Natural History and Epidemiology of Breast Cancer

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Breast Cancer and the Environment

A Life Course Approach

Report of the Institute of Medicine 2011

"Knowing is not enough; we must apply. Willing is not enough; we must do."
—Goethe

Among the environmental factors reviewed, those most clearly associated with increased breast cancer risk in epidemiological studies are:

- use of combination hormone therapy products
- current use of oral contraceptives
- exposure to ionizing radiation
- overweight and obesity among postmenopausal women (Greater physical activity is associated with decreased risk).
- alcohol consumption.
- active smoking.

Available from The National Academies Press at http://www.nap.edu/catalog.php?record_id=13263

Breast Cancer and the Environment

Report of the Institute of Medicine 2011

Evidence "less strong...possible association:"

- passive smoking
- shift work involving nights
- benzene, 1, 3-butadiene, and ethylene oxide.
- bisphenol A or BPA

Evidence showing "Non-Association:"

- non-ionizing radiation
- personal use of hair dyes

Evidence "too limited or inconsistent:"

- nail products
- phthalates

Breast Cancer and the Environment

Report of the Institute of Medicine 2011

Conclusions:

- There is a need for research on the etiology of breast cancer.
- incorporating new understanding of breast development over the life course...elucidating the molecular biology of tumorigenesis...and assessing the impact of a multitude of low level chemical exposures
- a focus...on exposures during adulthood...may miss critical windows during early life in which environmental exposures may influence risk for breast cancer later in life.
- People are exposed to a complex and changing mix of environmental agents over the course of a lifetime...discerning the effects of an individual agent, or knowing whether the components of the mixture may interact to influence the development of disease, is not straightforward.

California Breast Cancer Research Program -- Special Research Initiative

In 2004, the CBCRP Research Council (Council) completed a comprehensive review of the program and decided to allocate 30% of the funding between 2004 and 2009 to a Special Research Initiative (SRI) to support research that addressed:

1. The effects of the environment on the development of breast cancer; and
2. Disparities in breast cancer, i.e., the reasons why some groups of women are more likely to get breast cancer or to die from the disease.

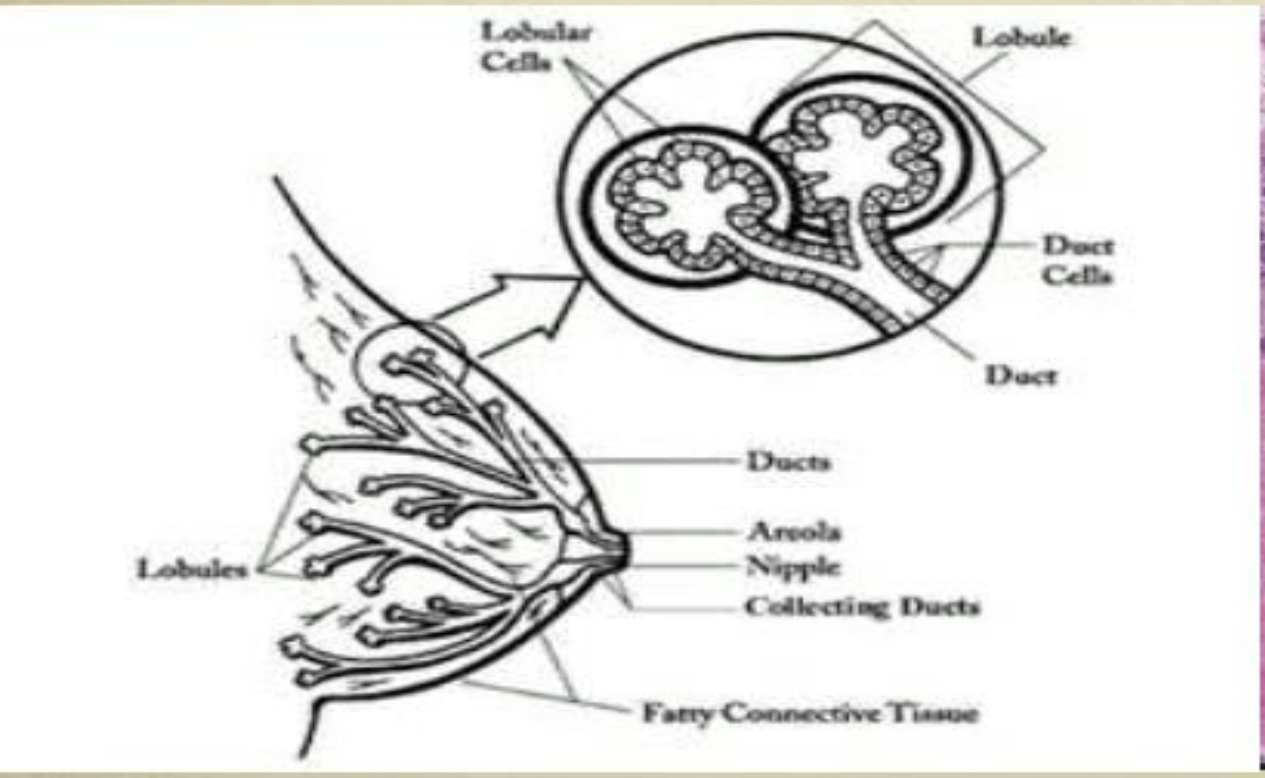
The SRI was so successful, that in 2012, CBCRPs Council increased the allocation to 50% of funding. The focus was expanded to include:

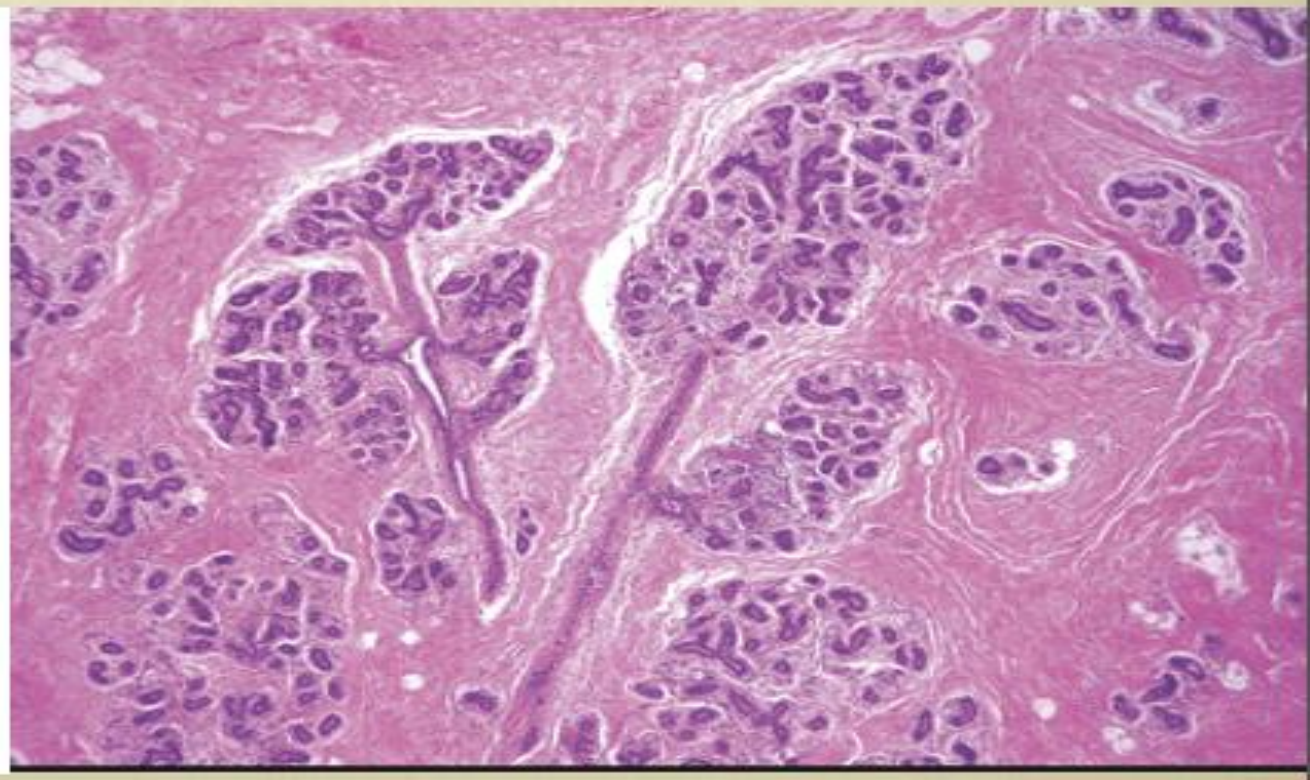
1. Population-level interventions (including policy research) on known and suspected risk factors and protective measures; and
2. Targeted interventions for high-risk individuals including new methods for identifying or assessing risk.

[http://www.cbcrp.org/sri/sri-funded-projects.pdf]

Breast Cancer Facts

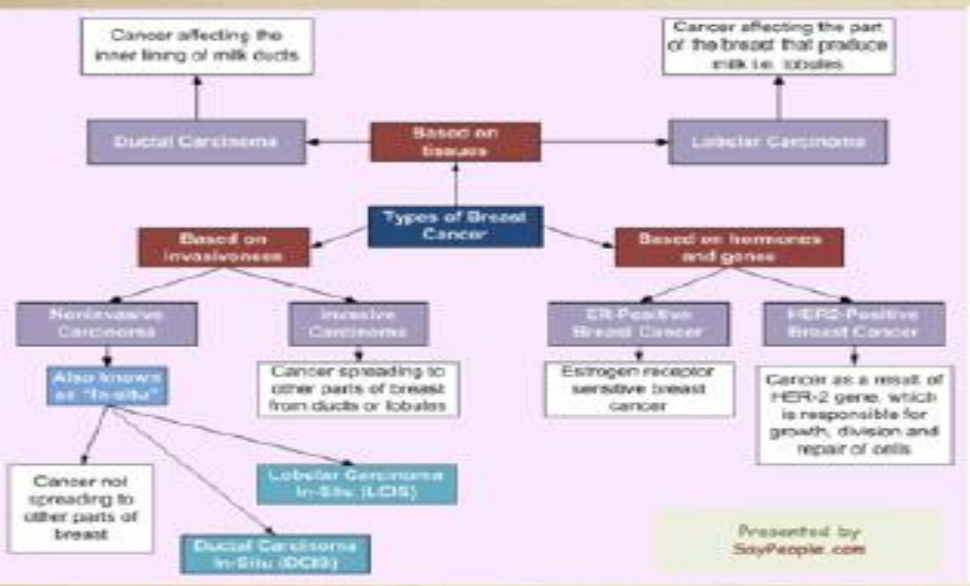
Breast cancer begins in ducts and lobules.

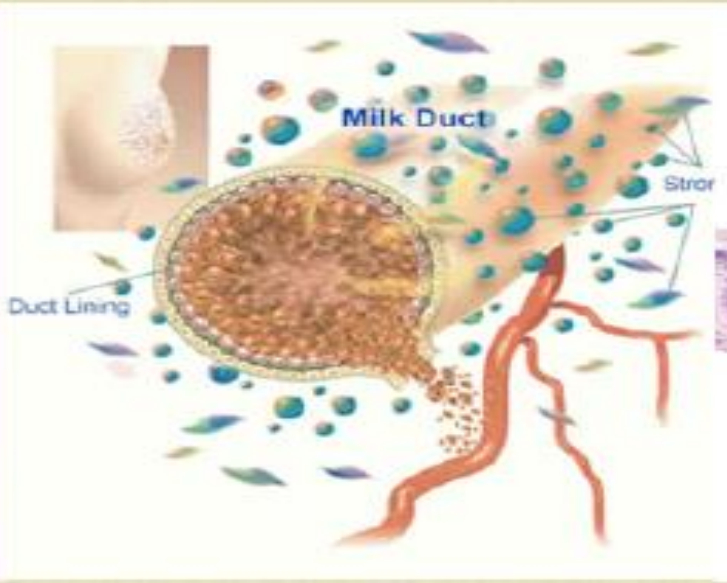


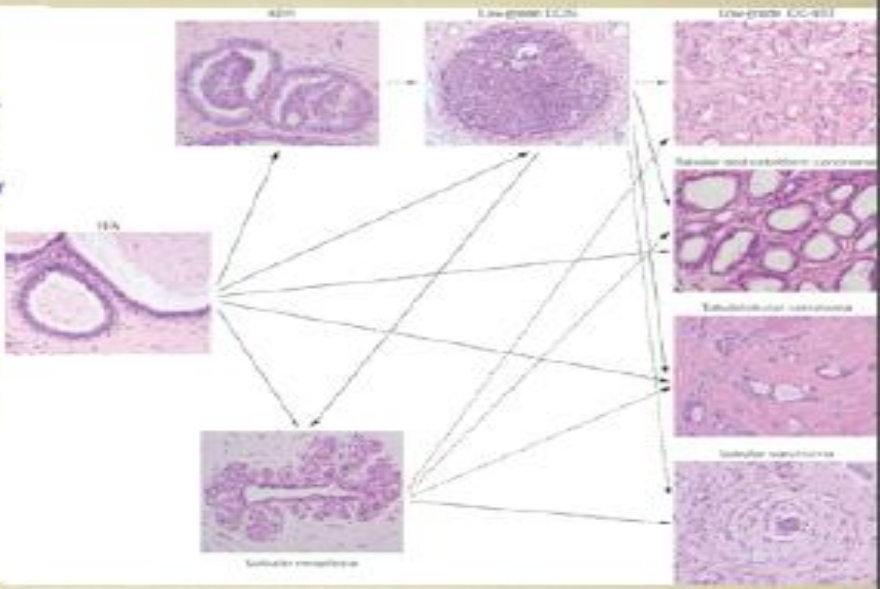


Breast Cancer Facts

Types of Breast Cancer





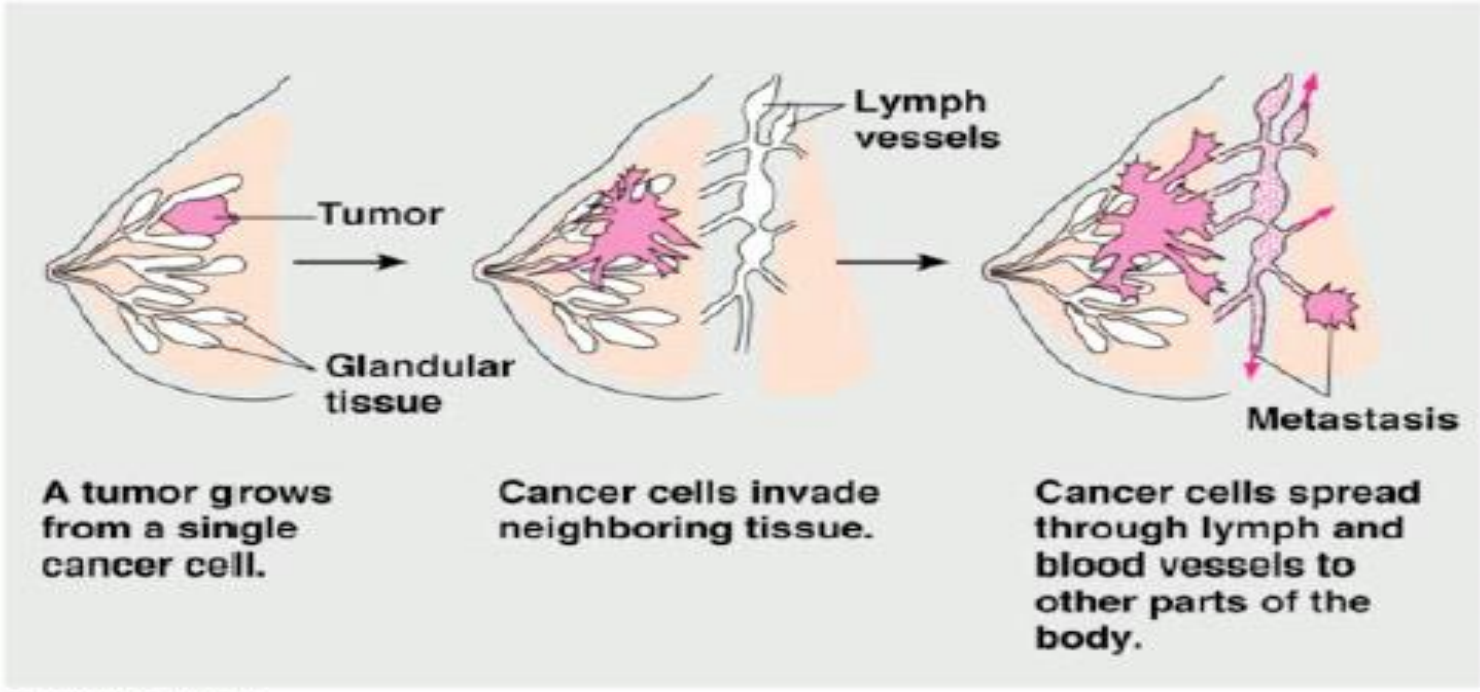


In situ breast cancers are confined within ducts (ductal carcinoma in situ or DCIS) or lobules (lobular carcinoma in situ or LCIS). LCIS (also known as lobular neoplasia) is not a true cancer, but an indicator of increased risk for developing cancer in either breast.

Most, but not all, invasive, or infiltrating breast cancers started in lobules or ducts but broke through the duct or lobule walls to invade the surrounding breast tissue.

Breast Cancer Facts

Staging of Breast Cancer



SEER:
Surveillance, Epidemiology, and End Results Summary Stage system is used in reporting by cancer registries and for public health research.

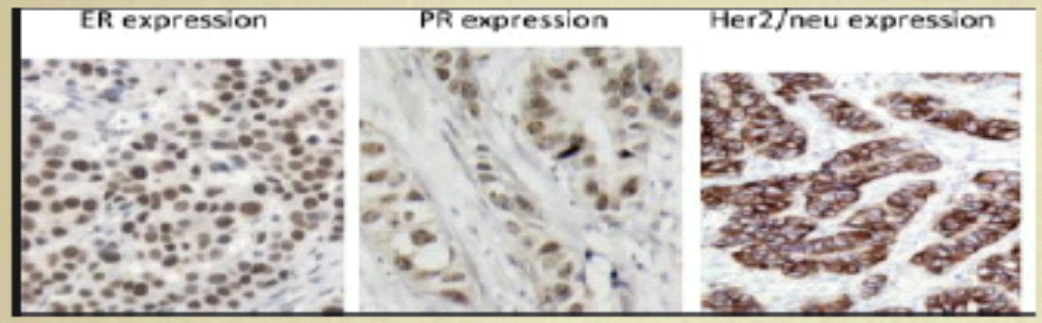
- Local-stage cancers are confined to the breast.
- Regional-stage tumors have spread to surrounding tissue or lymph nodes.
- Distant-stage cancers have metastasized (spread) to distant organs.

TNM (AJCC): Tumor size and how far it has spread within the breast and nearby organs (T), lymph node involvement (N), and presence or absence of spread to distant sites (M). Once T, N, and M are determined, a stage of 0, I, II, III, or IV is assigned. Stage 0 is in situ, stage I is the earliest stage of invasive cancer, and stage IV is the most advanced. The TNM staging system is commonly used in clinical settings.

Breast Cancer Facts

Molecular Markers and Genomic Assays

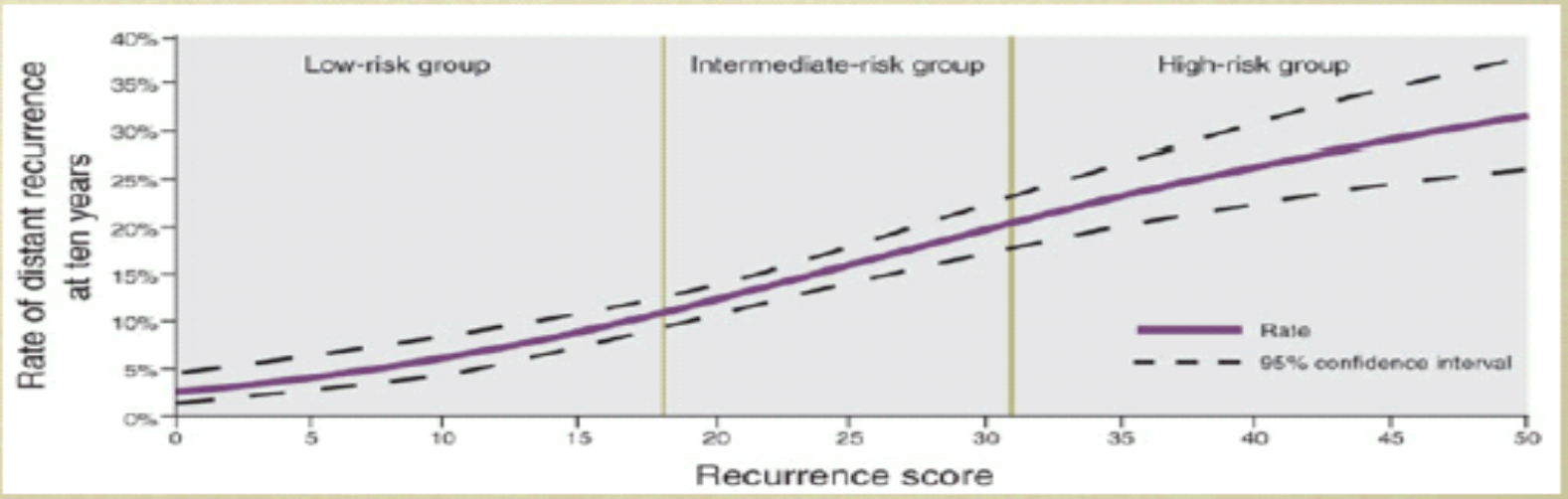
- ER, PR and HER-2/neu.



Estrogen Receptor Assay detects those breast cancers that utilize the hormone estrogen for growth. HER-2/neu is a normal gene that is responsible for activating growth pathways in the breast cancer cell. Both provide very effective targets for therapeutic intervention.

- Genomic Assays:

There are commercially available genomic assays that can be used to predict which breast cancers are most aggressive. They can be used to select patients for more aggressive therapy.



Breast Cancer Facts

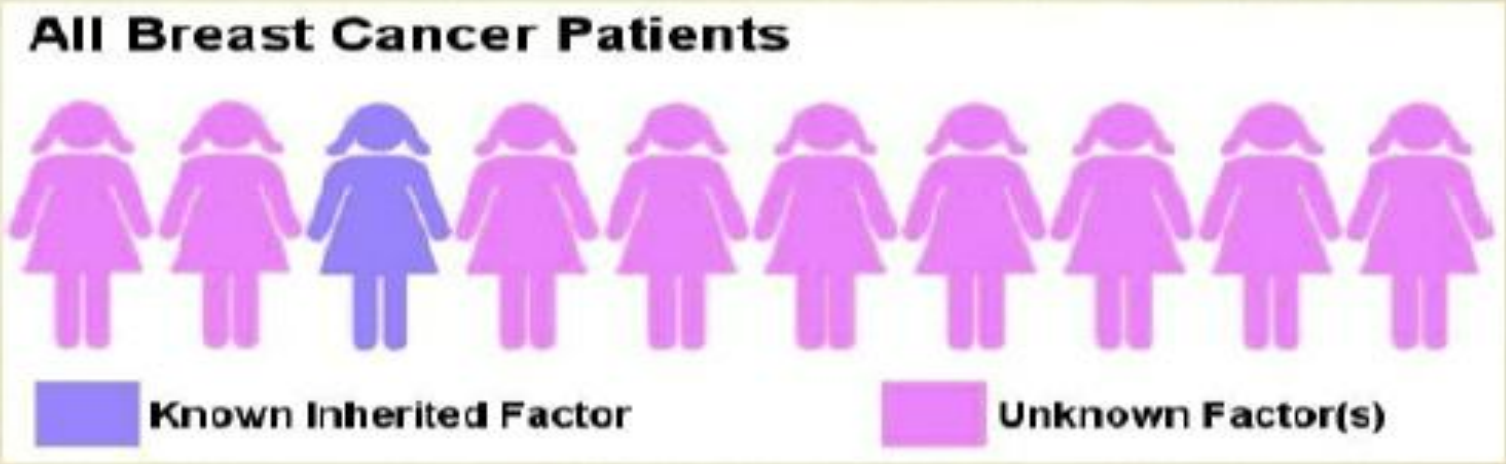
Genetics of Breast Cancer Risk

- About 1 in 10 women with breast cancer have a detectable inherited genetic risk.

- Hereditary Breast and Ovarian Cancer Syndrome (BRCA 1 and 2 gene mutation) - by far the most common of the gene mutations associated with Breast Cancer. Autosomal dominant genes found on Chromosome 13 and 17 and responsible for DNA repair.

Personal History:
- Breast cancer at <50 y.o.
- Bilateral breast cancer
- Ovarian cancer
- Triple negative breast cancer

Family History:
- 2 or more family members with breast cancer at <50 y.o.
- Breast and ovarian cancer
- Askenazi Jewish heritage
- Male breast cancer



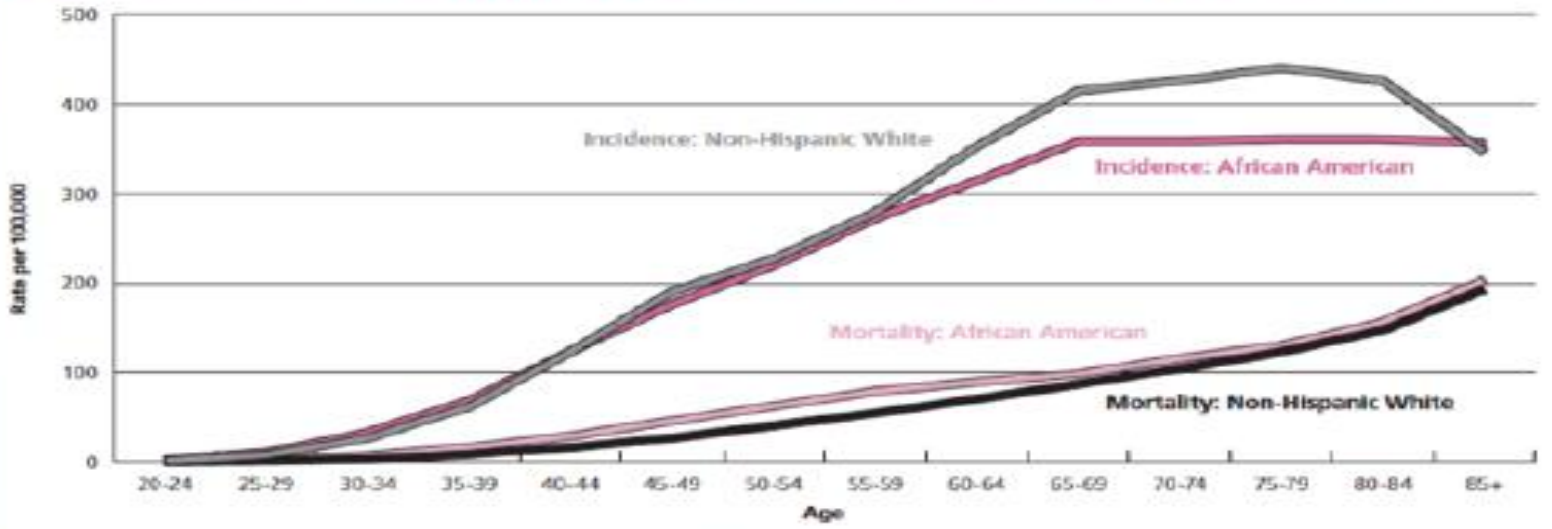
- Lynch Syndrome [MisMatch Repair (MMR) genes: MLH1 and MSH2], Li-Fraumeni Syndrome (TP53 gene mutation), Cowden Syndrome (PTEN gene mutation), Peutz-Jeghers Syndrome (STK11 gene mutation).

Breast Cancer Facts

Who Gets Breast Cancer?

The most common non-skin cancer among women, accounting for nearly 1 in 3 cancers diagnosed in US women. Incidence and death rates increase with age. Ninety-five percent of new cases and 97% of breast cancer deaths occur in women 40 years of age and older. The median age at the time of breast cancer diagnosis is 61 years.

Figure 1. Age-specific Female Breast Cancer Incidence (2004-2008) and Mortality (2003-2007) Rates



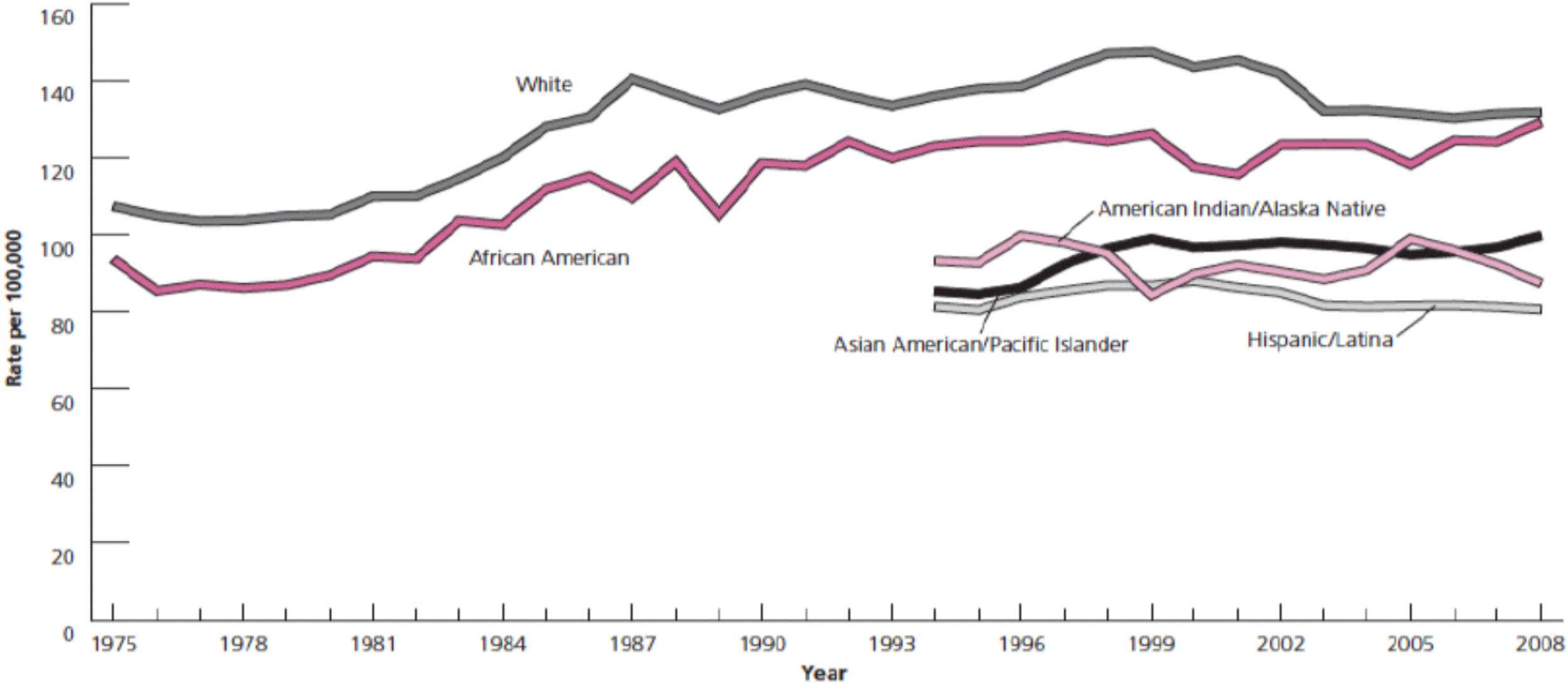
Sources: Incidence: North American Association of Central Cancer Registries. Mortality: National Center for Health Statistics, Centers for Disease Control and Prevention, as provided by the Surveillance, Epidemiology, and End Results Program, National Cancer Institute.

American Cancer Society, Surveillance Research, 2011

Incidence rates are higher in non-Hispanic white women compared to African American women for most age groups.

African American women have a higher incidence rate before age 40, and are more likely to die from breast cancer at every age.

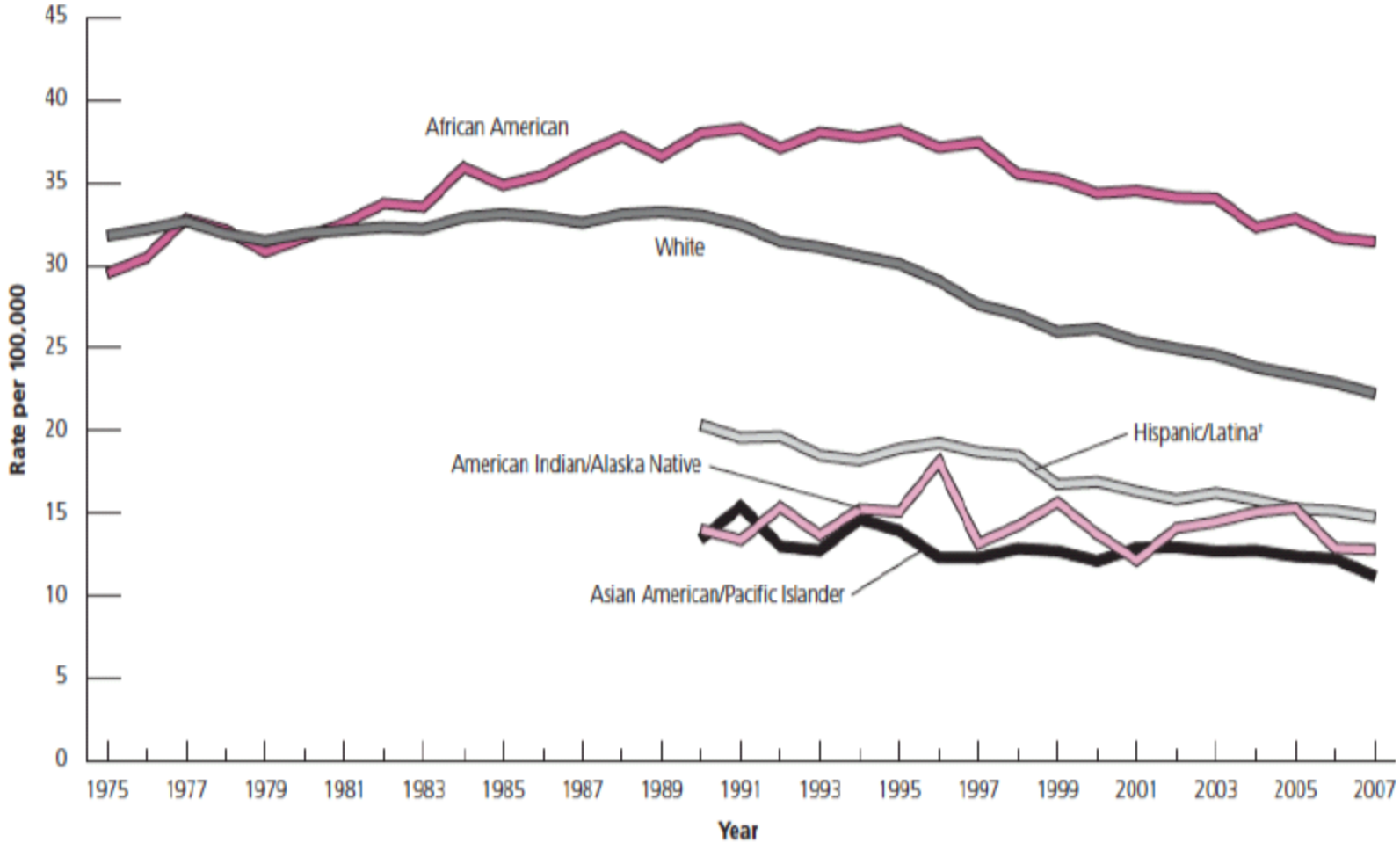
Figure 5a. Trends in Female Breast Cancer Incidence Rates* by Race and Ethnicity, US, 1975-2008



*Rates are age adjusted to the 2000 US standard population. Rates for Asain American/Pacific Islanders, Hispanic/Latinos, and American Indian/Alaska Natives are 3-year moving averages.

Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. Data for whites and African Americans are from the 9 SEER registries and were adjusted for reporting delays. Data for other races/ethnicities are from the 13 SEER registries. For Hispanics, incidence data do not include cases from the Alaska Native Registry. Incidence data for American Indians/Alaska Natives are based on Contract Health Service Delivery Area (CHSDA) counties.

Figure 5b. Trends in Female Breast Cancer Death Rates* by Race and Ethnicity, US, 1975-2007

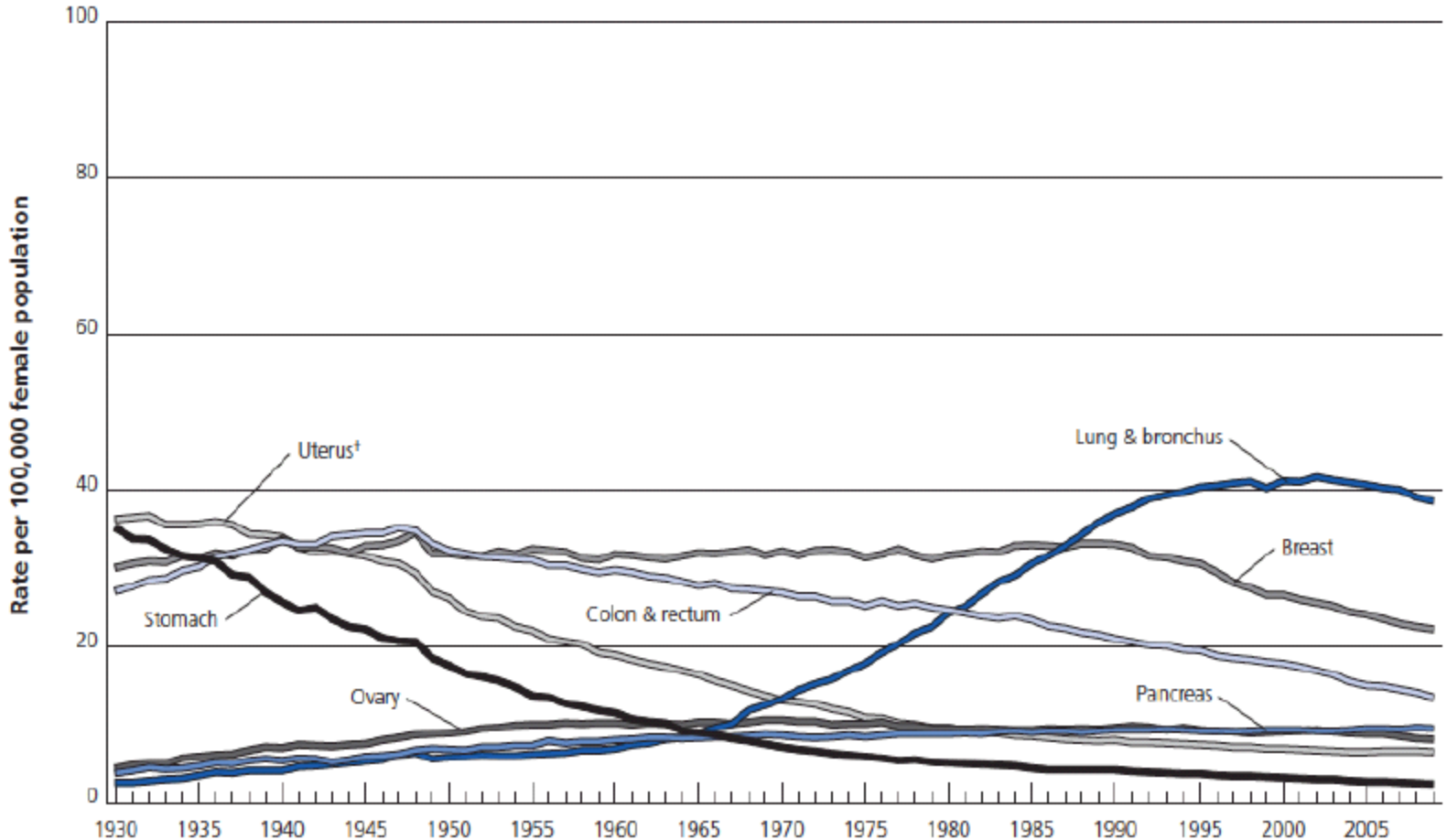


*Rates are age adjusted to the 2000 US standard population. † Information is included for all states except Connecticut, Louisiana, Maine, Maryland, Minnesota, Mississippi, New Hampshire, New York, North Dakota, Oklahoma, Vermont, and Virginia, as well as the District of Columbia.

Source: National Center for Health Statistics, Centers for Disease Control and Prevention, as provided by the Surveillance, Epidemiology, and End Results Program, National Cancer Institute.

American Cancer Society, Surveillance Research, 2011

Age-adjusted Cancer Death Rates*, Females by Site, US, 1930-2009



*Per 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the lung and bronchus, colon and rectum, and ovary are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

Why is Breast Cancer Mortality Down 30% in the last 25 years?

- Breast Cancer Screening - early detection and prevention.
- Improved treatment (and efficient clinical trials).

  Surgery is trending toward "less is better."

  Radiation limits risk of local and regional recurrence.

  Adjuvant systemic therapies reduce risk of systemic recurrence (the main cause of death from breast cancer).

  Treatment for recurrences is more effective.

Breast Cancer Facts

Signs, Symptoms and Diagnosis

- Breast cancer typically produces no symptoms when the tumor is small and most treatable, which is why it is so important for women to follow recommended screening guidelines for detecting breast cancer at an early stage, before symptoms develop.

- The most common physical sign is a painless lump.
- Sometimes breast cancer can spread to underarm lymph nodes and cause a lump or swelling, even before the original breast tumor is large enough to be felt.
- Less common signs and symptoms include breast pain or heaviness; persistent changes to the breast, such as swelling, thickening, or redness of the breast's skin; and nipple abnormalities such as spontaneous discharge (especially if bloody), erosion, inversion, or tenderness.
- Any persistent abnormality in the breast should be evaluated by a physician as soon as possible.

Screening Guidelines for the Early Detection of Breast Cancer, American Cancer Society (...and accepted by every major organization of breast cancer clinicians)

- Yearly mammograms, starting at age 40, and continuing for as long as a woman is healthy.
- A clinical breast exam should be part of a periodic health exam, about every three years for women in their 20s and 30s, and every year for women 40 and older.
- Women should know how their breasts normally feel and report any breast changes promptly to their health care providers. Breast self-exam is an option for women starting in their 20s.
- Women at increased risk (e.g., family history, genetic tendency, past breast cancer) should talk with their doctors about the benefits and limitations of starting mammography screening earlier, having additional tests (e.g, breast ultrasound and MRI), or having more frequent exams.

CLINICAL GUIDELINES | Annals of Internal Medicine

Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement

- THE USPSTF RECOMMENDS AGAINST ROUTINE SCREENING MAMMOGRAPHY IN WOMEN AGED 40 TO 49 YEARS.
- THE USPSTF RECOMMENDS BIENNIAL SCREENING MAMMOGRAPHY FOR WOMEN BETWEEN THE AGES OF 50 AND 74 YEARS.
- 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.

Ann Intern Med. 2009;151:716-726

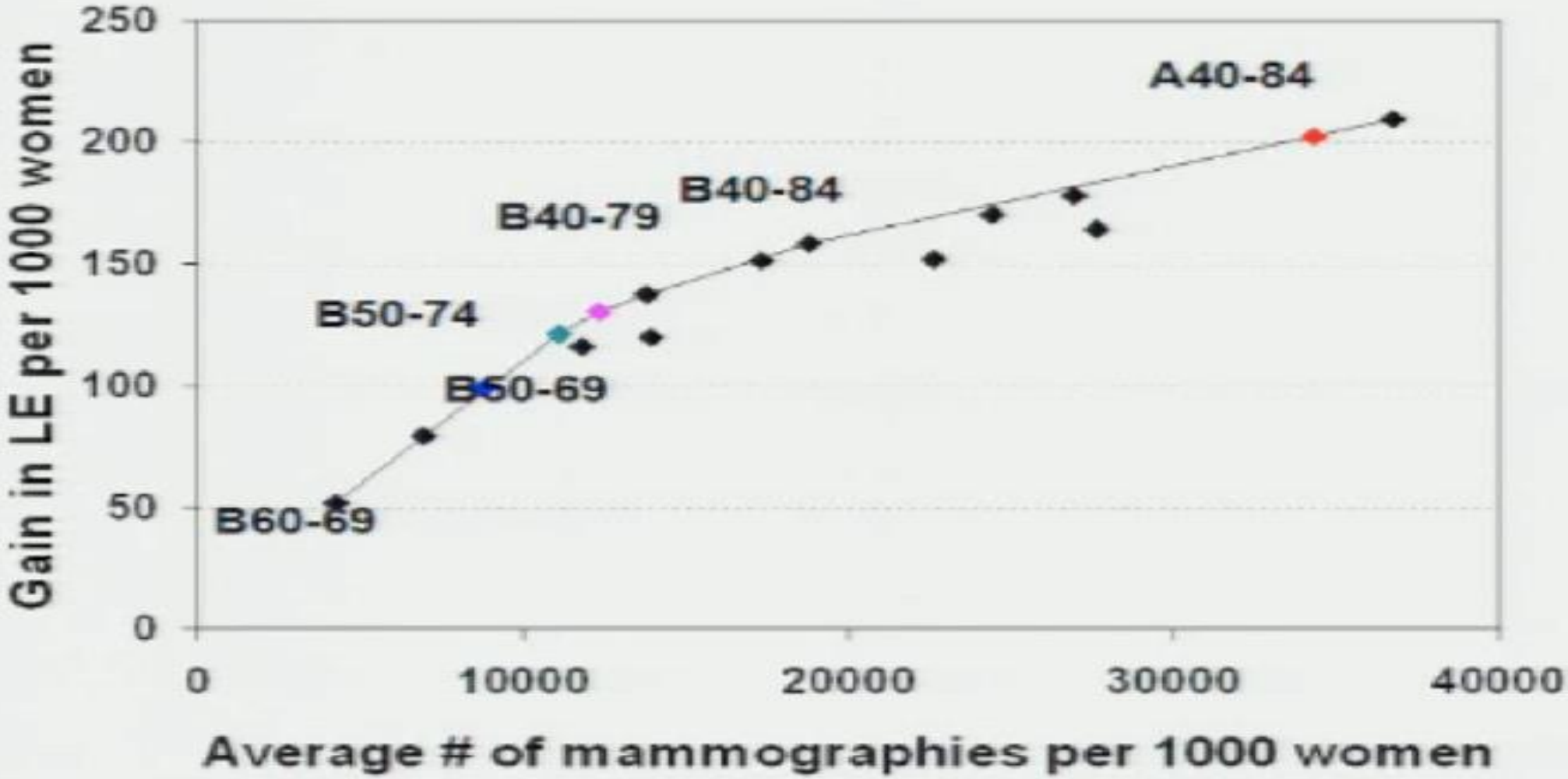
CLINICAL GUIDELINES | Annals of Internal Medicine

Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement

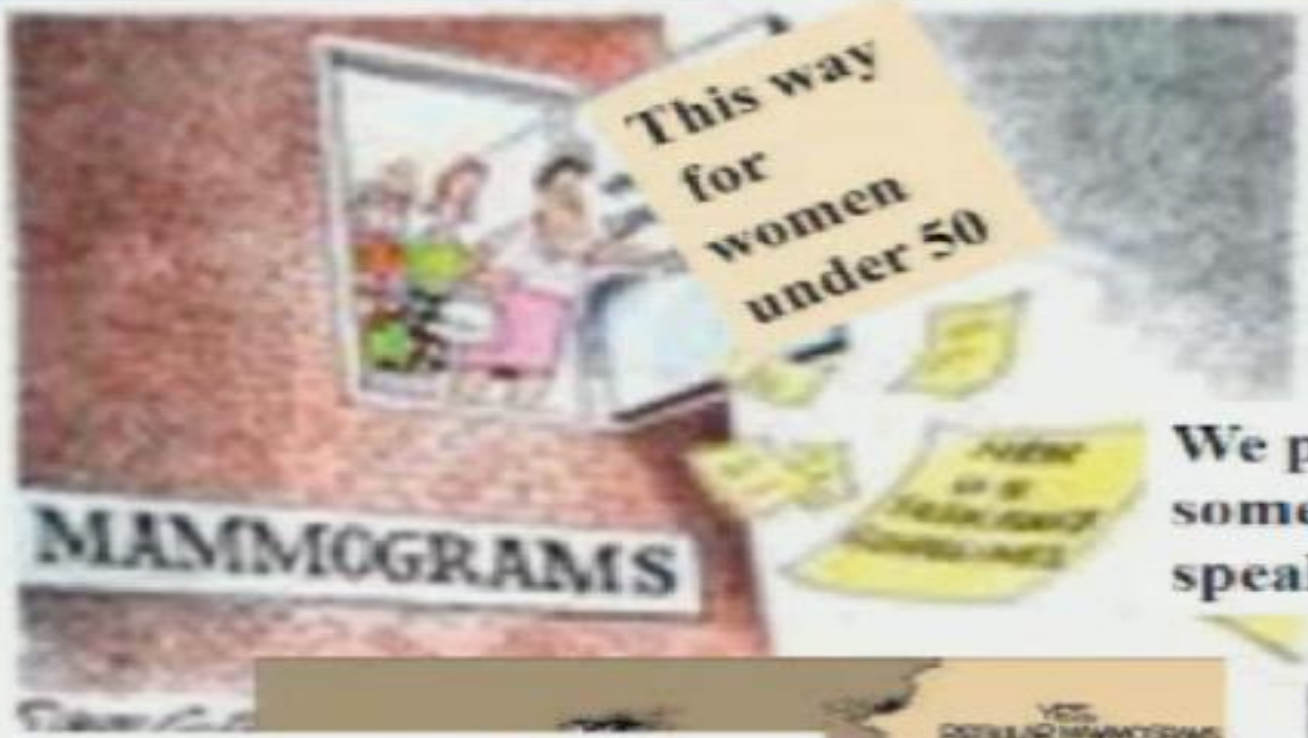
- THE USPSTF CONCLUDED THAT EVIDENCE WAS INSUFFICIENT TO RECOMMEND CLINICAL BREAST EXAMINATION BEYOND SCREENING MAMMOGRAPHY IN WOMEN 40 YEARS OR OLDER.
- THE USPSTF RECOMMENDED AGAINST TEACHING WOMEN HOW TO PERFORM BREAST SELF-EXAMINATION.
- THE USPSTF CONCLUDES THAT EVIDENCE WAS INSUFFICIENT TO ASSESS BENEFITS AND HARMS OF DIGITAL MAMMOGRAPHY OR MAGNETIC RESONANCE IMAGING INSTEAD OF FILM MAMMOGRAPHY .

Ann Intern Med. 2009;151:716-726

Results: Efficiency Frontier of Non-dominated Strategies - Life Years Gained

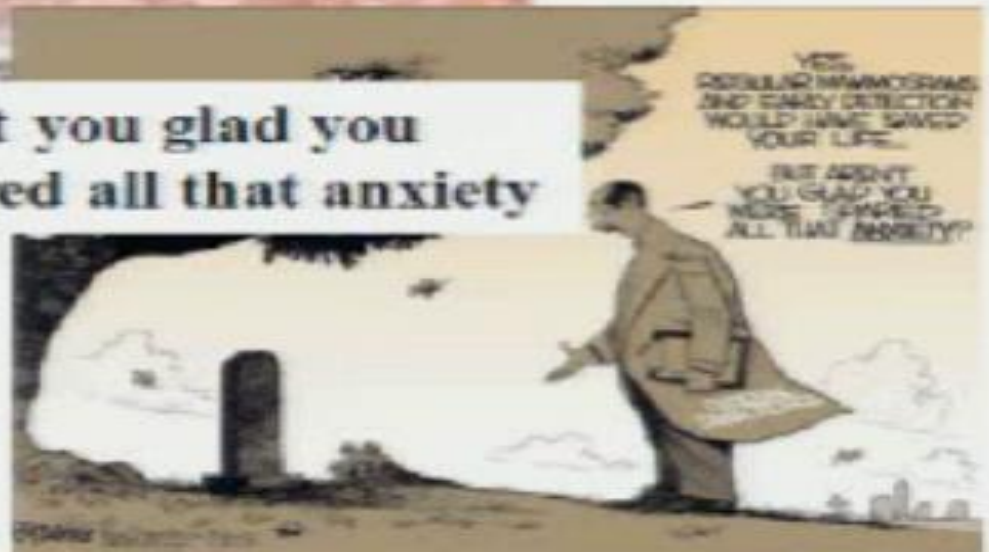


Public Response



We pray that the dearly departed can take some comfort knowing that, statistically speaking, she probably isn't dead

But aren't you glad you were spared all that anxiety



Scientific Responses

More Mammography Muddle:
Emotions, Politics, Science, Costs, and Polarization[1]

Editorials

The New Mammographic Screening Guidelines
What Were They Thinking?

Revealing Oz Behind the Curtain: USPSTF Screening Mammography Guidelines and the Hot Air Balloon

The 2009 U.S. Preventive Services Task Force Guidelines Ignore Important Scientific Evidence and Should Be Revised or Withdrawn[1]

Brawling Over Mammography

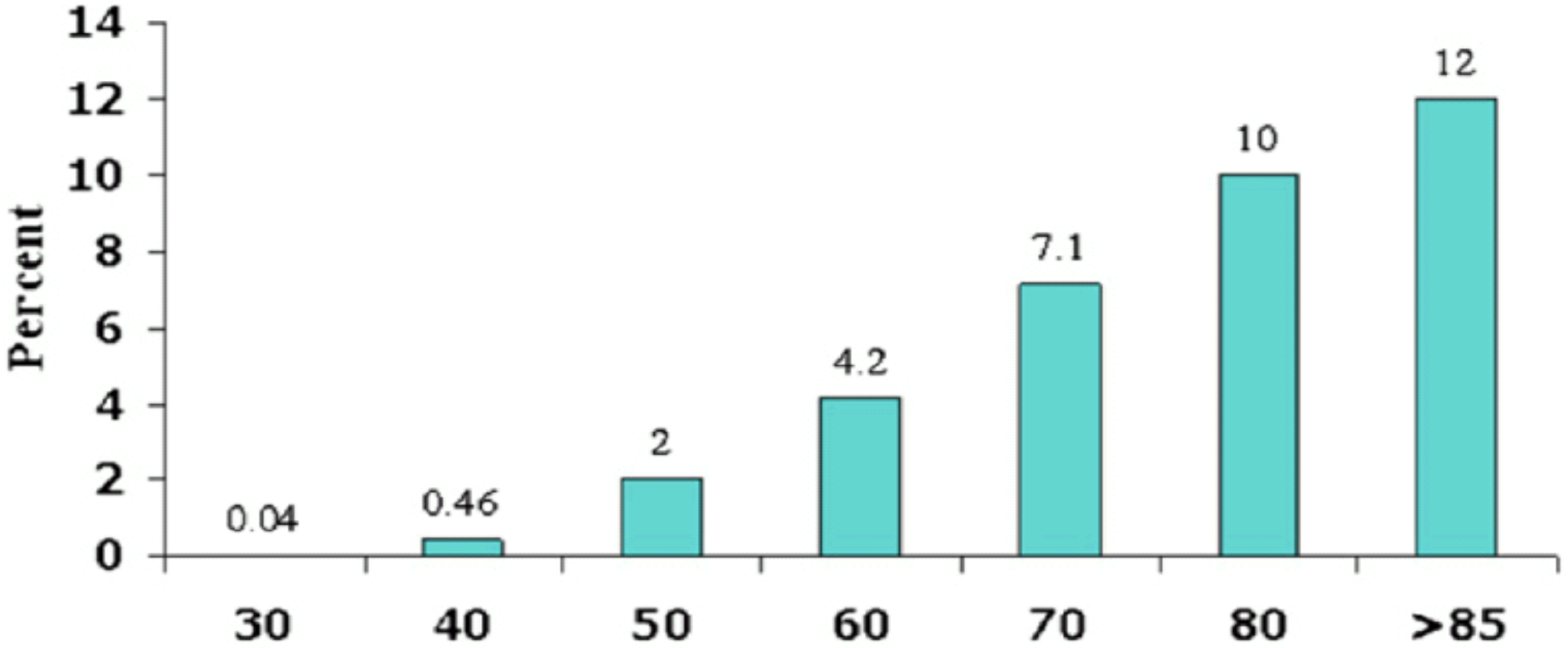
A scientific study of the benefits and harms of screening women in their 40s got buried by politics

Annals of Internal Medicine

EDITORIAL

When Evidence Collides With Anecdote, Politics, and Emotion: Breast Cancer Screening

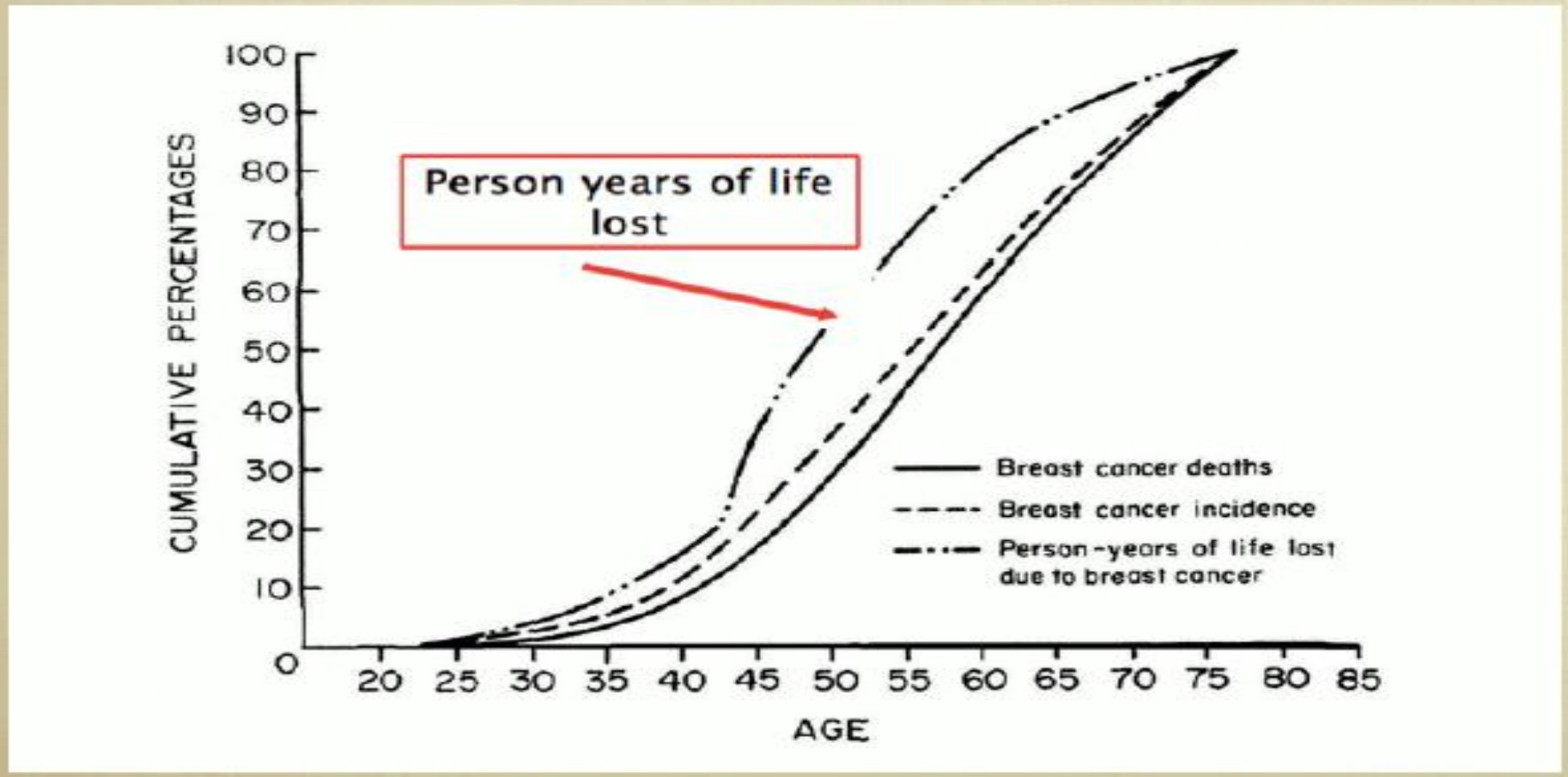
Probability of Developing Breast Cancer by Age



Greif JM. Mammographic screening for breast cancer. An invited review of the benefits and costs. Breast. 2010 Aug;19(4):268-72. Epub 2010 Apr 3. PMID:20371181.

Beginning screening at age 40.... the origins of a decision

That breast cancer diagnoses between ages 40-49 accounted for 34% of all premature mortality attributable to breast cancer led to setting age 40 as the lower boundary for the HIP trial.



Cumulative percentage distributions of breast cancer deaths, incidence, and person years of life lost to breast cancer, ages 20-79. Source: Shapiro S, et al, 1988

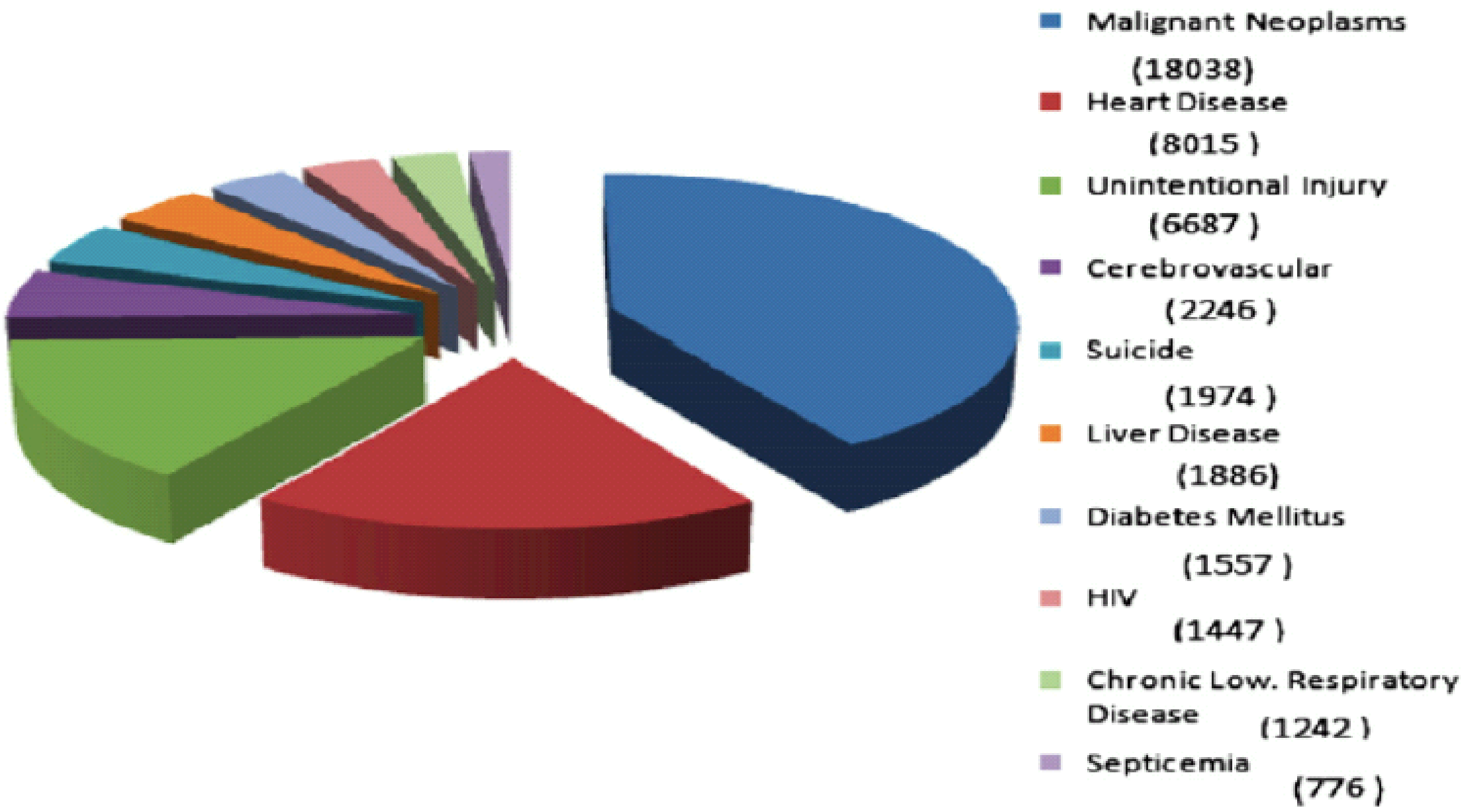


Fig. 2. Causes of death (actual numbers) in women between the ages of 40–50 in the United States, 2006.[13]

And, the most frequent female cancer in the 40-50 year age group, and all age groups, is breast cancer

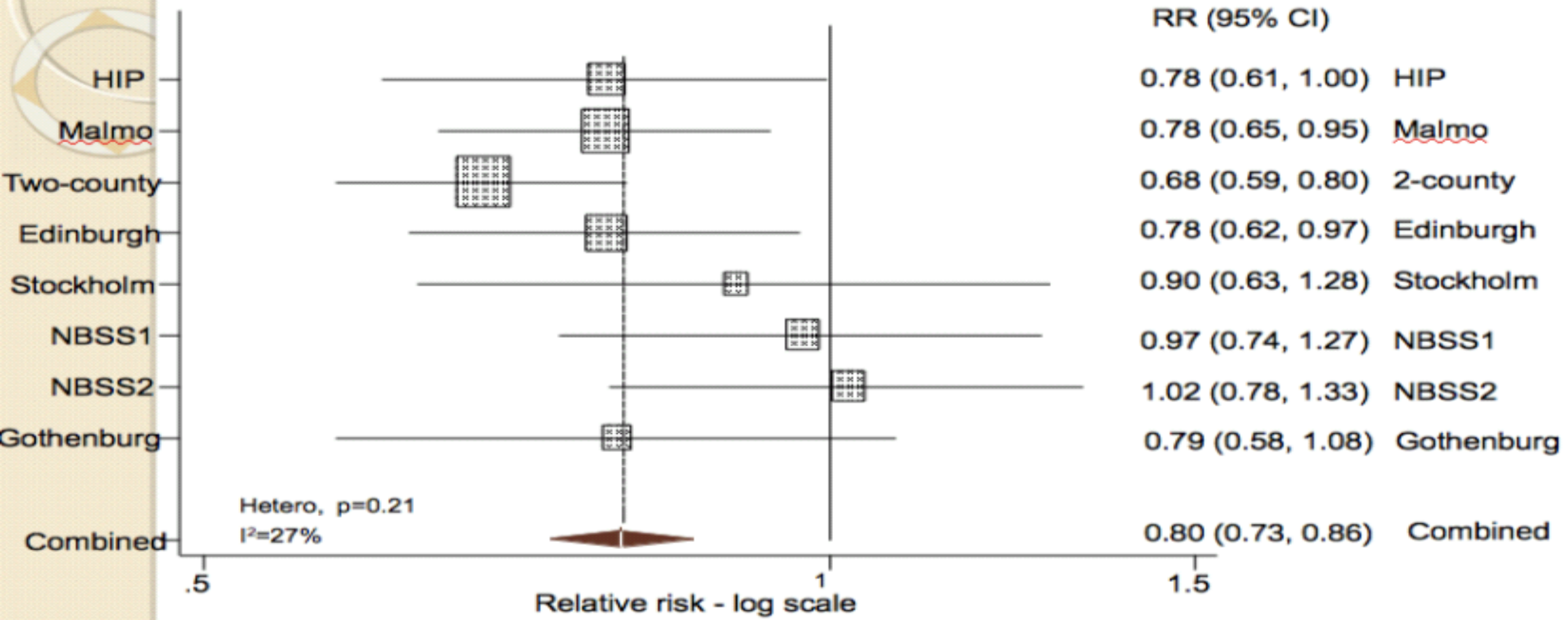
Estimated new female breast cancer cases and deaths by age (USA, 2009), rounded to the nearest 10.

Age	In situ cases	Invasive cases	Deaths
Younger than 45	6460	18,640	2820
45 and older	55,820	173,730	37,350
Younger than 55	24,450	62,520	8890
55 and older	37,830	129,850	31,280
Younger than 65	40,940	120,540	17,200
65 and older	21,340	71,830	22,970
All ages	62,280	192,370	40,170

Data source: Estimated cases are based on 1995–2005 incidence rates from 41 states as reported by NAACCR, representing about 85% of the US population. Estimated deaths are based on data from US mortality Data, 1969–2005, National Center for Health Statistics, Centers for Disease Control and Prevention, 2009. American Cancer Society, Surveillance Research, 2009.[12]

Greif JM. Mammographic screening for breast cancer. An invited review of the benefits and costs. Breast. 2010 Aug;19(4):268-72. Epub 2010 Apr 3. PMID:20371181.

RCTs – all ages



Overall, 20% reduction in breast cancer mortality associated with invitation to screening mammography

Hendrick RE. Benefit of screening mammography …meta-analysis of randomized controlled trials. J Natl Cancer Inst Monogr 22:87–92, 1997.

"All the News That's Fit to Print"

The New York Times

Late Edition

Today, sun and some clouds, cold, high 27. Tonight, snow late, 1 to 3 inches, low 23. Tomorrow, heavy snow, sleet, rain, 6 to 10 inches, high 35. Weather map is on Page A22.

VOL. CLXIII . . . No. 56,410 © 2014 The New York Times NEW YORK, WEDNESDAY, FEBRUARY 12, 2014 $2.50

VAST STUDY CASTS DOUBTS ON VALUE OF MAMMOGRAMS

DEATH RATE NO LOWER

A 25-Year Project Finds Breast Cancer Tests Can Be Harmful

By GINA KOLATA

One of the largest and most meticulous studies of mammography ever done, involving 90,000

HOUSE APPROVES HIGHER DEBT LIMIT WITHOUT CONDITION

Boehner Ends 3 Years of Showdowns — Sharp Setback for Conservatives

By JONATHAN WEISMAN and ASHLEY PARKER

WASHINGTON — Ending three years of brinkmanship in which the threat of a devastating default on the nation's debt was used to wring conservative concessions from President Obama,

positive step in moving away from the political brinkmanship that's a needless drag on our economy," Jay Carney, the White House press secretary, said in a statement.

The study included 89,835 women enrolled at 15 centers in six Canadian provinces. During the 5-year mammographic-screening period, 666 invasive cancers were diagnosed in the mammography arm and 524 in the control group. Additionally, 180 women randomized to mammography died of breast cancer, as did 171 in the control group. The hazard ratio (HR) for breast cancer-specific mortality during the screening period was 1.05 for mammography versus control.

During the entire study, 3,250 women in the mammography group developed breast cancer compared with 3,133 in the control group, and 500 breast cancer deaths occurred in the mammographically screened patients versus 505 in the control group, resulting in an HR of 0.99.

Quick Retorts from ACR, SBI, ACS and others...

The publication drew a quick and forceful response from the American College of Radiology (ACR) and the Society of Breast Imaging (SBI). In a joint statement, officials of the two organizations characterized the results as "an incredibly misleading analysis based on the deeply flawed and widely discredited Canadian National Breast Screening Study (CNBSS)." Noting the 32% rate of cancer detection by mammography, the ACR and SBI said "this extremely low number is consistent with poor-quality mammography." Mammography alone should detect twice that many cancers, they added. The organizations noted that a prior outside review of the CNBSS confirmed the poor quality of mammography in the study.

The ACR/SBI statement also questioned the randomization process used by CNBSS, pointing out that all women had a clinical breast examination prior to allocation, providing investigators with advance knowledge about which patients had breast lumps or enlarged lymph nodes.

The findings should come as no surprise, said Richard Wender, MD, of the American Cancer Society (ACS). "The CNBSS has been an "outlier" from the initial report, and the lack of benefit with mammography wouldn't be expected to change with additional follow-up."

What about "Risk of Radiation" from Mammographic Screening?

If a woman had annual screening mammography for fifty years (two x-ray views per breast @ 0.3 cGy per study), beginning at age 40 years and continuing until age 90, she will have received a total of 10 rads to 20 rads per breast over the course of 50 years and will have increased her risk of developing breast cancer by 0.0012%.

THE ROANOKE TIMES
Monday, September 20, 2004

STEPHANIE KLEIN-DAVIS | The Roanoke Times

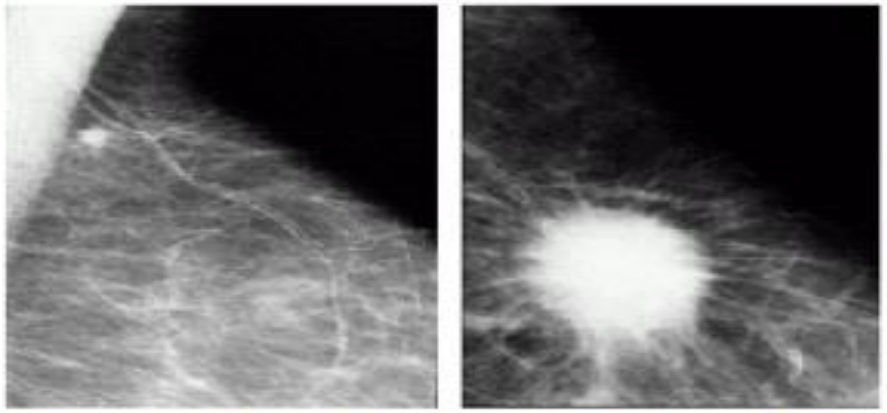
Mellisa Williamson, 35, a Bullitt Avenue resident, worries about the effect on her unborn child from the sound of jackhammers.

TRAFFIC: Official says wait for end result

The Importance of Screening Interval

When screening women every 24 months, women < age 50 have worse tumor characteristics and higher interval cancer rates (sojourn time is less). To successfully screen women under age 50, the screening interval should be less (12 months).

The **preclinically detectable phase** is the period during which asymptomatic breast cancer is detectable



Sojourn time Time is the time it takes to become clinically detectable

Expected Relative Mortality By Screening Interval, by Age Group

Screening Interval	40-49	50-59	60-69
1 Year	0.64%	0.54%	0.56%
2 Years	0.82%	0.61%	0.61%
3 Years	0.96%	0.66%	0.66%

Source: Falun Report. Int J Cancer 1996;68:693-99

Abstract #24, 2009 ASCO Breast Cancer Symposium, San Francisco.

Death from breast cancer occurs predominantly in women not participating in mammographic screening

Author(s):
B. Cady, M. Webb, M. Webb, J. Michaelson, B. I. Smith; Cambridge Hospital, Brookline, MA; Harvard College, Cambridge, MA; Massachusetts General Hospital, Boston, MA

Death from Breast Cancer

Results:

Of Massachusetts Breast Cancer Deaths:

74.8% occur in the 20% of unscreened women

25.2% occur in the 80% of screened women

38% of deaths in screened women from palpable interval cancers

83% occur from palpable cancers

17% occur from non-palpable cancers

2011 CARBHC Screening Results

- Total cancers detected through screening mammography: 262
- Total cancers detected in patients who are not included in current USPHS TF screening guidelines: **70**
- # of Women ages 40-49: **26**
- # of Women beyond the age of 74: **44**

Is Breast Self Exam Useful?

Method of Diagnosis amongst consecutive women with newly diagnosed Breast Cancer at a University Cancer Center Clinic:

- Mammogram: 16%
- Health Care Provider: 9%
- Spouse: 2%
- **Patient Herself /Self Exam: 75% (p<0.05, CI 61-85%)**
  - No significant difference by education, income level, insurance status, or frequency of mammography!
  - Much less likely to be early stage (O.R. 3.9, p<0.05) than if found on mammogram.

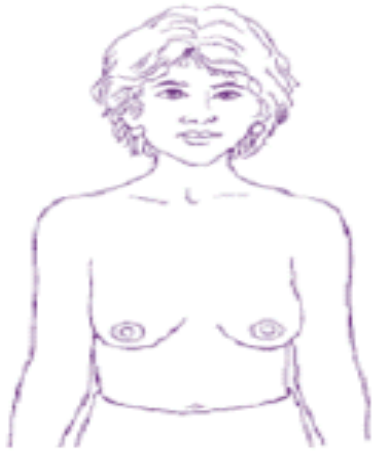
Rosenberg A, et al: Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007.

Follow the *7 "Ps"* of BSE:

1 *Positions* (Stand & Lie Down)

Stand to *look* at your breasts:

Standing in front of a mirror, in each of 3 positions, look for changes in size and shape of the breasts, color and texture of the nipples and skin and direction your nipples point.



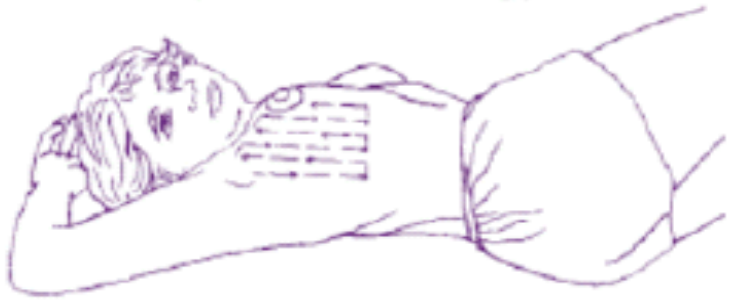
arms relaxed at side

arms raised above head

hands on hips

Lie down to *feel* your breasts:

Side-lying Position: Lie on the opposite side of the breast to be examined with your shoulder and hip facing the wall. Rotate just the shoulder (on the same side as the breast to be examined) back to the flat surface. Put the back of your hand on your forehead. Use this position to examine the outer half of your breast to the nipple.



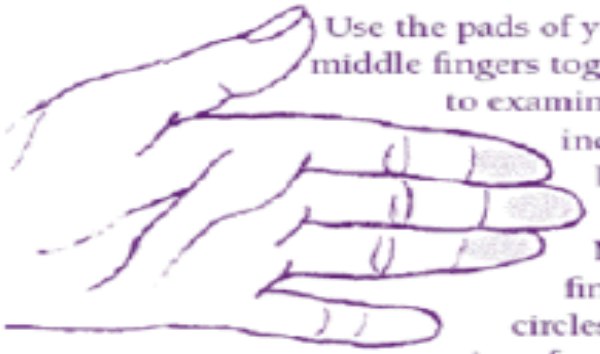
Flat position: When you get to the nipple, lie flat on your back with your arm at a 90° angle to examine the other half of the breast.

Use your left hand to palpate the right breast and your right hand to palpate the left.

2 *Perimeter* (Where to Feel)

The exam area has five sides starting in your armpit down the imaginary **seam of your blouse**, across your **braline**, up your **breast bone**, across your **collarbone** and **back to your armpit**. Most breast cancers are found in the upper outer area of the breast (shaded area).

3 *Palpation with Pads of Fingers* (How to Feel)



Use the pads of your three middle fingers together, to examine every inch of your breast tissue. Move your fingers in circles about the size of a dime.

CALIFORNIA Breast Cancer Research PROGRAM

The Cost of Breast Cancer in California

Institution: University of California, San Francisco
Investigator(s): Wendy Max , Ph.D. -
Award Cycle: 2003 (Cycle IX) **Grant #:** 9PB-0025
Award Type: Request for Applications
Research Priorities
Health Policy & Health Services>Health Policy and Health Services: better serving women's needs

1. In 2001 there were 12,934 cases of breast cancer treated in CA. Total costs (hospital charges, doctors fees, medications, etc.) were $279 million.

2. 4,226 women died of breast cancer in CA in 2001. These deaths cost the state $1.1 billion in lost productivity and 100,000 years of life lost. (Average $272,000 and 22.9 years per life lost).

3. Stage of disease at diagnosis was the single most important factor in treatment costs: $21,320 for Stage 0

$26,747 for Localized Disease

$40,096 for Regional Disease

$52,288 for Metastatic Disease

[http://www.cbcrp.org/]

From Cancer Patient to Cancer Survivor
Lost in Transition
A Report of the Institute of Medicine 2006

- There are more than 20 million cancer survivors living in the U.S.
- Some cancer survivors recover with a renewed sense of life and purpose.
- What has often not been recognized is the toll taken by both cancer and its treatment—on health, functioning, sense of security, and well-being.
- Long-lasting effects of treatment may be apparent shortly after its completion or arise years later.
- Personal relationships change and adaptations to routines and work may be needed.
- The survivor's health care is forever altered.

Cancer Survivorship

IOM Recommendations:

- Health care providers, patient advocates, and other stakeholders work to raise awareness of the needs of cancer survivors, establish cancer survivorship as a distinct phase of cancer care, and act to ensure the delivery of appropriate survivorship care.

- Patients completing primary treatment be provided with a comprehensive care summary and follow-up plan that is clearly and effectively explained. This "Survivorship Care Plan" should be written by the principal provider(s) who coordinated oncology treatment and, the service should be reimbursed by third-party payers of health care.

Essential Components of Survivorship Care

- Prevention of recurrent and new cancers.
- Surveillance for cancer spread, recurrence, or second cancers.
- Assessment of medical and psychosocial late effects.
- Intervention for consequences of cancer and its treatment: lymphedema, sexual dysfunction, pain and fatigue, psychological and social distress, concerns related to employment, finances, insurance, and disability.
- Coordination between specialists and primary care providers.

Conclusions:

- Breast Cancer is a heterogeneous disease, about which much is known, but much more needs to be discovered.
- It may be desirable to examine alternatives to current screening strategies, but, hopefully, this does not translate into less effective breast cancer screening strategies that aim simply to reduce costs.
- Treatment of breast cancer is very effective and will continue to improve as newer and more important molecular targets for medications are discovered.
- With growing numbers of breast cancer survivors, recognition of and planning for their unique needs is imperative.

The Carol Ann Read Breast Health Center, Oakland, CA