% of women invited to be screened actually participated (noncompliance)
- Women in the control group often sought screening on their own (contamination)
- Often used poor quality or single view exams
- Subgroup analysis on 40-49 year old women performed when studies not designed for this

Reflections on the USPSTF Guideline

- The mortality benefit of mammography is likely underestimated by the USPSTF studies
- The harms of screening are lower with digital mammography and are not as detrimental as estimated by the USPSTF
- There is no other effective screening tool for detection of early curable breast cancer…yet

Harms of Screening:

- 8-10% Recall rate
  - Of those recalled:
    - 45% Nothing found on repeat/spot films
    - 20%: Probably benign (6mo repeat)
    - 15% recommended to have a biopsy
    - 2 to 5% will have cancer
- Anxiety
  - Good patient education can help
  - Same day screening results at many sites and those with elevated anxiety
  - Rapid recall of abnormal mammograms, additional imaging and biopsy

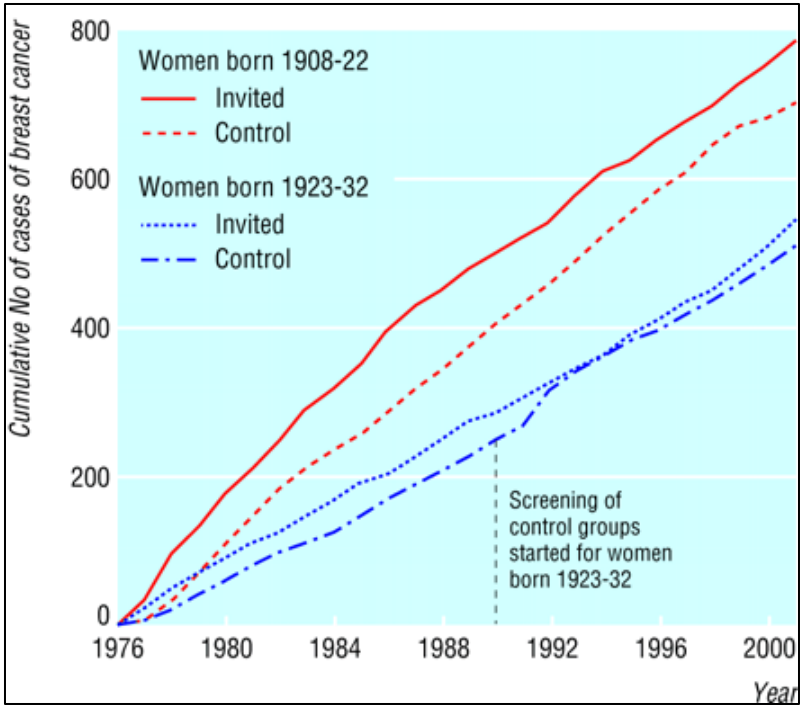
Harm of Screening: Radiation Exposure

- Less ionizing radiation with digital mammography
- The risk of radiation induced breast cancer is much less than benefit of mammography
- Annual screening from age 40-50 results in 36.5 lives saved per life lost

Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2 2006
Average glandular dose 2-4 mGy (200-400 mrad)
Radiation exposure to breasts is 2-4 mSv

Harms of Screening - Overdiagnosis

- Malmo screening trial (43,000 women 1976-1986):
  - Over-diagnosis rate was 10%
- Undiagnosed cancer at autopsy
  - Invasive breast cancer: 1.3%
  - Ductal carcinoma in situ: 8.9%



Zackrisson S, Andersson I, Janzon L. Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. BMJ 2006; 332.

Other Screening Guidelines: ACS

Women at average risk:

Ages 20 to 39

- clinical breast examination at least every three years

Age 40 and over

- annual screening mammography and clinical breast exam

Breast self-exam (BSE) is an option for women starting in their 20s

Elderly women

- continue screening as long as woman is in reasonably good health and would be a candidate for cancer treatment

Women at high (>20% lifetime) risk:

- Annual mammogram and MRI beginning at 30

Women at moderate (15-20% lifetime) risk:

-Annual mammo age 40 + discuss adding MRI to yearly screening (based on risk/benefit)

Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57:75-89

Clinical and self exams:

Organization	Guideline Year	Clinical Breast Exam	Breast Self-Examination
USPSTF	2009	Insufficient evidence	Not Recommended
ACS	2010	Age 20-39: every 3yr Age ≥ 40, annual	Optional, >age 20
NCCN	2011	Age 20-39: every 1-3yr Age ≥ 40, annual	Optional, >age 20
NCI	2010	No age recommendation	Optional
ACP	2007	Not stated	Not stated
ACOG	2003	Age ≥ 20yr, annually	Optional
Amer College of Radiology	2008	Not stated	Not stated
Canadian Task Force- Preventative	2011	Every 1-3 yr, for ages <40 or >70	Not Recommended

Adapted from: Breast-Cancer Screening Ellen Warner, M.D. N Engl J Med 2011; 365:1025-1032.

Breast Density

- Sensitivity and specificity reduced by density
  - Sensitivity 33 to 81%
  - False positives increased
- Breast density is a significant independent risk factor for breast cancer
  - 4-5x relative risk
- Some state laws mandate patient notification and ultrasound evaluation

Cecchini RS, Costantino JP, Cauley JA. Baseline mammographic breast density and the risk of invasive breast cancer in postmenopausal women participating in the NSABP study of tamoxifen and raloxifene (STAR).
Cancer Prev Res. 2012;5(11):1321-9.

Risk assessment tools

- Gail model
  - http://www.cancer.gov/bcrisktool/
- Cancer risk assessment software
  - http://www4.utsouthwestern.edu/breasthealth/cagene/default.asp
  - http://www.hughesriskapps.net/
- Creighton Hereditary Cancer Prevention Clinic
  - http://medschool.creighton.edu/medicine/centers/hcc/index.php

Additional References:

AHRQ (Agency for Healthcare Research and Quality) http://www.guideline.gov/syntheses/synthesis.aspx?id=39251

Mamounas EP, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer CE Jr, Taghian A, Wickerham DL, Wolmark N. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol. 2012;30(32):3960-6.

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Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57:75-89[Erratum, CA Cancer J Clin 2007;57:185.]

Habbema JD, van Oortmarssen GJ, van Putten DJ, Lubbe JT, van der Maas PJ. Age-specific reduction in breast cancer mortality by screening: an analysis of the results of the Health Insurance Plan of Greater New York study. J Natl Cancer Inst 1986;77:317-320.

Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up: a randomized screening trial of mammography in women age 40 to 49 years. Ann Intern Med 2002;137:305-312.

Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet 2002;359:909-919[Erratum, Lancet 2002;360:724.]

Bjurstam N, Bjorneld L, Warwick J, et al. The Gothenburg Breast Screening Trial. Cancer 2003;97:2387-2396

Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. Lancet 2006;368:2053-2060.

Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. J Natl Cancer Inst 2000;92:1490-1499.

Alexander FE, Anderson TJ, Brown HK, et al. 14 Years of follow-up from the Edinburgh randomised trial of breast-cancer screening. Lancet 1999;353:1903-1908.

Humphrey LL, Helfand M, Chan BKS, Woolf SH. Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002;137:347-360

Jonsson H, Bordas P, Wallin H, Nystrom L, Lenner P. Service screening with mammography in northern Sweden: effects on breast cancer mortality -- an update. J Med Screen 2007;14:87-93

Mandelblatt JS, Cronin KA, Bailey S, et al. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. Ann Intern Med 2009;151:738-747

ACS Definitions

High Risk:

- Known BRCA1 or BRCA2 mutation
- First degree relative with BRCA1 or 2 and no testing themselves
- Radiation therapy to the chest between the ages of 10 and 30 yrs
- Have Li-Fraumeni, Cowden, or hereditary diffuse gastric syndromes, or a first degree relative with one of these syndromes
- Risk assessment tools> 20% lifetime

Moderate Risk:

- Personal history of breast cancer, DCIS, lobular neoplasia, atypical ductal hyperplasia
- Have dense breasts at mammography
- Risk assessment tools 15-20% lifetime