Natural History and Epidemiology of Breast Cancer

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DIALOGUE FOR ACTION™ ON CANCER SCREENING

prevent cancer FOUNDATION

Epidemiology, Natural History and Early Detection of Breast Cancer

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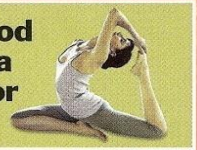
TIME Investigation: Tipping the Scales of Justice In Alabama

Stay-at-Home Dads: Why Real Men Change Diapers

Overdoing a Good Thing: How Yoga Might Be Bad for Your Health



TIME

Why Breast Cancer Is Spreading Around The World

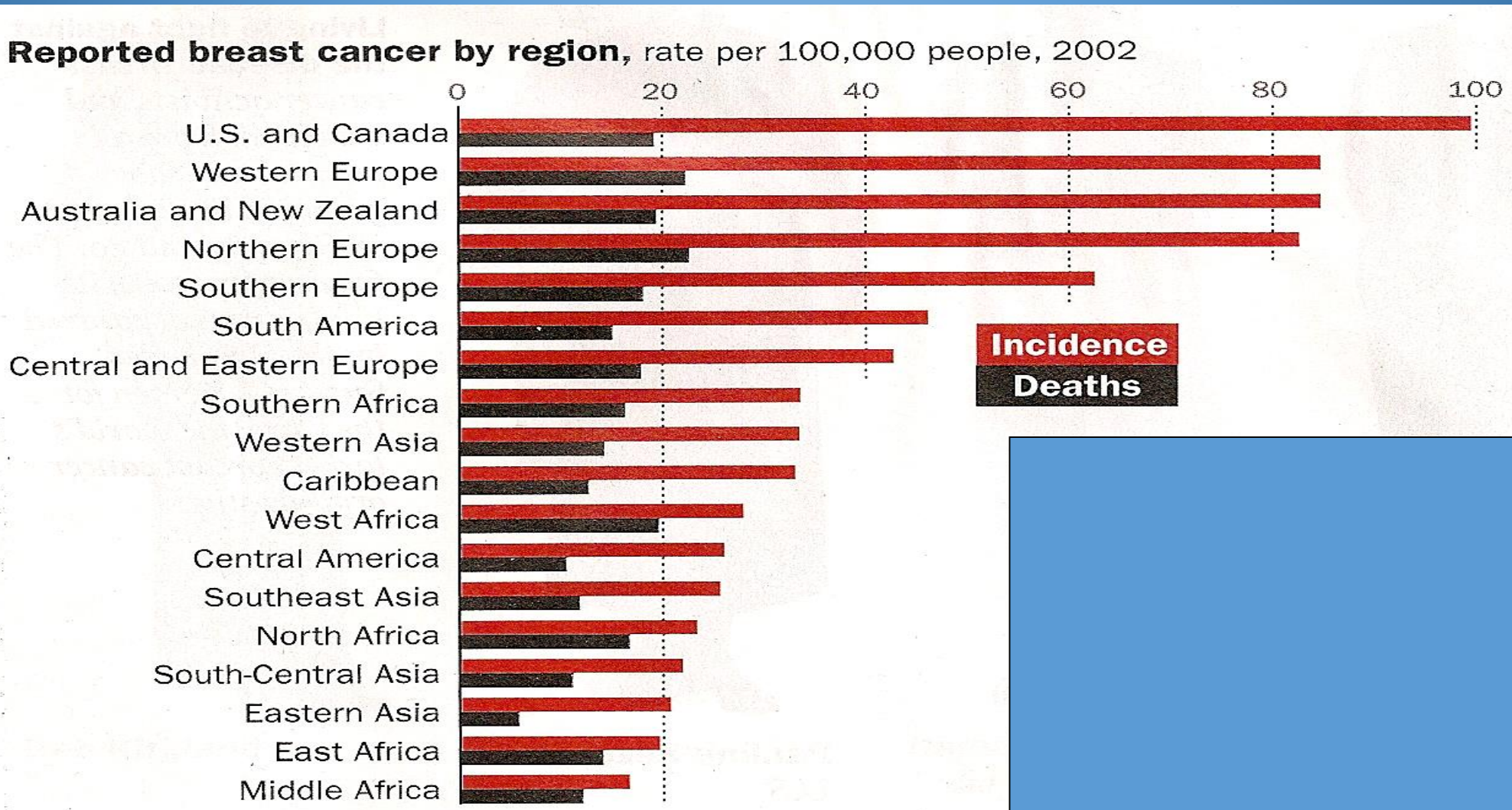
Plus: A guide to the latest treatments

$4.95US

42

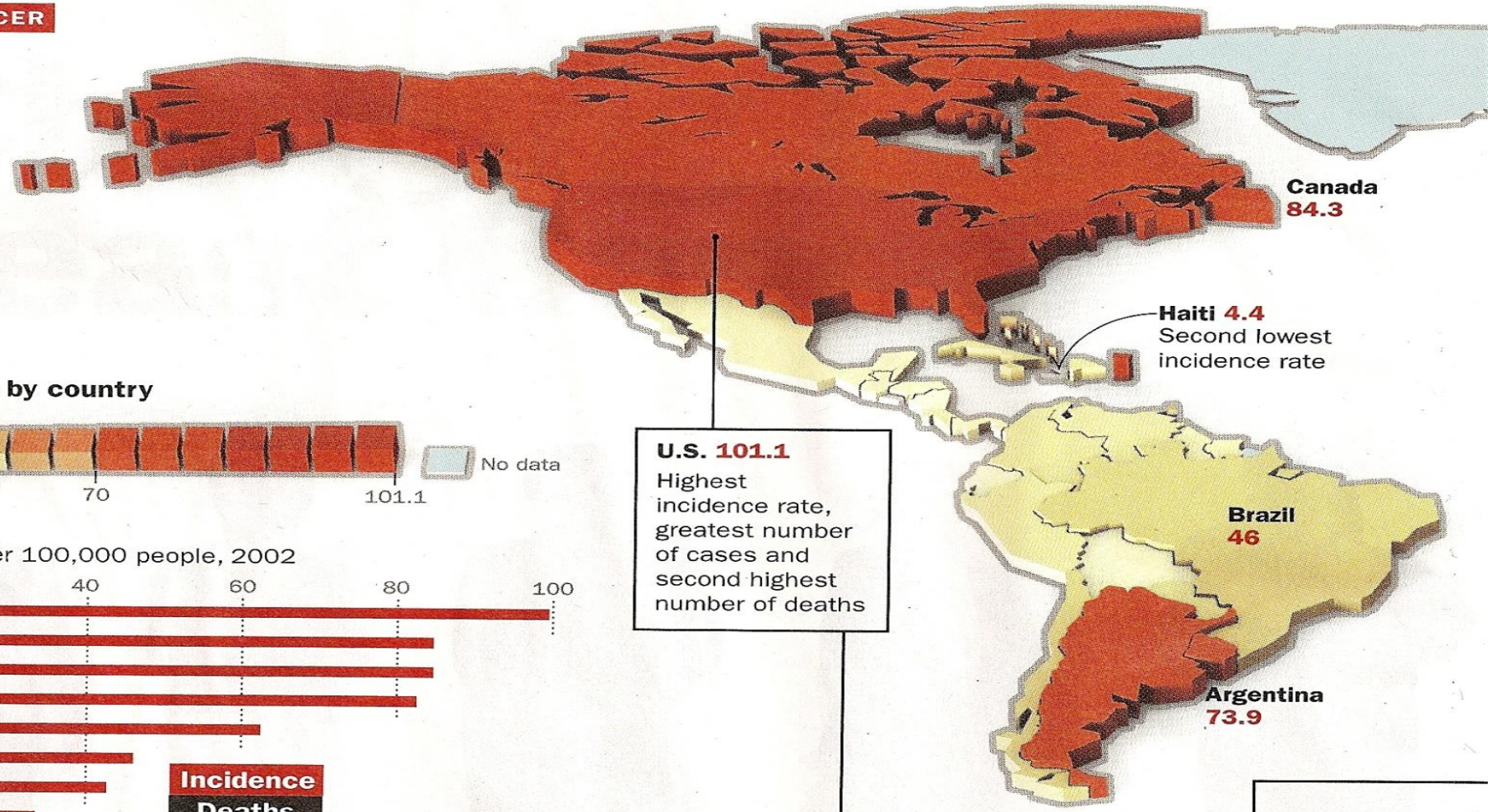
0 70989 10090 9

www.time.com

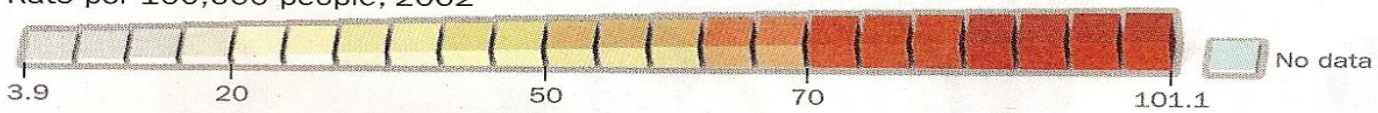

Reported breast cancer by region, rate per 100,000 people, 2002
0
20
40
60
80
100
U.S. and Canada
Western Europe
Australia and New Zealand
Northern Europe
Southern Europe
South America
Central and Eastern Europe
Southern Africa
Western Asia
Caribbean
West Africa
Central America
Southeast Asia
North Africa
South-Central Asia
Eastern Asia
East Africa
Middle Africa
Incidence
Deaths

A Disease Breaks Free

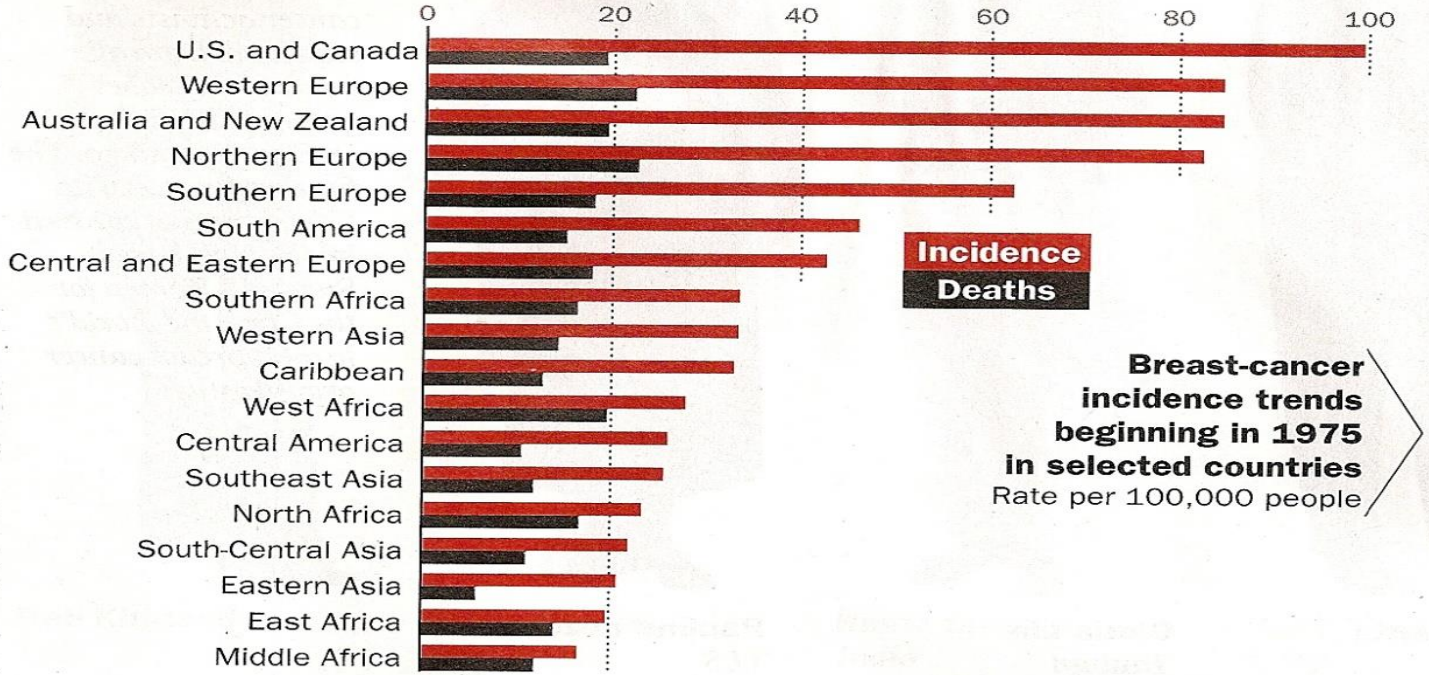
Breast cancer is on the rise. Big countries have the most cases but not always the highest incidence (cases per 100,000 people). Rates in the developing world may be even worse than the spotty data show



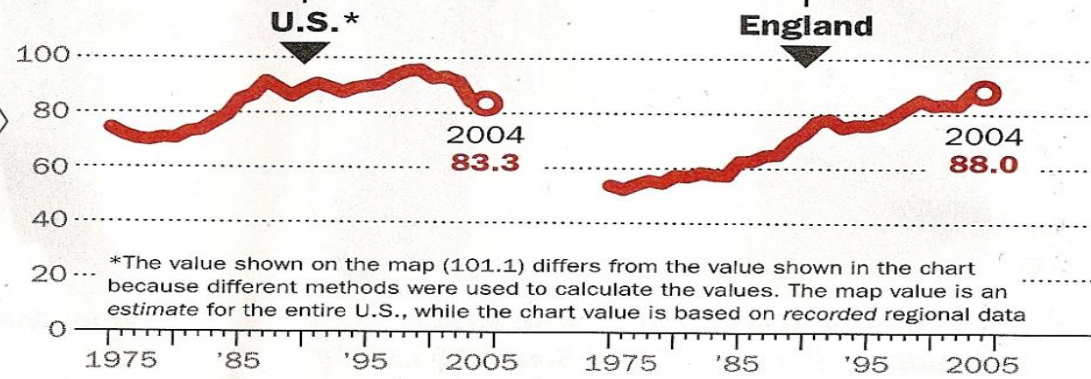
The map shows breast-cancer incidence by country
Rate per 100,000 people, 2002



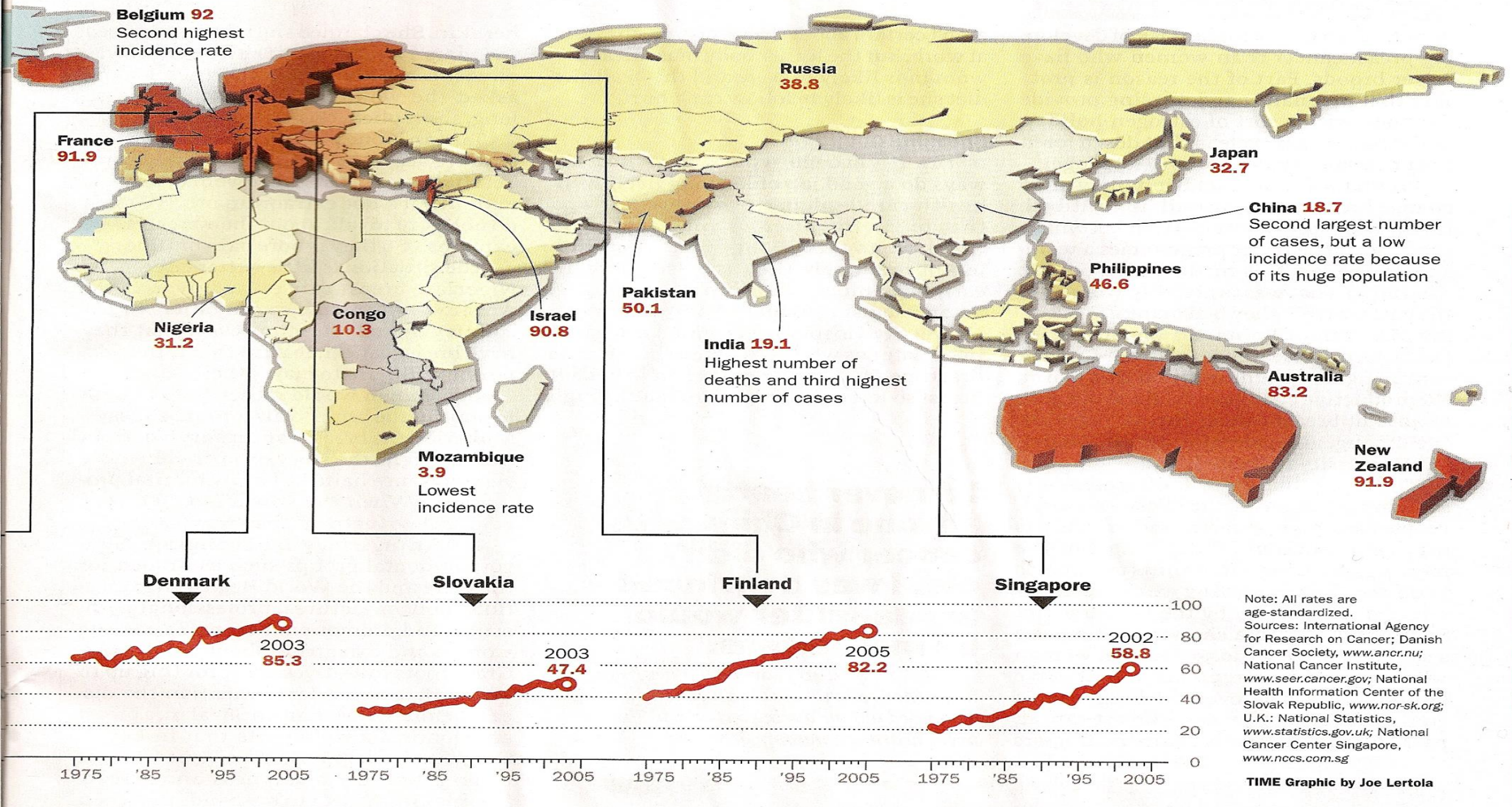
Reported breast cancer by region, rate per 100,000 people, 2002



Breast-cancer incidence trends beginning in 1975 in selected countries
Rate per 100,000 people



*The value shown on the map (101.1) differs from the value shown in the chart because different methods were used to calculate the values. The map value is an *estimate* for the entire U.S., while the chart value is based on *recorded* regional data



Note: All rates are age-standardized.
Sources: International Agency for Research on Cancer; Danish Cancer Society, *www.ancr.nu;* National Cancer Institute, *www.seer.cancer.gov;* National Health Information Center of the Slovak Republic, *www.nor-sk.org;* U.K.: National Statistics, *www.statistics.gov.uk;* National Cancer Center Singapore, *www.nccs.com.sg*

TIME Graphic by Joe Lertola

Lifetime Risk of Breast Cancer

- American Women
  - 1 in 8 will develop breast cancer
  - 12.15% of women born today
  - Over 87% will ***NOT*** develop breast cancer
- European Women
  - 1 in 9
  - 11% of women born today
  - 89% will not develop breast cancer

Lifetime Risk of Breast Cancer in the US

- 13.2 percent for 2000 through 2002
- 12.7 percent for 2001 through 2003
- 12.3 percent for 2002 through 2004
- 12.0 percent for 2003 through 2005
- 12.1 percent for 2004 through 2006

US Women Today with Breast Cancer History

- 2,591,855
- Breast Cancer Detected Early is a ***CURABLE*** disease
- ***BREAST CANCER IS NOT A DEATH SENTENCE!!!!!***

Decrease in Mortality from Breast CA

- From 1975-1990 the death rate from breast cancer increased by 0.4% annually
- Between 1990 and 2002 the rate decreased by 2.3% annually
- Percentage of decline was greater among younger women
  - 1990-2002 decreased by 3.3% in women < 50
  - 2.0% in women > 50

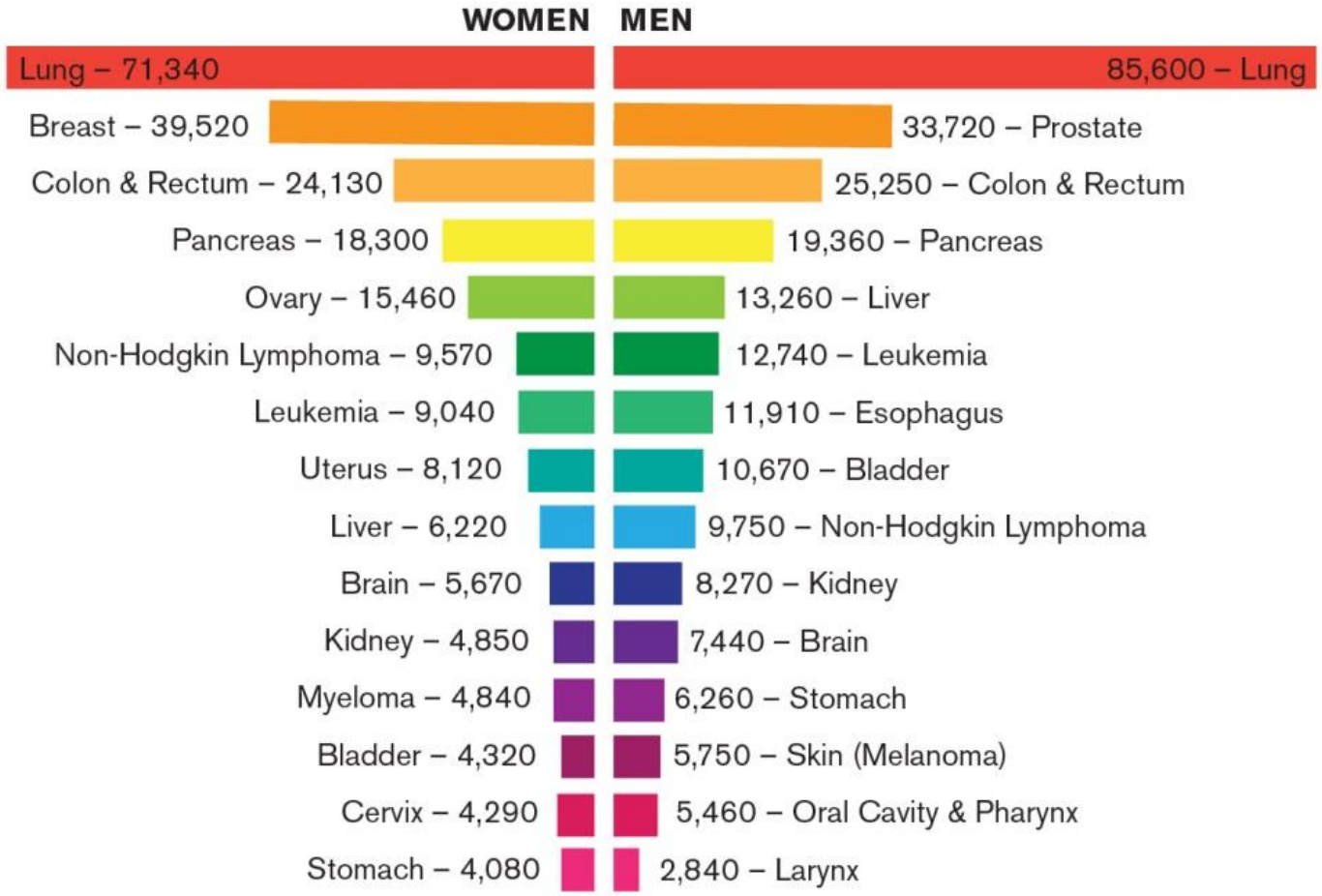
American Cancer Society Breast Cancer Fact and Figures 2005-2006

Breast Cancer

- Optimal would be prevention
- Initial approaches to significant risk reduction with goal of prevention
  - TAMOXIFEN as a risk reduction strategy (44% reduction of ER+, PR+ Breast cancer)
- must detect when localized and there by curable

Leading Cancer Killers

Estimated number of cancer deaths for 2011.



Source: Cancer Facts & Fictures 2011, American Cancer Society

Five Year Survival for Breast Cancer

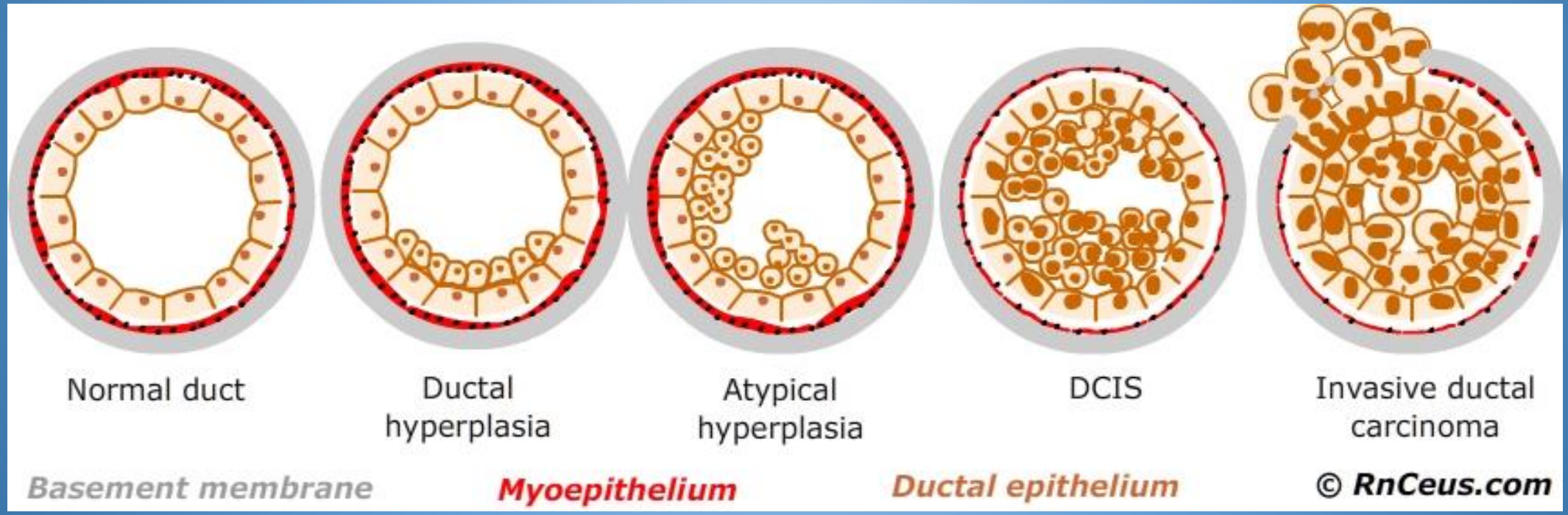
Early Stage	95%
Late Stage	20%

How Does Breast Cancer Occur?

- Multi-factorial
  - Spontaneous mutation
  - Familial
  - Gene mutations
    - BrCA 1 /2
  - Complex interaction of host and tumor
    - Immune
  - More common in developed nations
  - Increasing in developing nations

The multi-step model of carcinogenesis

- Normal breast tissue transitions to atypical hyperplasia and *in situ* carcinoma before transitioning to invasive cancer



Lakhani SR. The transition from hyperplasia to invasive carcinoma of the breast. J Pathol. 1999 Feb;187(3):272-8.
Shackney SE1, Silverman JF. Molecular evolutionary patterns in breast cancer. Adv Anat Pathol. 2003 Sep;10(5):278-90.

Breast Cancer

- Not all breast cancer has an obligatory in-Situ phase
- Rarely have DCIS component in cancer of BrCA-1 patients
  - Do see it in BrCA-2 patients

Benign, Malignant and Something in Between

- Atypical hyperplasia an overproduction and accumulation of abnormal cells in the breast
- Signifies and increased risk of breast cancer (4-5 X)
- Possible pre-cursor to breast cancer
- Atypia at minimally invasive biopsy warrants surgical excision to exclude cancer in the area of the atypia
  - 10 – 25% likelihood of malignancy at surgical excisional biopsy
  - Ongoing studies to utilize molecular markers to determine which atypia warrant surgical excision and which are innocuous
  - Until then, all to surgical excision

Atypia

- ADH associated with higher risk than previously thought
  - 3.88 fold increased risk
  - If multi-focal 10.35 fold increased risk
  - Younger women (<45) have a higher risk of cancer with Atypia
    - 6.76 fold
- Family history of cancer not contributory

Degnim, Visscher, Berman et al *JCO July 1, 2007 vol. 25 no. 19 2671-2677*

Atypia (ADH and ALH)

- Recent study demonstrating far higher risk associated with atypia
  - 30% at 25 years of follow-up of 698-patient cohort of women with atypical hyperplasia
  - 5 years, the incidence was 6.6%. It then climbed to 12.6% at 10 years, 19.4% at 15 years, 23.1% at 20 years, and 30.3% at 25 years
    - In a normal, healthy population, only about 8% of women would be expected to develop breast cancer in a similar 25-year period
  - 15 Year Follow Up;
    - Single focus 14.2%
    - 23.3% for women with two foci and
    - 34.4% for women with three foci or more
- Relative risk reductions in the atypical hyperplasia subgroups ranged from 41% to 79

Hartmann, Degnim, Santen, Dupont, Ghosh. Atypical Hyperplasia of the Breast — Risk Assessment and Management Options N Engl J Med 2015; 372:78-89

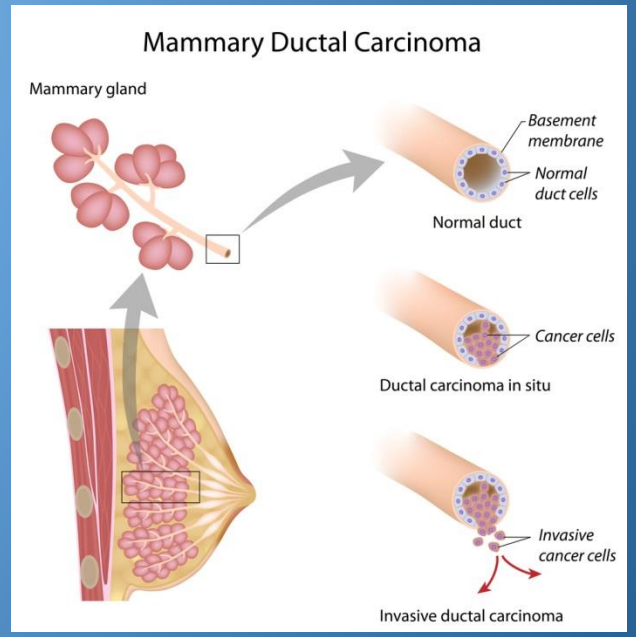
Lobular Neoplasia

- Group of lobular atypia
  - ALH, LCIS
- At minimally invasive biopsy associated with ~ 25% upgrade at surgical excision
  - More controversial than ADH

Brem RF, Lechner MC, Jackman Rj et al. Lobular neoplasia at percutaneous breast biopsy: variables associated with carcinoma at surgical excision. AJR Am J Roentgenol. 2008 Mar;190(3):637-41

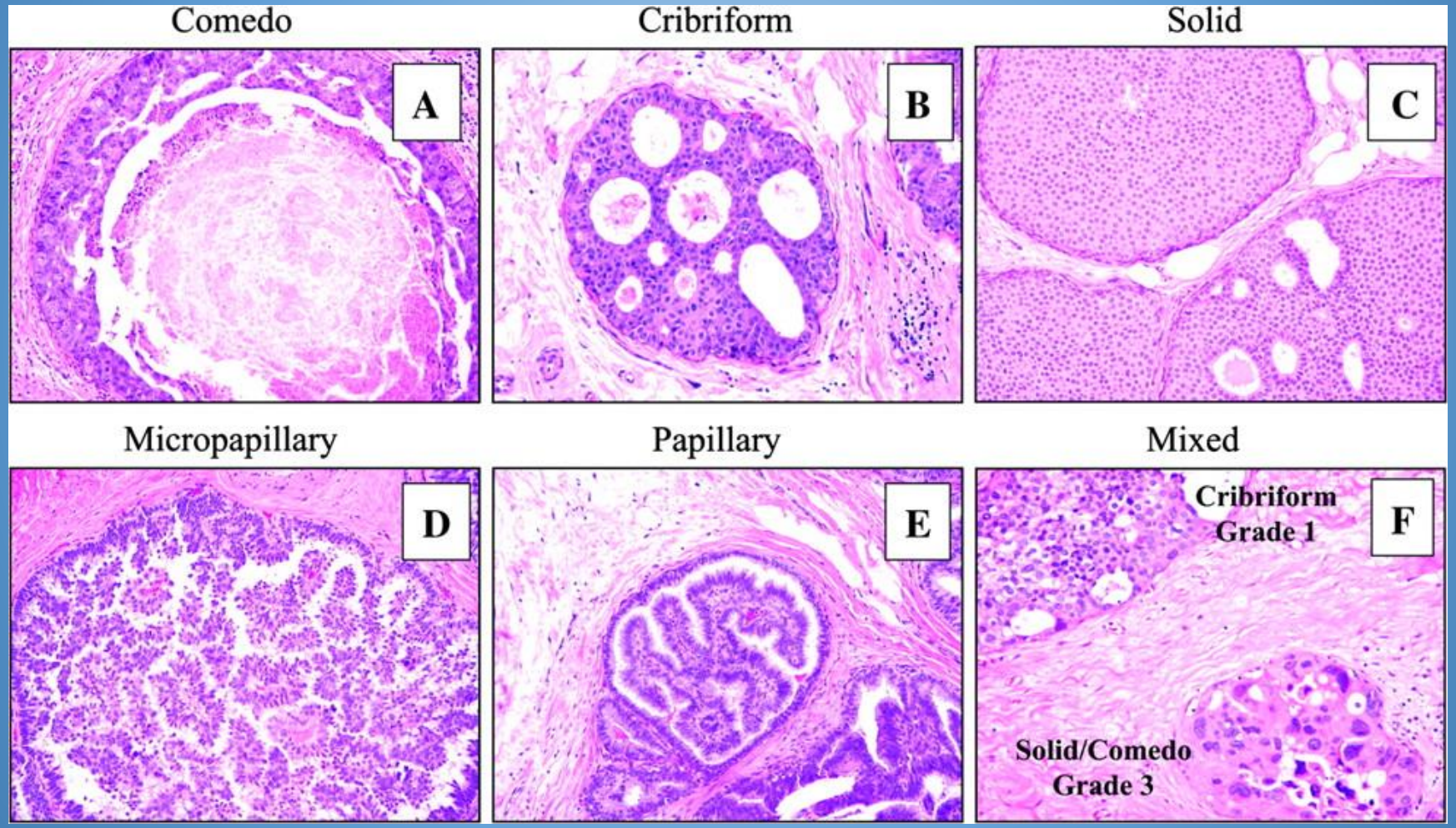
Noninvasive Breast Cancers

- In Situ
  - **<u>Ductal Carcinoma In Situ</u>**
    - Potential to progress to invasive
    - about 1/3 of DCIS cases will develop into invasive cancer if untreated
    - Need molecular markers to determine which DCIS have the biological potential to break through the basement membrane and which do not
    - Treatment is lumpectomy and radiation therapy or mastectomy



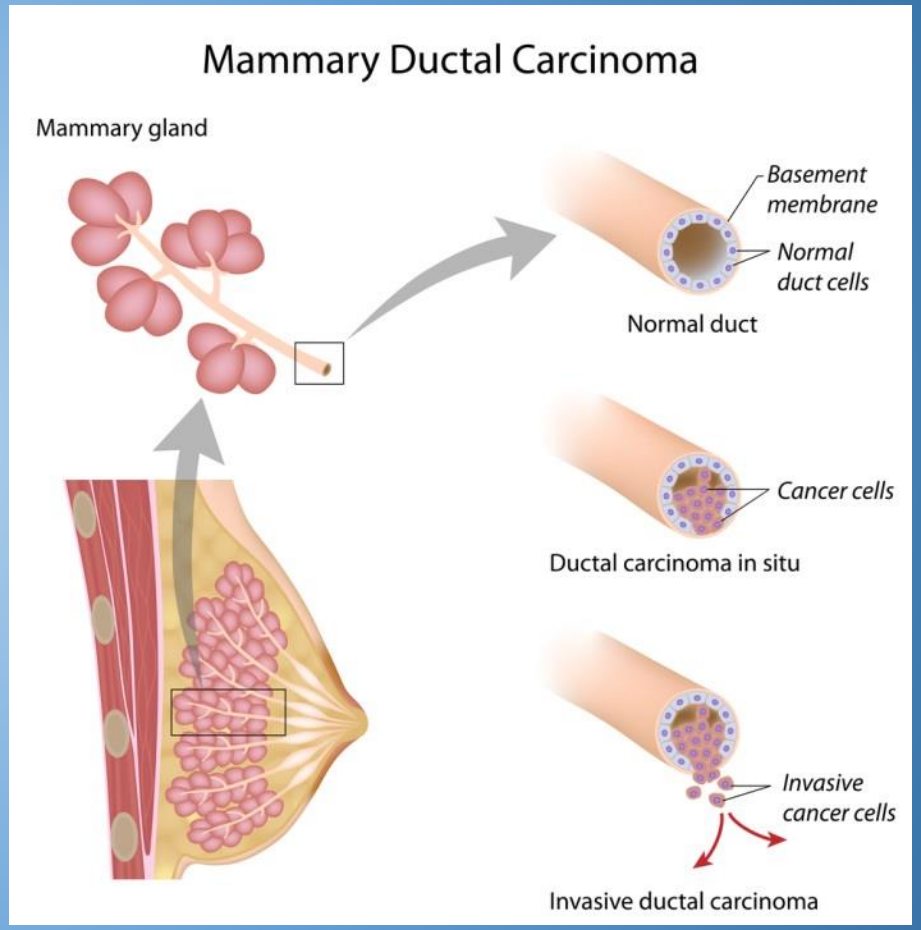
American Cancer Society. Breast Cancer Facts and Figures. 2013-2014.

DCIS


Comedo
A
Cribriform
B
Solid
C
Micropapillary
D
Papillary
E
Mixed
Cribriform
Grade 1
F
Solid/Comedo
Grade 3

Invasive Cancers

- Infiltrating carcinoma have broken through the basement membrane
- Potential for metastases



Young JL Jr, Roffers SD, Ries LAG, Fritz AG, Hurlbut A, eds. SEER Summary Staging Manual - 2001: Codes and Coding Instructions. Bethesda, MD: National Cancer Institute; 2001. NIH Pub. No. 01-4969.
American Cancer Society. Breast Cancer Facts and Figures. 2013-2014.

Breast Cancer Screening

- X-ray Mammography
  - Proven mortality reduction
    - 30% reduction in breast cancer mortality
      - Half due to screening
- Screening Breast Ultrasound
  - Adjunct imaging for increased risk and limitation of mammography in women with dense breast tissue
- Magnetic Resonance Imaging (MRI)
  - Physiologic imaging
  - BrCA +
  - Post RT for Hodgkins during adolescence
- Breast Specific Gamma Imaging (BSGI)
- Screening options vary depending upon level of risk and age
- Goal is to detect breast cancer when it is a localized and treatable disease
  - 95% stage 0 and 1 breast cancer curable

Berry DA,Cronin KA, Plevritis SK et al. Effect of Screening and Adjuvant Therapy on Mortality from Breast Cancer.
N Engl J Med 2005;353:184-1792.

Risk/ Individualized Screening

- Normal risk
  - < 15% lifetime risk
    - Mammography
- Intermediate Risk
  - 15-20% lifetime risk
    - Screening breast ultrasound
- High Risk
  - >20% lifetime risk
    - Physiologic Imaging
      - MRI
      - BSGI

Breast Cancer Screening

- Mainstay for breast cancer screening
- Proven mortality reduction
  - Overall 30% reduction in mortality from breast cancer
    - Half due to screening
    - Half due to improved therapy
- Recommendations
  - Annual mammography 40 + (ACS, ACR, ACS)
  - 5-10 years earlier than age at diagnosis of first degree relative
  - BrCA+ age 25-30

American Cancer Society. Breast Cancer Facts and Figures. 2013-2014
Rosenberg RD, Yankaskas BC, Abraham LA, et al. Performance benchmarks for screening mammography. Radiology. Oct 2006;241(1):55-66.
Nelson HD, Tyne K, Naik A, et al. Screening for Breast Cancer: Systematic Evidence Review Update for the US Preventative Services Task Force. Rockville MD, 2009.
Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. N Engl J Med. Nov 22 2012;367(21):1998-2005.

Screening Mammography: Controversy

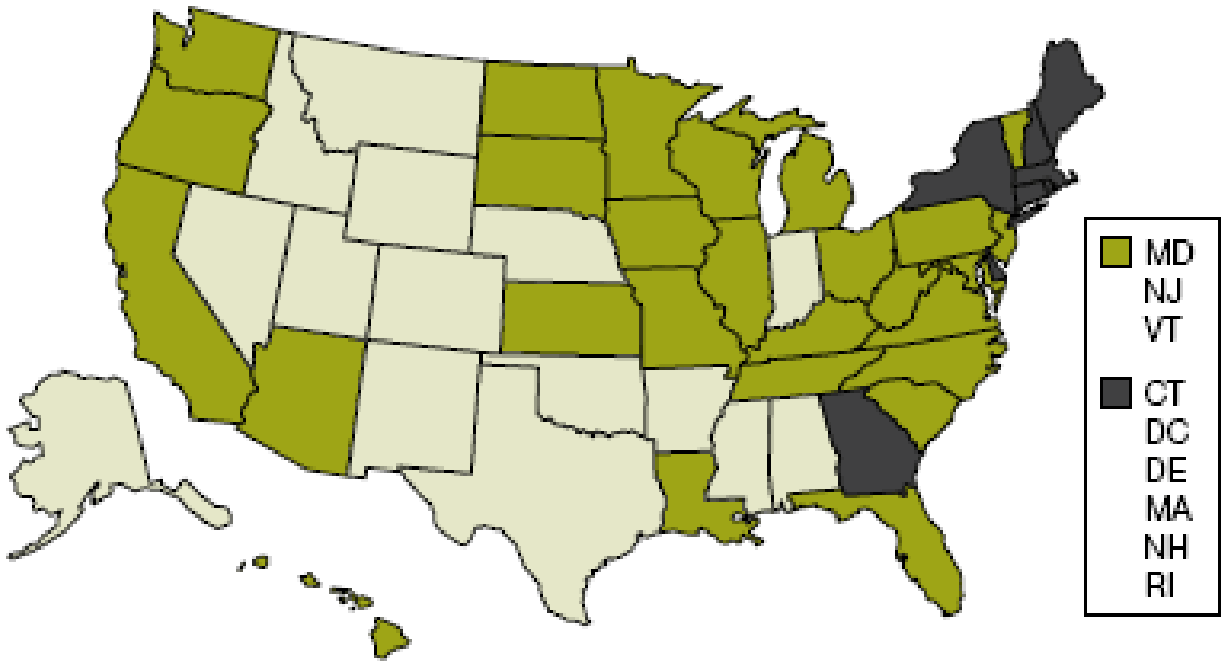
- Controversies
- Imperfect examination
  - 85% sensitivity
  - Decreases to 65% in women with dense breast tissue
    - Women with dense breast tissue are the largest population of intermediate risk women
      - Dense tissue is a strong independent risk factor (2-6 fold increased risk)
      - Additional imaging modalities to dectect mammographically occult cancer are now available
        - Dense breast inform acts are now law in 21 states and increasing

Dense Breast Tissue

- 21 states have enacted density inform laws
- National bill before congress
- Perfect storm
  - Mammography is less sensitive
  - Risk is increased
  - Therefore additional screening modalities are necessary
    - Screening breast ultrasound
      - Hand held
      - Automated
      - Nearly doubles number of cancers detected
      - Clinically significant cancers
        - Invasive
        - Small
        - Node negative

Brem RF, Tabár L, Duffy SW. Assessing Improvement in Detection of Breast Cancer with Three-dimensional Automated Breast US in Women with Dense Breast Tissue: The SomoInsight Study. Radiology. 2015;274(3):663-73

Breast Cancer Screening Prevalence,* 2008



* Mammogram use in past 2 years among women aged 50–74 years in the United States.

Source: CDC, Behavioral Risk Factor Surveillance System, 2008.

Screening: Breast Ultrasound

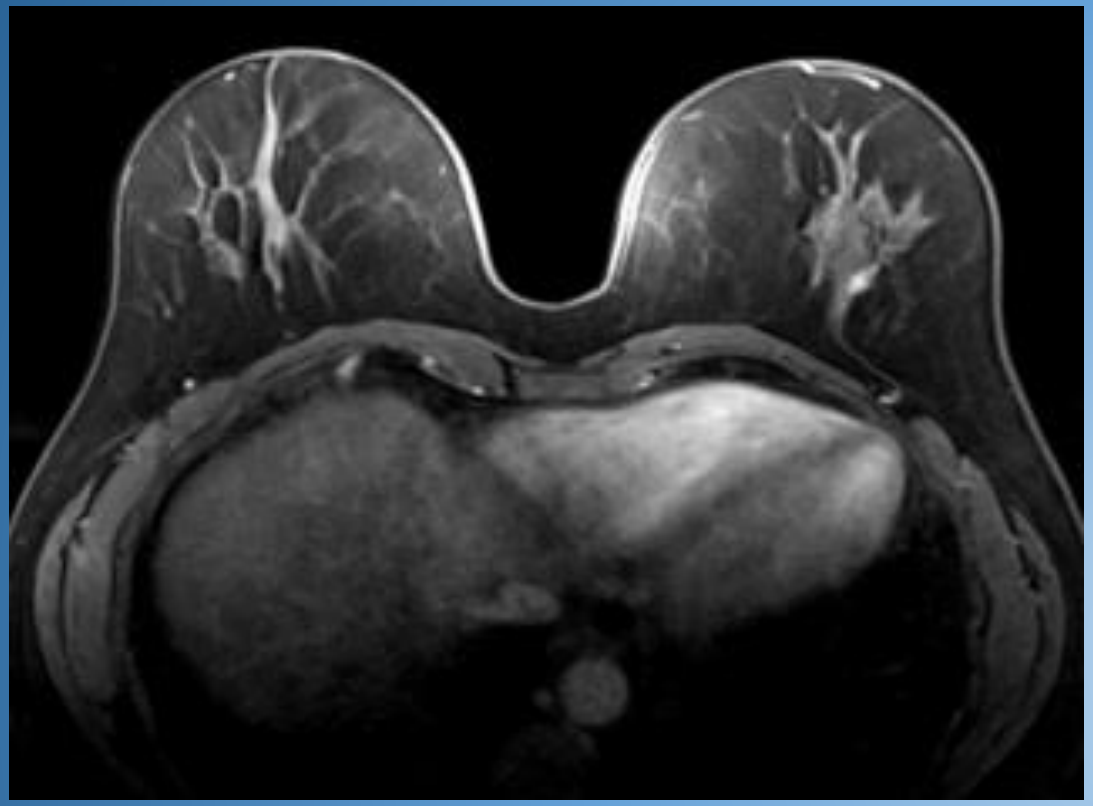
- Whole breast US has been studied as a supplemental screening tool in high-risk women with dense breasts, improving sensitivity from 50% to 77.5% when used in addition to mammography
- However, screening breast ultrasound yields elevated false-positive rates compared to mammography alone, revealing a positive predictive value (PPV3) for biopsy of only 8.9% compared with 23% for mammography

Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA 2008;299(18):2151-63

Screening: MRI

- Breast MRI is now recommended as a supplemental screening tool to mammography for high-risk women (≥20-25% lifetime risk) starting at 30 years old
- MRI uses a physiologic approach, requiring injection of contrast
- Sensitivity of 88-95%
- Associated with increased cost, inaccessibility to patients who are obese or have implanted devices or renal insufficiency, and workflow issues
- Used in women with newly diagnosed breast cancer
  - 10% have occult focus of breast cancer

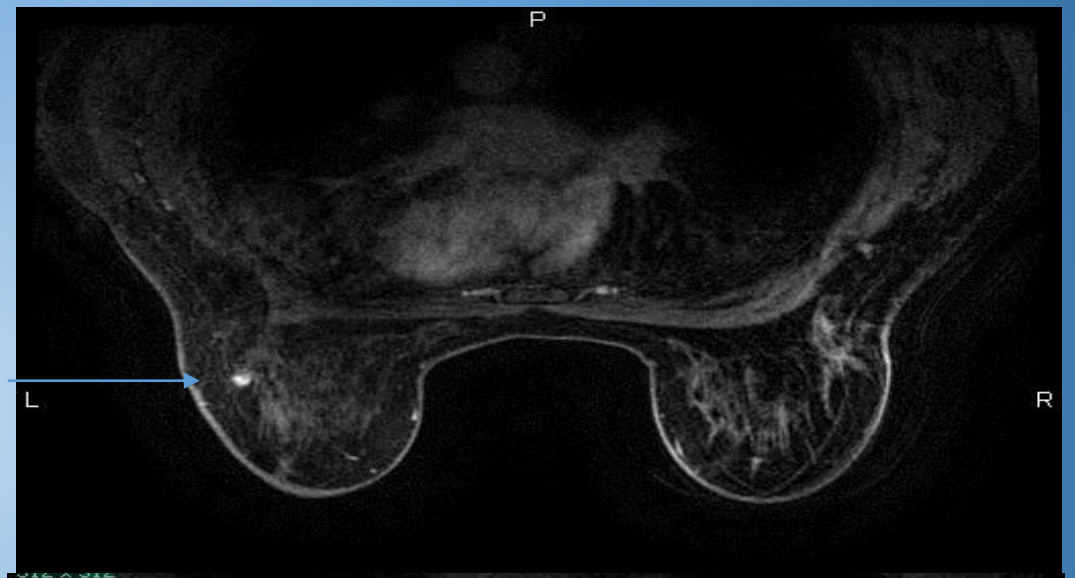
Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57(2):75-89.
Bluemke DA, Gatsonis CA, Chen M, et al. Magnetic Resonance Imaging of the Breast Prior to Biopsy. JAMA. 2004;292(22):2735-2742. doi:10.1001/jama.292.22.2735.

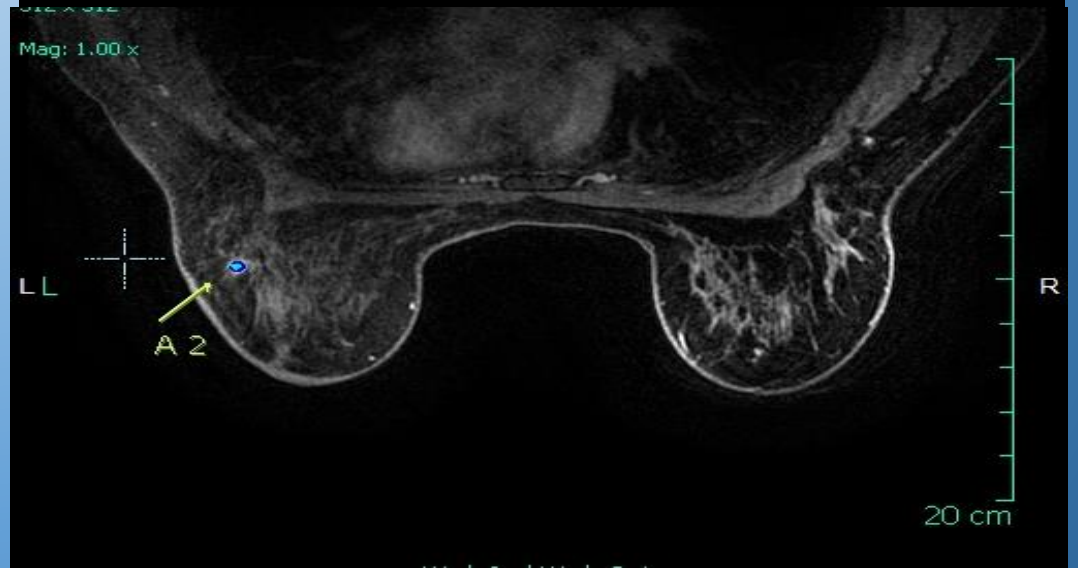


MRI 10.17.2013

New 6mm spiculated enhancing mass anterior and inferolateral to the lumpectomy site –

MRI 10.1.2014





Screening: BSGI

- Breast-specific gamma imaging (BSGI) detects breast cancer with a sensitivity of 92-96%, similar to MRI
- Has been shown to reliably detect cancers as small as <2mm and occult lesions not seen on mammography
- BSGI uses a radiotracer isotope, technetium 99m sestamibi, to identify physiological differences between breast cancer and normal breast tissue
- The efficacy of BSGI has been shown to be independent of breast density
  - Important for women at increased risk who begin screening when breast tissue tends to be denser

Johnson N, Sorenson L, Bennetts L, et al. Breast-specific gamma imaging is a cost effective and efficacious imaging modality when compared with MRI. Am J Surg 2014;207(5):698-701; discussion 701.

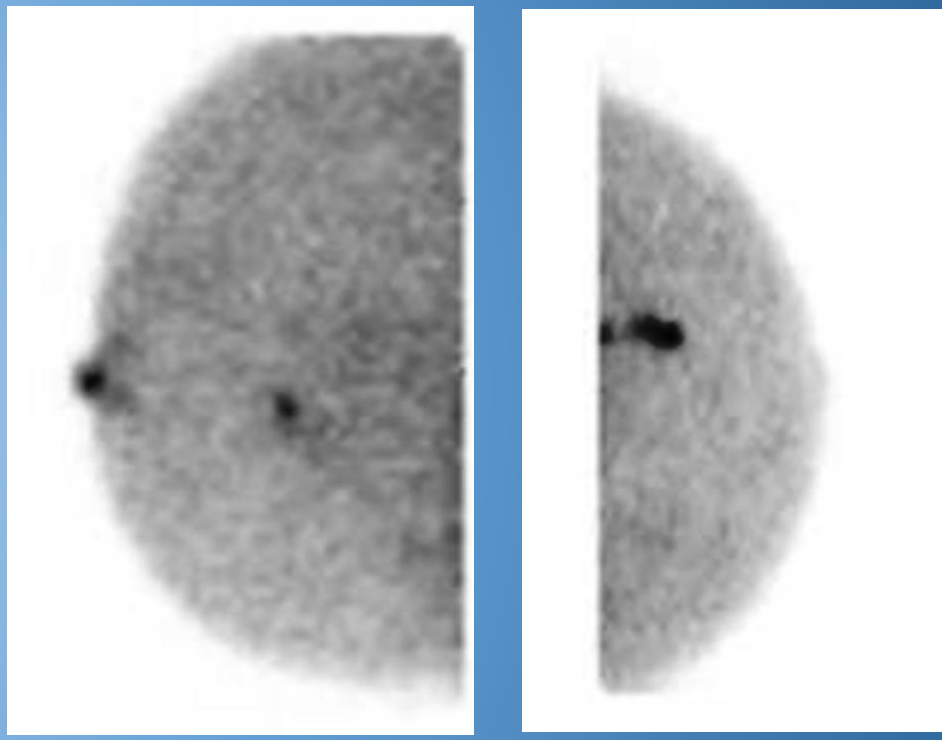
Brem, R.F., Petrovitch I, Rapelyea JA, et al. Breast-specific gamma imaging with 99m-Tc-sestamibi and magnetic resonance imaging in the diagnosis of breast cancer: A comparative study. Breast Journal 2007;13(5):465-469.

Sun Y, Wei W, Yang HW, Liu JL. Clinical usefulness of breast-specific gamma imaging as an adjunct modality to mammography for diagnosis of breast cancer: a systemic review and meta-analysis. Eur J Nucl Med Mol Imaging 2013;40(3):450-63.

Zhou, M., Johnson, N., et al. Clinical utility of breast-specific gamma imaging for evaluating disease extent in the newly diagnosed breast cancer patient. Am J Surg 2009;197,159-163.

Breast Specific Gamma Imaging

- FDA cleared
- Can be performed in any patient with venous access
- Physiologic option for women who cannot undergo MRI
  - 15% of our population
- Sensitivity 88-96%
  - ? Higher specificity
  - Can reliably detect cancers as small as 2 mm
- 10% of women with newly diagnosed breast cancer have additional focus



Rechtman,Lenihan, Lieberman,Teal,Torrente, Rapelyea, Brem.Breast-specific gamma imaging for the detection of breast cancer in dense versus nondense breasts. AJR Am J Roentgenol. 2014 Feb;202(2):293-8

Brem,Shahan,Rapelyea et al. Detection of occult foci of breast cancer using breast-specific gamma imaging in women with one mammographic or clinically suspicious breast lesion.Acad Radiol. 2010 Jun;17(6):735-43.

Risk Based Screening

- Normal Risk
  - Mammography
- Intermediate Risk
  - Mammography and screening ultrasound
- High Risk
  - Mammography alternating with physiologic imaging every six months
    - MRI/BSGI
  - Perhaps in BrCA 1, where DCIS not an issue, consider only screening with MRI

Breast Cancer Risk Factors

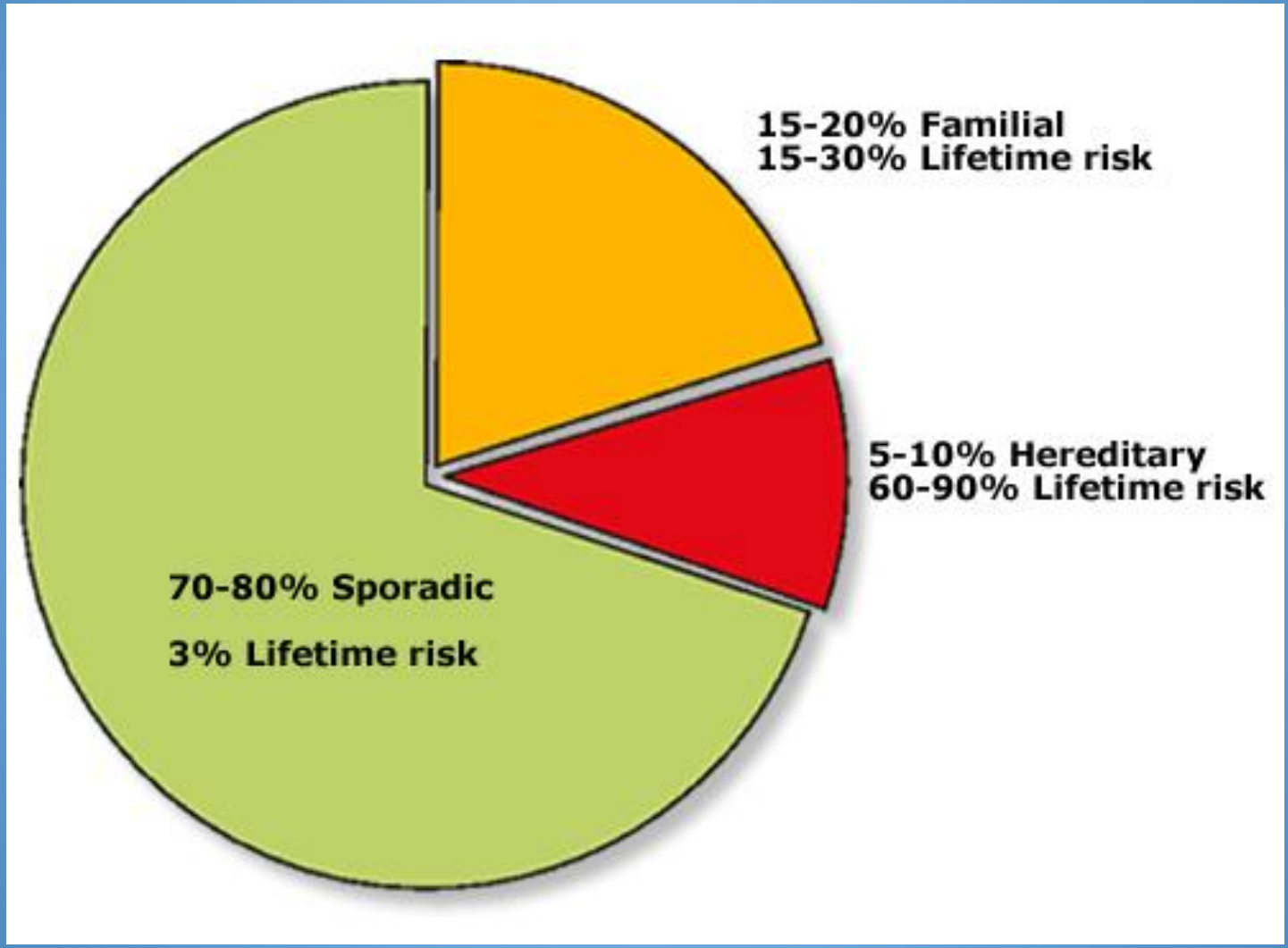
- Numerous
- Scientifically Proven
- Scientifically suggested

- Modifiable
- Non-modifiable

Risk Factors

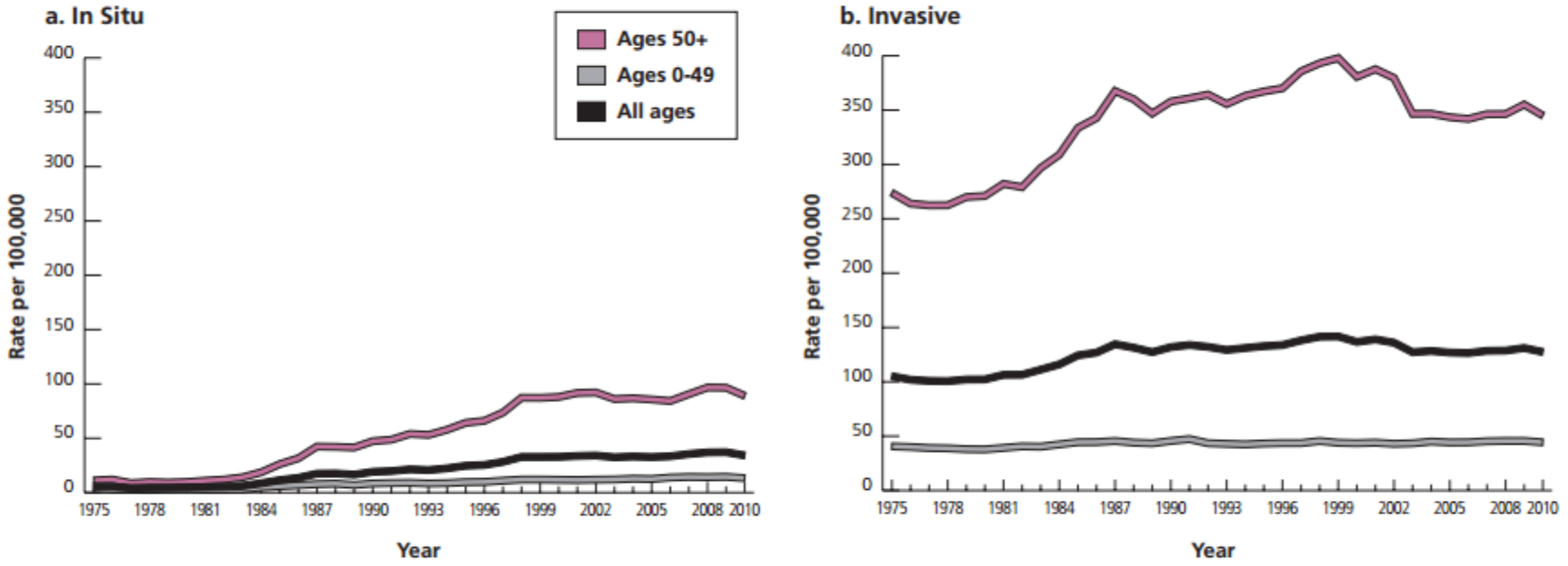
Factor	Relative risk	High risk group
Age	>10	Elderly
Geographical location	5	Developed country
Age at menarche	3	Menarche before age 11
Age at menopause	2	Menopause after age 54
Age at first full pregnancy	3	First child in early 40s
Family history	⩾2	Breast cancer in first degree relative when young
Previous benign disease	4-5	Atypical hyperplasia
Cancer in other breast	>4	
Socioeconomic group	2	Groups I and II
Diet	1.5	High intake of saturated fat
Body weight:		
Premenopausal	0.7	Body mass index >35
Postmenopausal	2	Body mass index >35
Alcohol consumption	1.3	Excessive intake
Exposure to ionizing radiation	3	Abnormal exposure in young females after age 10
Taking exogenous hormones:		
Oral contraceptives	1.24	Current use
Hormone replacement therapy	1.35	Use for ⩾10 years
Diethylstilbestrol	2	Use during pregnancy

McPherson K, Steel CM, Dixon JM. Breast cancer–epidemiology, risk factors, and genetics. BMJ. 2000;321(7261);624-628.


15-20% Familial
15-30% Lifetime risk
5-10% Hereditary
60-90% Lifetime risk
70-80% Sporadic
3% Lifetime risk

Risk Factors: Age

Figure 4. Incidence Rates* of In Situ and Invasive Female Breast Cancer by Age, Adjusted for Delayed Reporting, US, 1975-2010



*Rates are age adjusted to the 2000 US standard population within each age group.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 9 Registries, National Cancer Institute.

American Cancer Society, Surveillance and Health Services Research, 2013

American Cancer Society. Breast Cancer Facts and Figures. 2013-2014.

Risk Factors: Family & Personal History

- Family history of breast cancer
  - Especially in first-degree relative
  - Higher if more than one first-degree relative developed breast cancer
  - Compared to women without a family history:
    - 1.8x higher with 1 first-degree relative
    - Nearly 3x higher with 2
    - Nearly 4x higher with 3 or more
  - However, the majority of women with one or more first-degree relatives do not develop breast cancer!
- Family history of ovarian cancer
- Women with a history of breast cancer have higher risk of developing a second breast cancer

American Cancer Society. Breast Cancer Facts and Figures. 2013-2014

Risk Factors: Genetic Predisposition

- Up to 10% of breast cancer cases result from inherited mutations, including **BRCA1** and **BRCA2**
  - Present in <1% of general population, but more prevalent in those of Ashkenazi (Eastern European) Jewish descent
  - BRCA1: 44%-78% develop breast cancer by age 70
  - BRCA2: 31%-56% develop breast cancer by age 70
- Early breast cancers
  - 50% by age 50
  - Most breast cancers in women in 20's due to genetic mutation

American Cancer Society. Breast Cancer Facts and Figures. 2013-2014

Schwartz GF, Hughes KS, Lynch HT, et al. Proceedings of the international consensus conference on breast cancer risk, genetics, & risk management, April, 2007. Cancer. Nov 15 2008;113(10):2627-37

Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. May 2003;72(5):1117-30.

Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. Apr 10 2007;25(11):1329-33.

Turnbull C, Rahman N. Genetic predisposition to breast cancer: past, present, and future. Annu Rev Genomics Hum Genet. 2008;9:321-45.

Recommendations for Genetic Testing for BRCA mutations

- Women of Ashkenazi descent should be referred for genetic evaluation for any of the following:
  - A first-degree relative with breast or ovarian cancer
  - Two second-degree relatives with breast or ovarian cancer
- Women *not* of Ashkenazi descent should be referred for genetic evaluation for any of the following:
  - Two first-degree female relatives (mothers, sister, daughters) with breast cancer, one of whom was diagnosed younger than age 50
  - Three or more first or second-degree female relatives (includes grandmothers, aunts) diagnosed with breast cancer
  - Both breast and ovarian cancer among first and second-degree relatives
  - A first-degree relative diagnosed with bilateral breast cancer
  - Two or more first or second-degree relatives diagnosed with ovarian cancer
  - A male relative with breast cancer

U.S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. Ann Intern Med. Sep 6 2005;143(5):355-61.
American Cancer Society. Breast Cancer Facts and Figures. 2013-2014

Risk Factors: Lifestyle

- **Exogenous hormone use**: combined estrogen and progestin increases risk
- **Obesity**: increases the risk of postmenopausal breast cancer
  - 1.5x higher in overweight women, 2x higher in obese women
  - Likely due to high estrogen levels: fat tissue is the largest source of estrogen in postmenopausal women
- **Physical activity**: women who get regular physical exercise have 10%-20% lower risk of breast cancer, compared with women who are inactive
- **Diet**: no conclusive evidence of relationship between diet and breast cancer

American Cancer Society. Breast Cancer Facts and Figures. 2013-2014

Risk Factors: Lifestyle

- **Alcohol**: increases risk by about 7%-12% for each 10g (~1 drink) of alcohol consumed per day
- **Tobacco**: limited evidence; recent meta-analysis shows that smokers had a 12% higher risk compared to non-smokers
- **Oral contraceptives**: may increase risk by 10%-30%
  - Significant decrease in ovarian cancer risk
- **Radiation**: increases risk of breast cancer

American Cancer Society. Breast Cancer Facts and Figures. 2013-2014

Risk Factors: Other

- Dense breast tissue
  - Women with extremely dense breast tissue have 4-6 fold increased risk compared to women with the least dense breasts
  - Density decreases with age, pregnancy, and menopause
  - Women with dense breast tissue recommended for supplemental screening, as mammographic detection of breast cancer may be impaired

American Cancer Society. Breast Cancer Facts and Figures. 2013-2014
Boyd NF, Rommens JM, Vogt K, et al. Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol. 2005;6(10):798–808.
Boyd NF, Dite GS, Stone J, et al. Heritability of mammographic density, a risk factor for breast cancer. N Engl J Med. Sep 19 2002;347(12):886-94.

Prevention

- Chemoprevention
  - Tamoxifen and raloxifene significantly reduce risk of breast cancer in women known to be at increased risk (up to 40%)
  - Contraindication and side effect
    - endometrial cancer, blood clots, cataracts
- Prophylactic surgery
  - 90% risk reduction

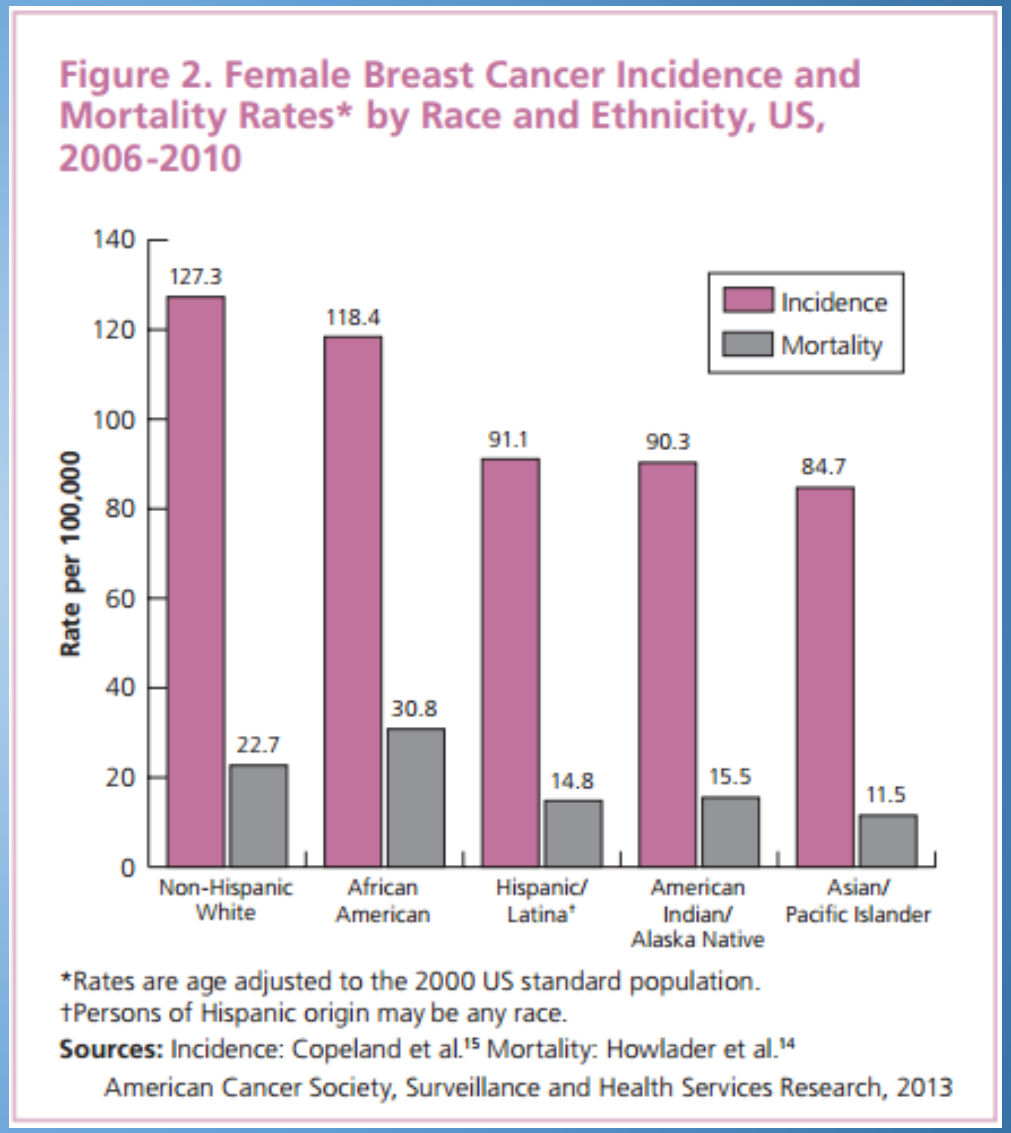
American Cancer Society. Breast Cancer Facts and Figures. 2013-2014

Nelson HD, Smith ME, Griffin JC, Fu R. Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventative Services Task Force. Ann Intern Med. Apr 16 2013;158(8):604-14.

Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: The PROSE Study Group. J Clin Oncol. 2004;22(6):1055-62.

Epidemiology

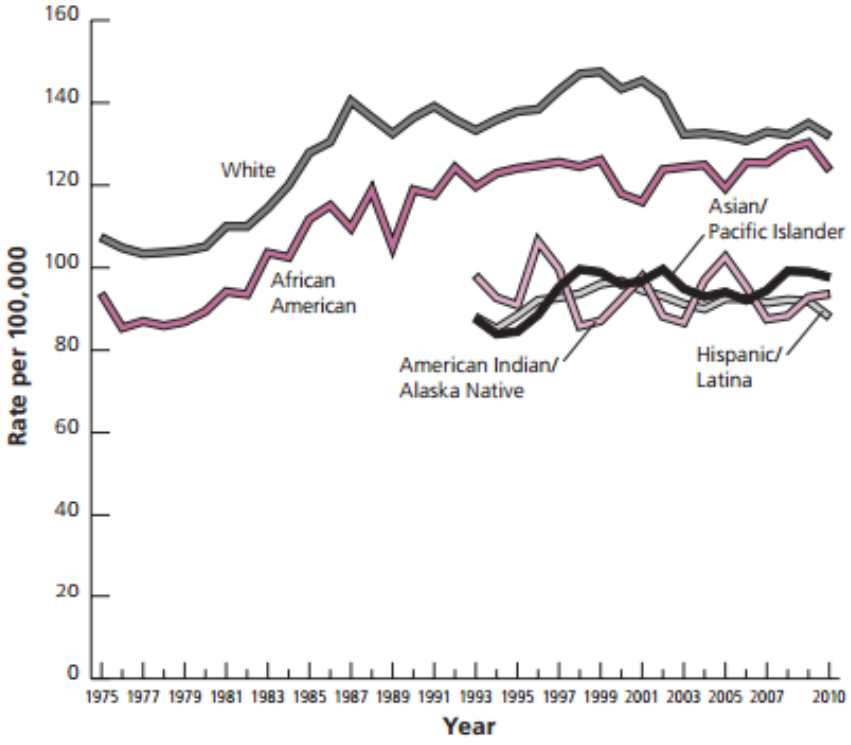
- Breast cancer incidence rates highest in Caucasian women and African American women
- African American women have higher incidence rate before age 40,
- African American women have higher mortality rate
- Asian/Pacific Islander women have lowest incidence and death rates



American Cancer Society. Breast Cancer Facts and Figures. 2013-2014

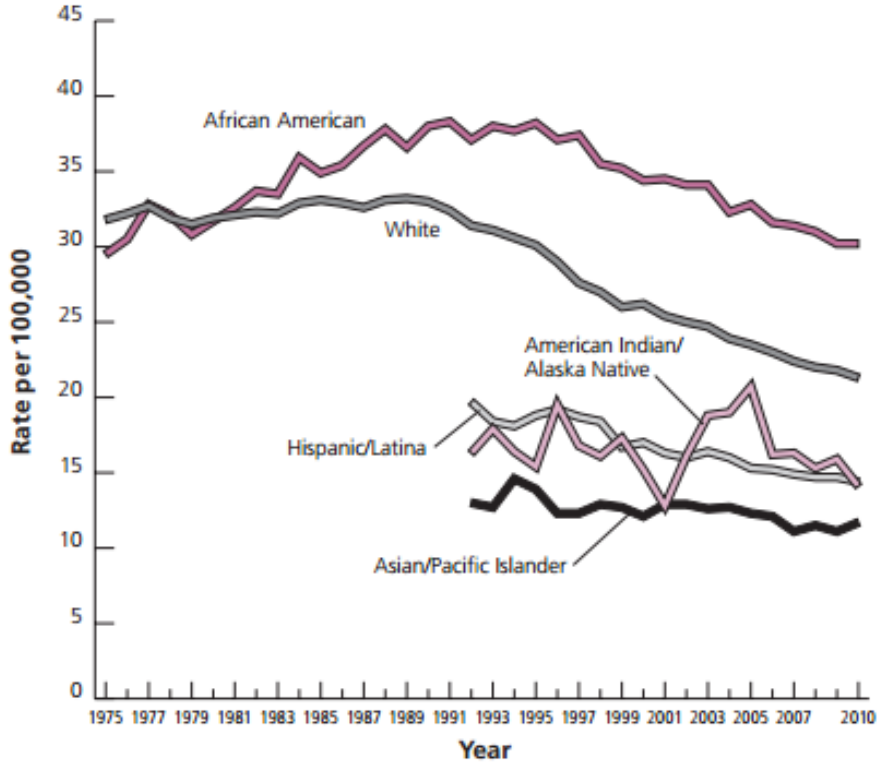
Epidemiology

Figure 5a. Trends in Female Breast Cancer Incidence Rates* by Race and Ethnicity, US, 1975-2010



*Rates are age adjusted to the 2000 US standard population.

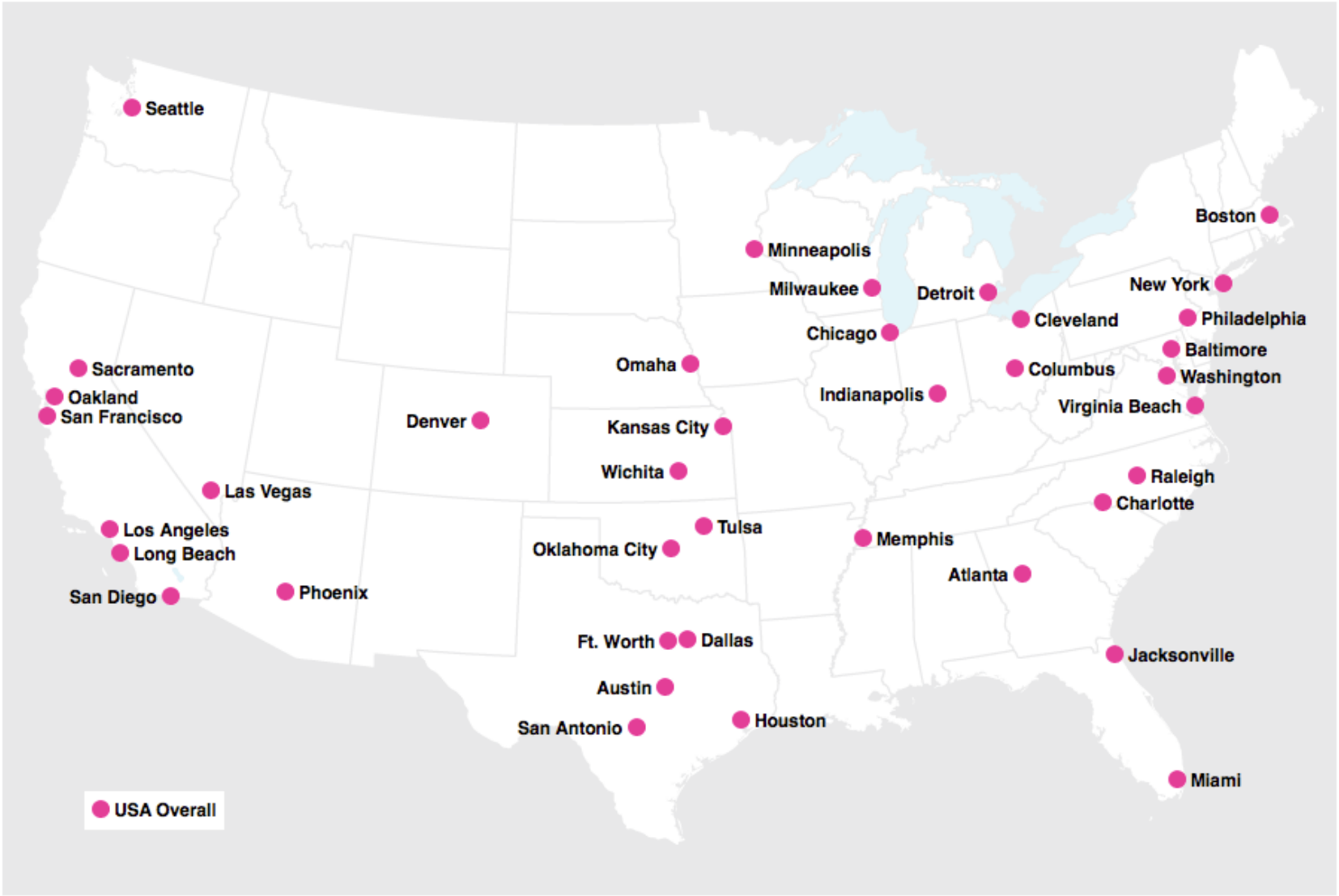
Figure 5b. Trends in Female Breast Cancer Death Rates* by Race and Ethnicity, US, 1975-2010



*Rates are age adjusted to the 2000 US standard population.

American Cancer Society. Breast Cancer Facts and Figures. 2013-2014

2014 Racial Disparity in Breast Cancer Mortality Study



The 2014 Racial Disparity in Breast Cancer Mortality Study, a national study conducted by Sinai Urban Health Institute and the Avon Foundation for Women, found a black:white disparity in breast cancer mortality in 39 of the most populous U.S. cities, with 35 of those cities experiencing a widening disparity over a 20-year period from 1990 to 2009.

Why?

- Access
- Biology
- Information
- GW Mobile Mammography Program

Collaboration: PCF and GW Medical Faculty Associates

Address barriers to mammography

- Financial: free
- Language: Bi-lingual patient navigators
- Partner with Community Leaders


BREAST CANCER
PREVENTION
TIPS

What can we do

- Risk based screening
- Educate and empower women
- Improve disparities
- Modifiable Risk Factors
- RESEARCH
  - Define atypia and high risk lesions with molecular markers
  - Further appropriate and individualized screening protocols
- Collaborations!!!
- Multi-disciplinary
- Women
- Community leaders