Window of Susceptibility for Environmental Exposures: The Menopausal Transition

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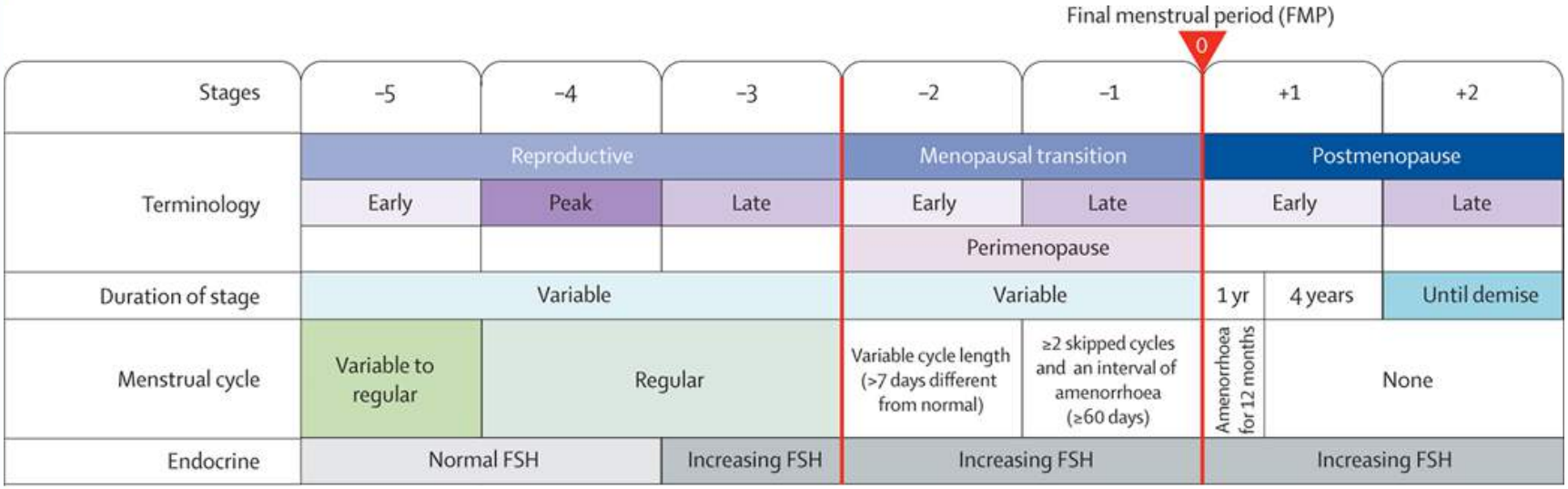
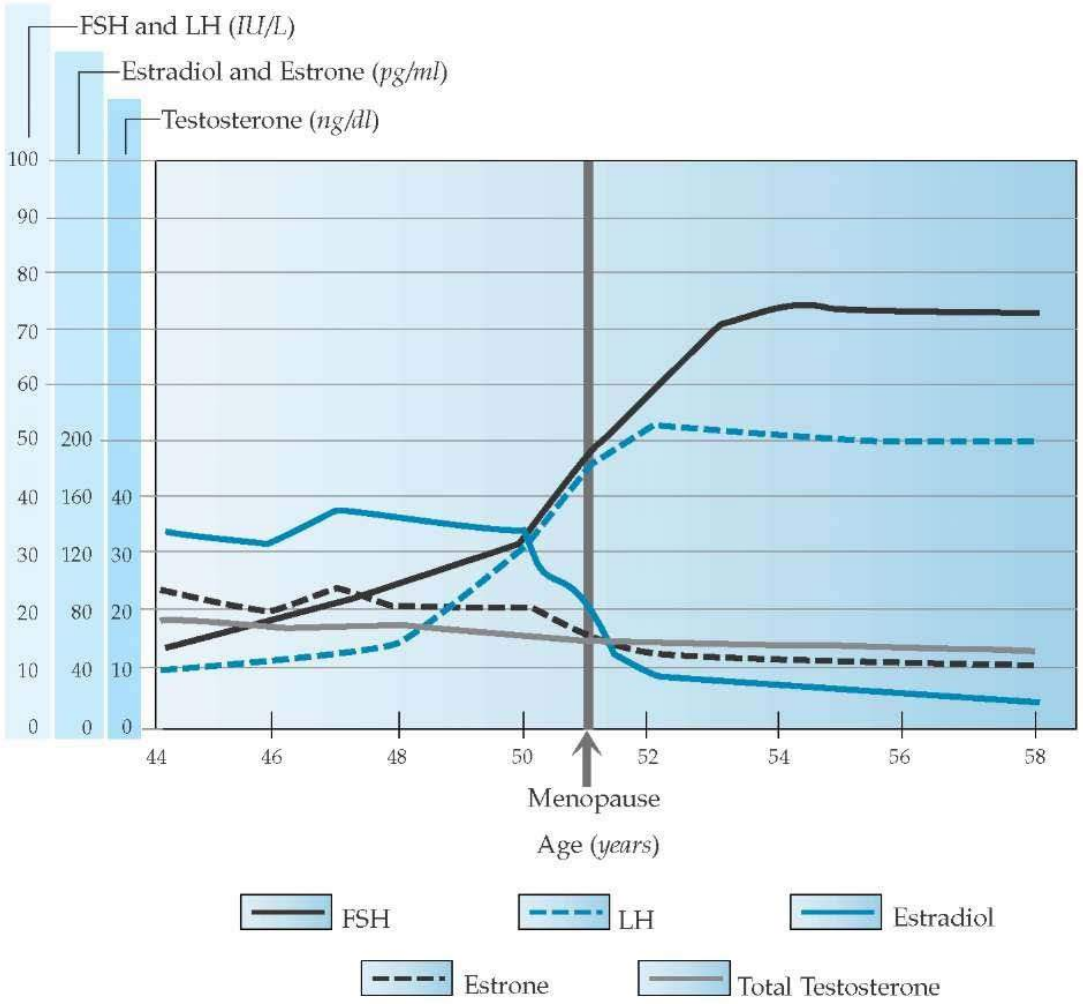
Menopausal transition defined by profound physiological changes

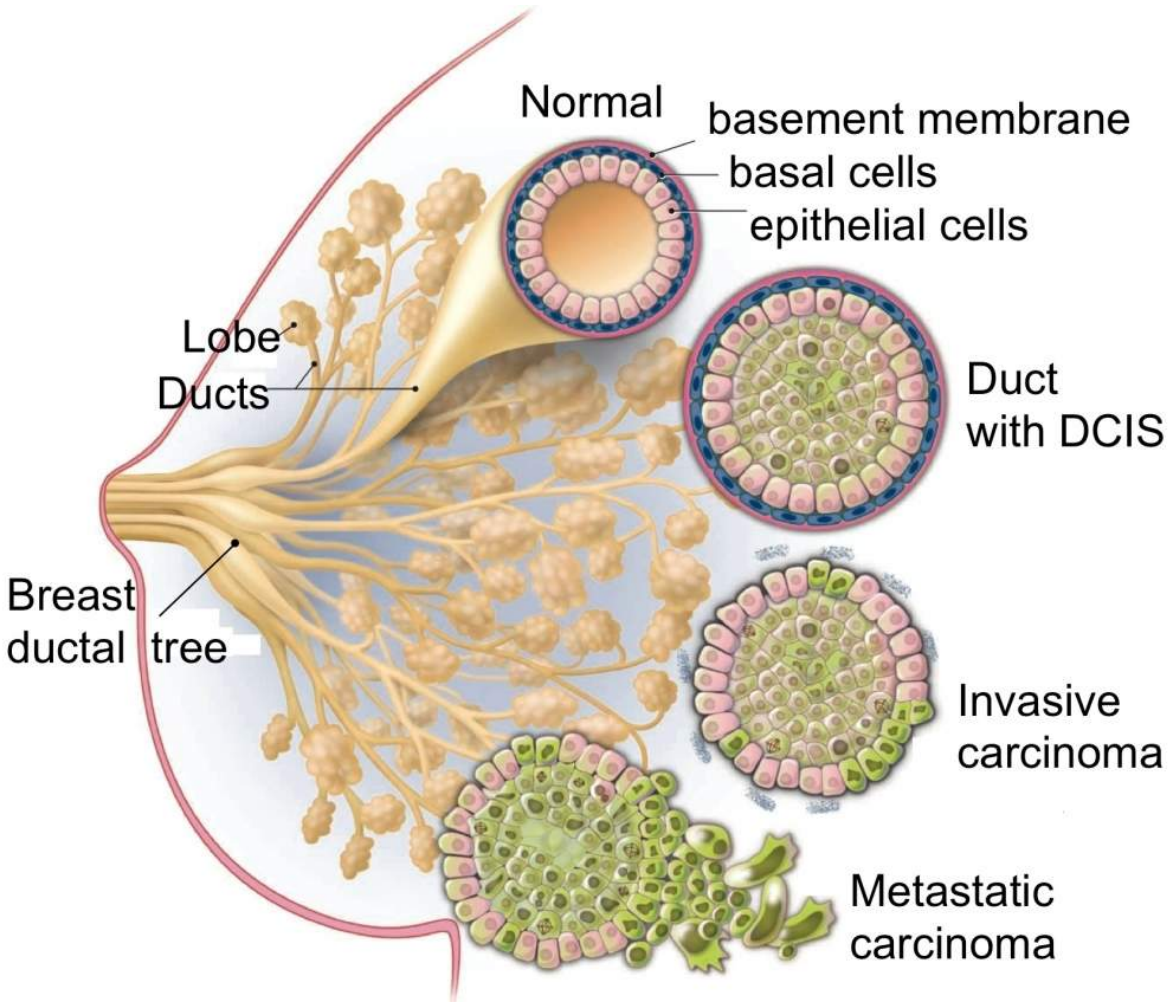


Menopause defined by sustained rise in FSH and LH



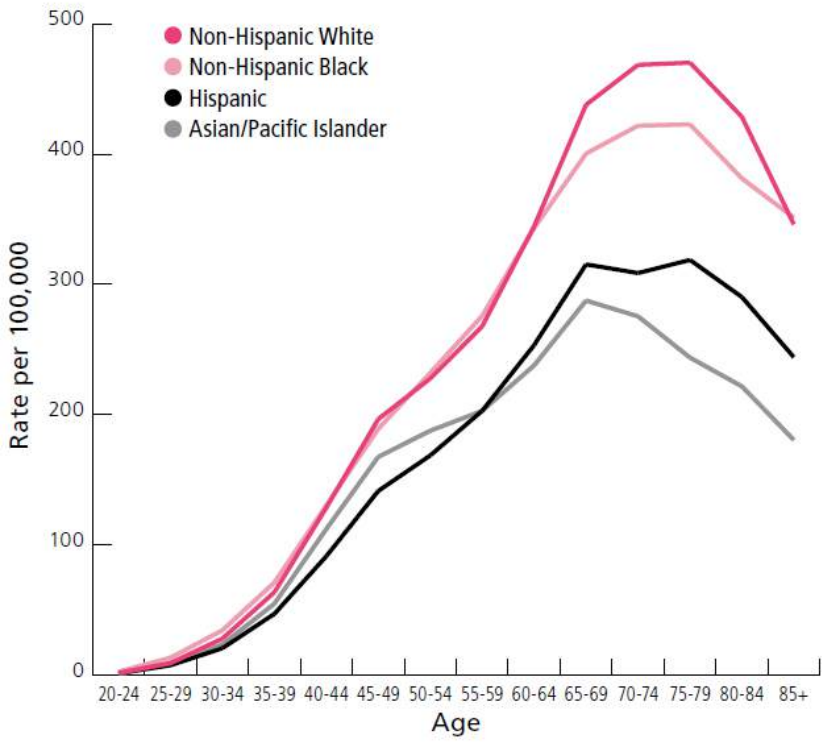
Rationale for studying the menopausal transition as a window of susceptibility

Breast cancer develops in the ducts and lobes (terminal ductal lobular units, TDLUs)



Breast cancer incidence increases with age, plateaus after menopause, and declines after age 80

Figure 1. Age-specific Female Breast Cancer Incidence Rates by Race/Ethnicity, 2010-2014, US



Note: Rates are per 100,000 and age adjusted to the 2000 US standard population.

Sources: Incidence: North American Association of Central Cancer Registries (NAACCR), 2017. Mortality: National Center for Health Statistics, Centers for Disease Control and Prevention, 2017.

American Cancer Society, Inc., Surveillance Research, 2017

- About 75% of breast cancers are diagnosed among women 50 years or older
- Greatest increase in rate of breast cancer occurs during peri- and early postmenopausal years

Cancer Facts and Figures, 2017; DeSantis, CA Cancer J Clini 2017; Benz, Crit Rev Oncol Hematol, 2008

Older women are more likely to be diagnosed with a luminal (ER+) breast cancer

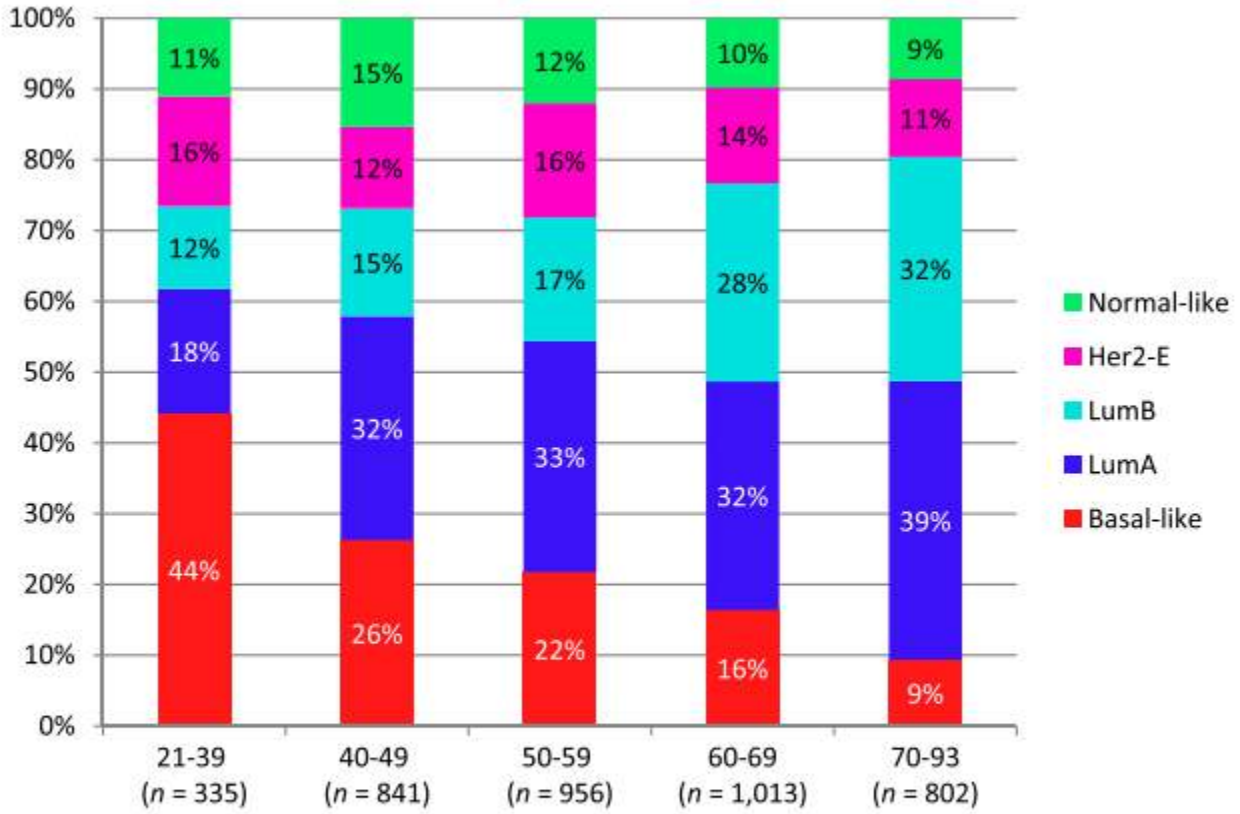


Figure 2. PAM50 intrinsic subtypes by age. The sum of the first column is 101% because of rounding.

Jenkins EO et al, The Oncologist 2014

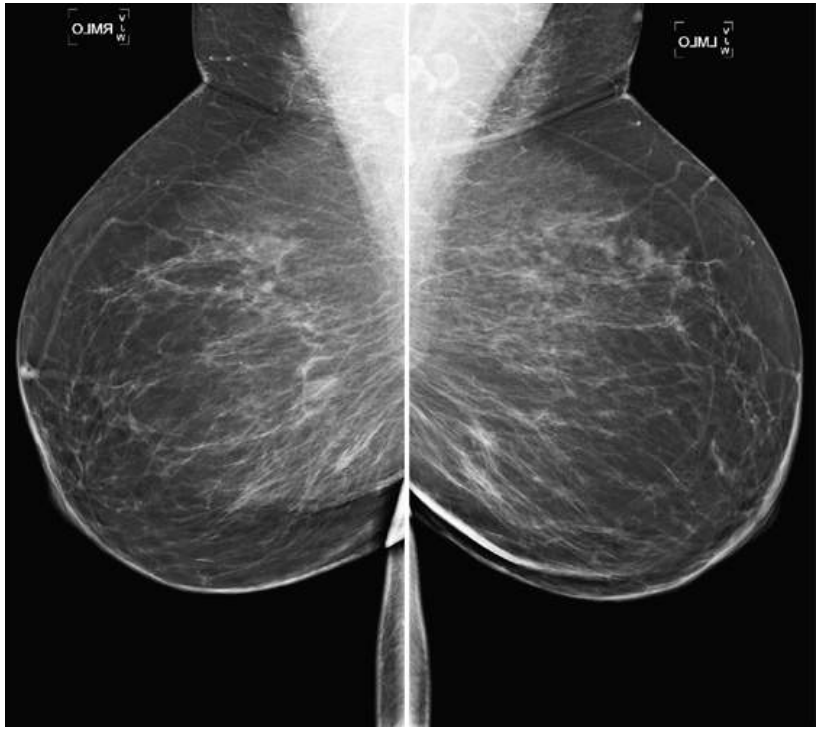
The breast also undergoes profound changes in tissue composition known to be associated with breast cancer

Measurement of breast tissue composition	Source of information
Mammographic density	Mammograms
TDLU characteristics	Fixed tissue specimens
Digital histological analysis	Fixed tissue specimens

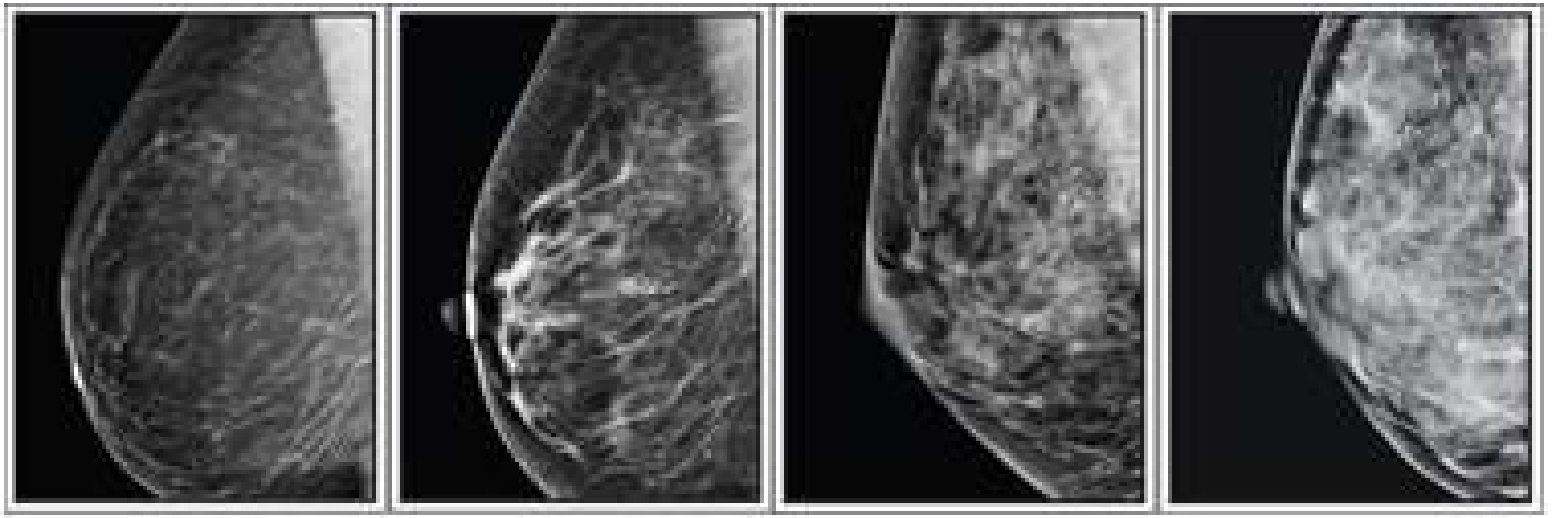
Mammographic density

Mammograms distinguish between tissue components

- Dense tissue
  - Fibroglandular (stromal and epithelial) tissue appears white on mammogram
- Nondense tissue
  - Adipose (fat) tissue appears black on mammogram
- Measurements
  - Absolute amount
  - Percent dense tissue



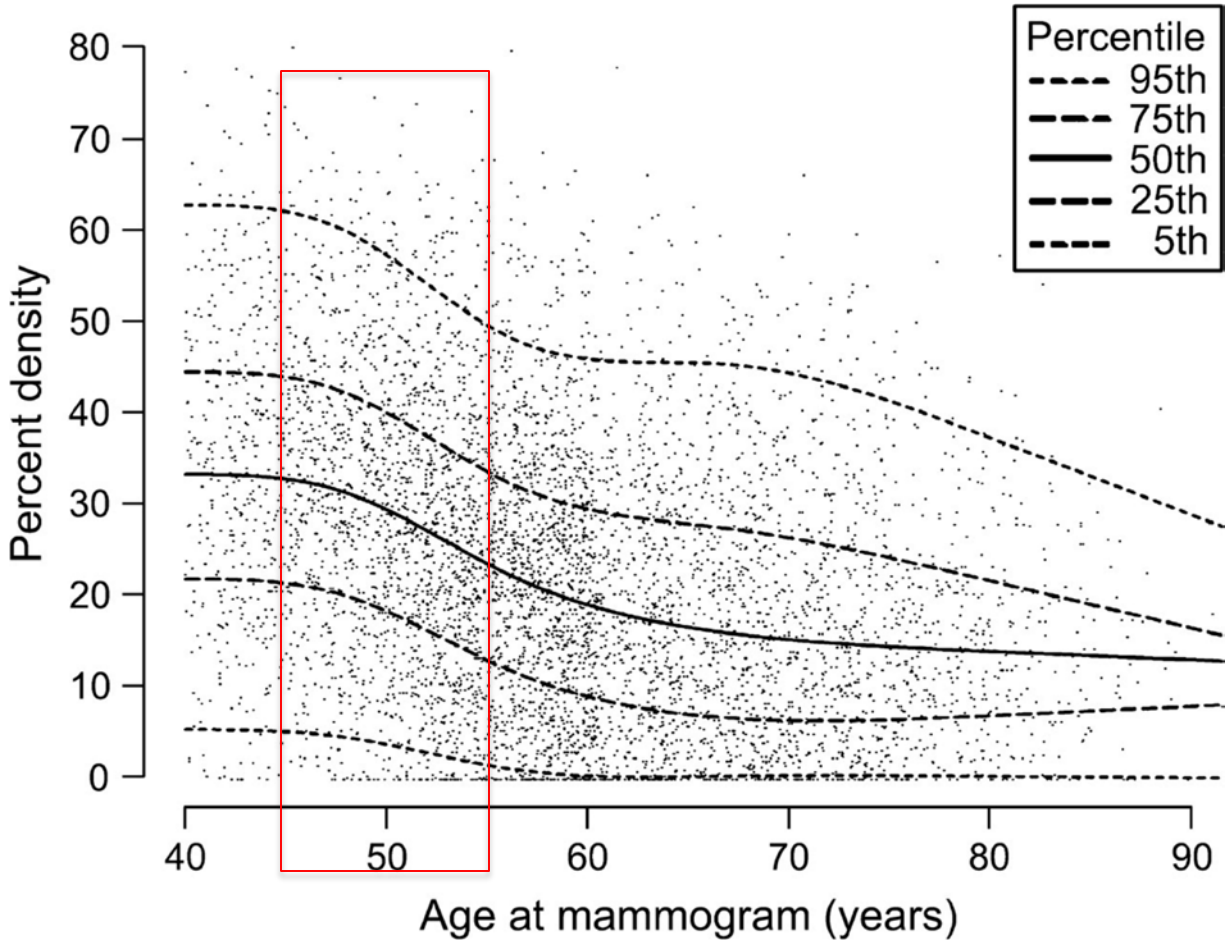
Mammographic density describes proportion of fibroglandular tissue content



4-fold higher breast cancer risk than women with fatty breasts

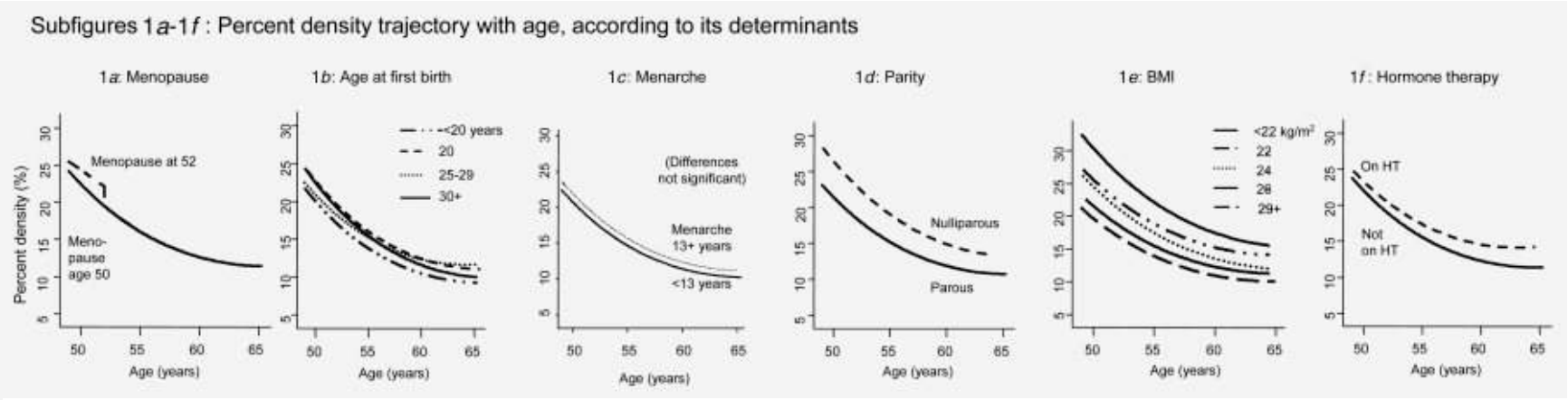
McCormack, CEBP 2006

Mammographic density declines are greatest between ages 45-55



Keleman, Am J Epidemiol. 2008;167(9):1027-1036

Age-related decline in mammographic density varies by known breast cancer risk factors



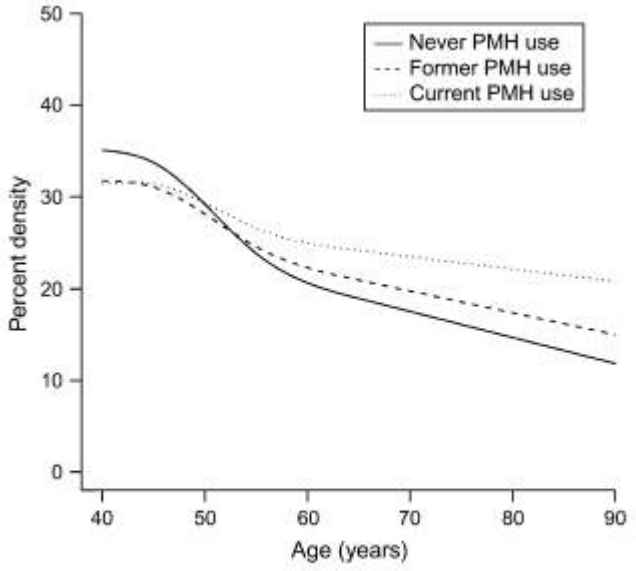


FIGURE 3. Longitudinal patterns of mammographic density by postmenopausal hormone (PMH) use and age among postmenopausal women, Minnesota Breast Cancer Family cohort, 1990–2003.

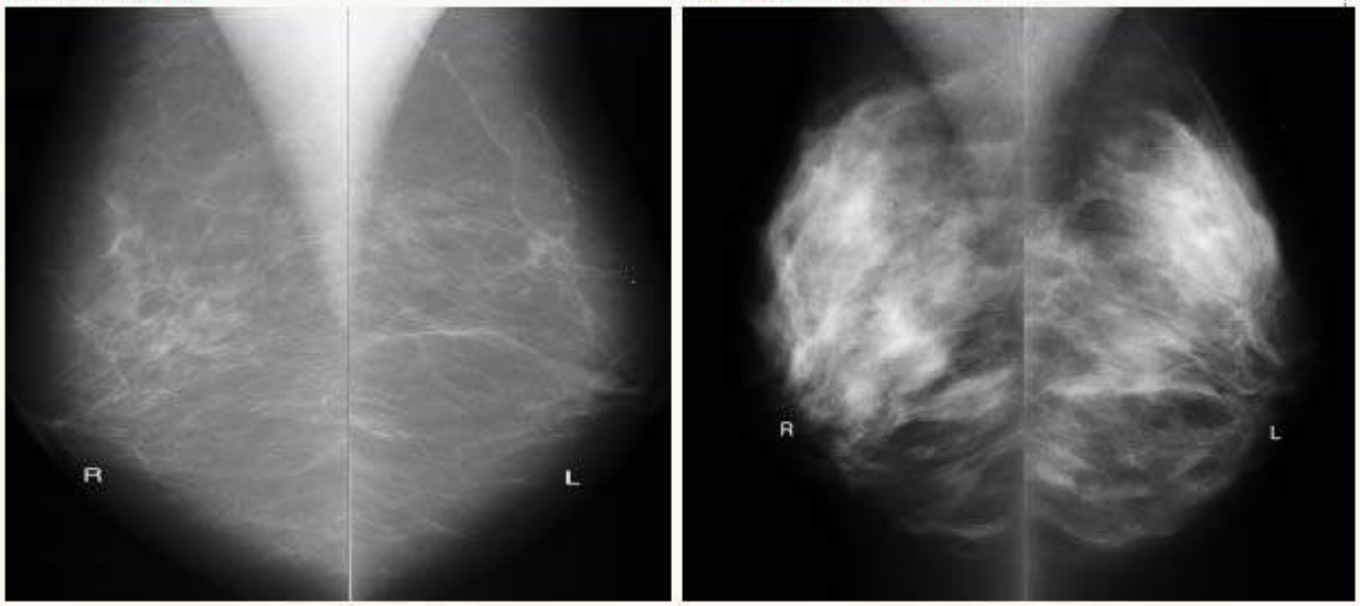
McCormack, Inter J Cancer 2010; Keleman, Am J Epidemiol. 2008

Menopausal hormone therapy increases breast density ~3-6% average over 1-2 years

Dramatic increase in MBD in a postmenopausal woman after 1 year of PMH therapy

A. Before PMH use

B. One year after starting PMH

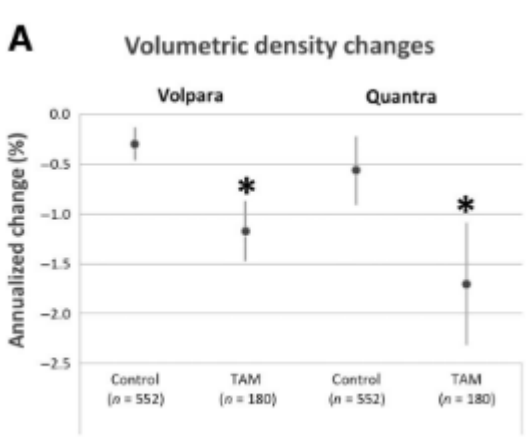


MBD, mammographic breast density; PMH, postmenopausal hormone.

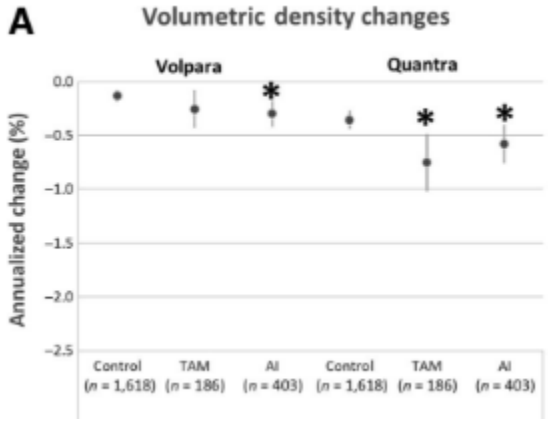
Note: Studies evaluating MBD by quantitative measures to assess the influence of PMH use (conventional estrogen and progesterone) suggest that these hormones are associated with an absolute increase of 3% to 6% in MBD.[11-12]

Ghosh and Vachon, Menopausal Medicine, 2010

Mammographic density is a preventative and therapeutic target



Premenopausal cases with mammograms before diagnosis and after treatment



Postmenopausal cases with mammograms before diagnosis and after treatment

- Preventative use resulting in reductions in density also had 50-60% lower breast cancer risk

Huo, BCRT, 2014; Cuzick, JNCI, 2011; Li, JCO, 2013; Engelmann, CEBP, 2017

Breast composition

Breast composition determined using digital histologic analysis in normal tissue

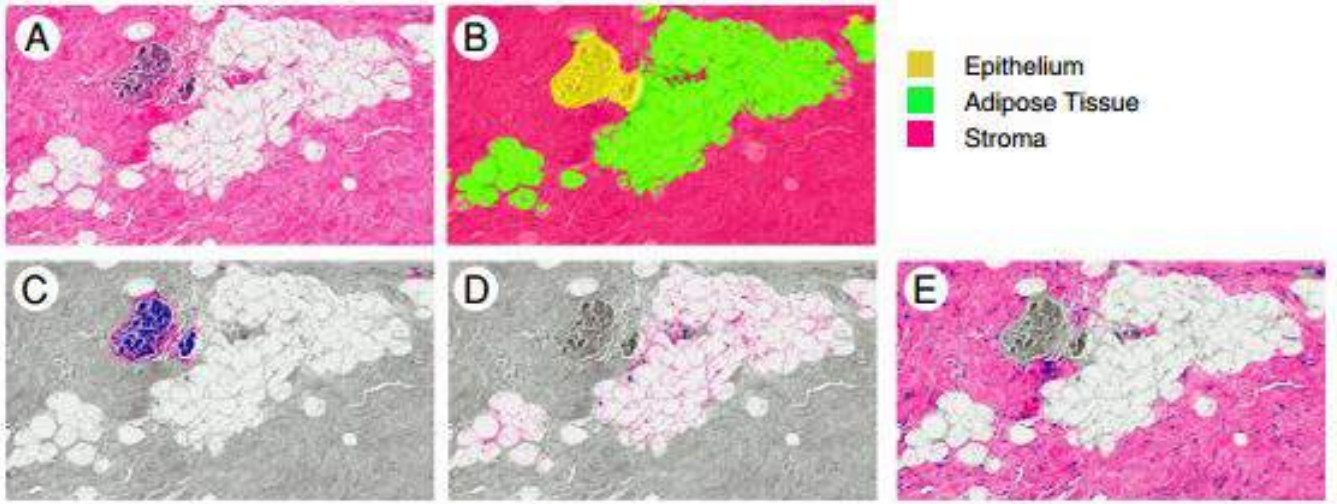


Fig. 1 Quantitative histologic data obtained with novel morphometric methods. Panels A to E represent the images of the H&E slides taken at resolution ×10. A, Image of H&E slide with no annotations. B, Image from panel A with annotation overlay of epithelial area in yellow, adipose tissue area in green, and stromal area in pink as demonstrated in the key in the figure. C, Image from panel A with annotation overlay of epithelial nuclei in blue. D, Image from panel A with annotation overlay of adipose tissue nuclei in blue. E, Image from panel A with annotation overlay of stromal nuclei in blue. C to E, Areas shown in gray are excluded from analysis.

Stromal, adipose tissue, and epithelial % area and nuclear density

Stromal area and epithelial density decrease, and adipose area increases with age

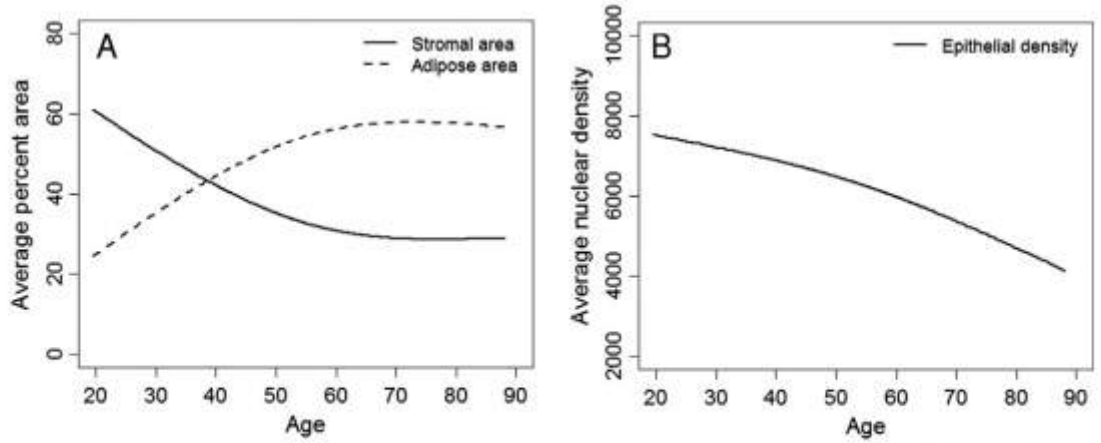


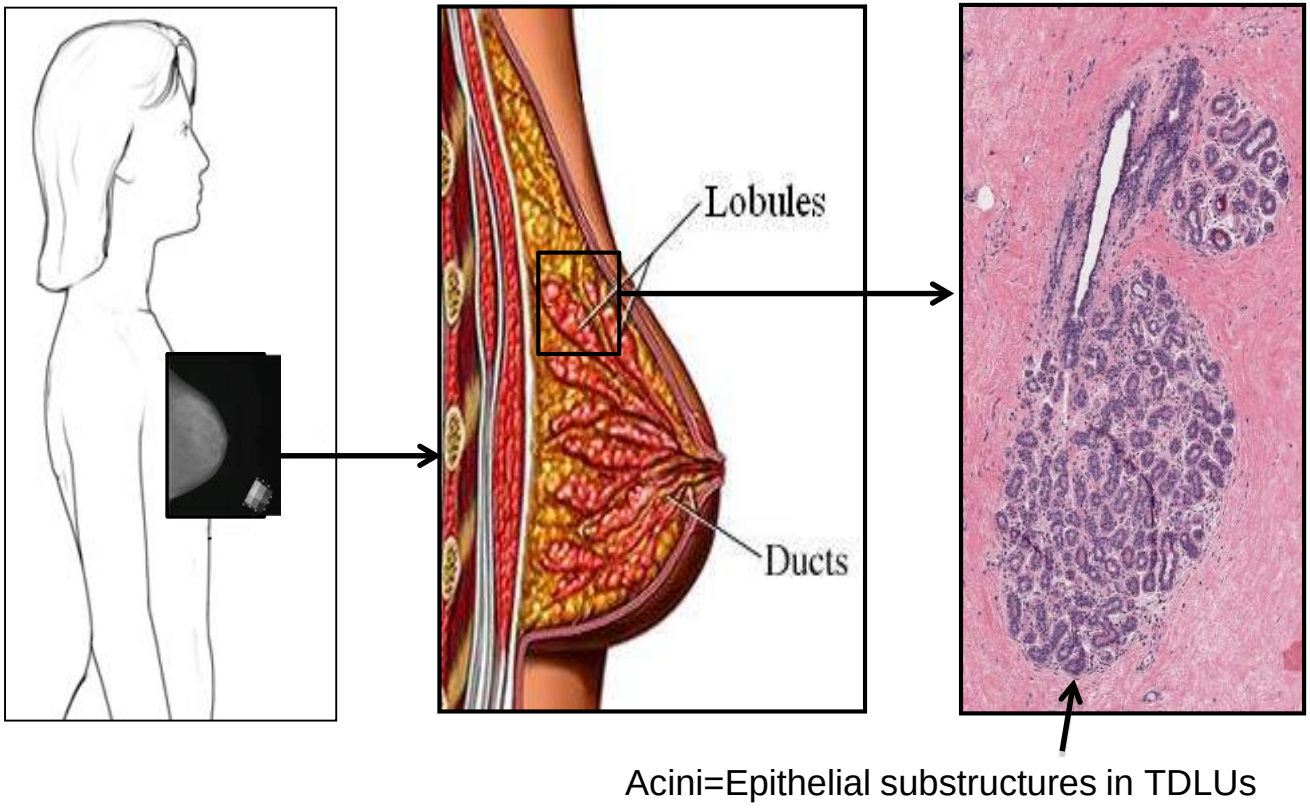
Fig. 2 Cubic spline curves for stromal area, adipose area, and epithelial nuclear density by age. Spline curves were generated from cubic spline models with a knot specified at 55 years of age to visualize the relationship between age and breast tissue composition. A, Stromal area and adipose tissue area are shown as percentage of total area. B, Epithelial nuclear density is in nuclei per square millimeter of epithelium.

- % epithelial area did not vary by age

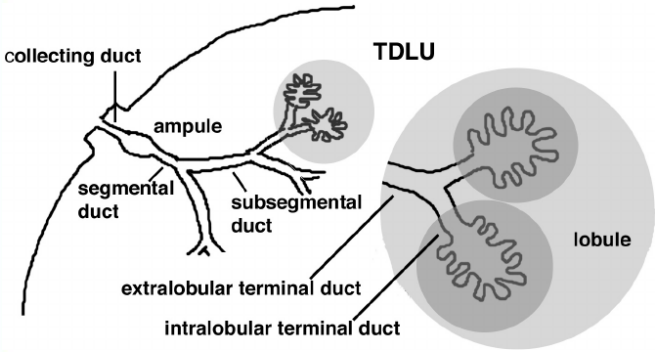
Sandhu, Human Pathology, 2016

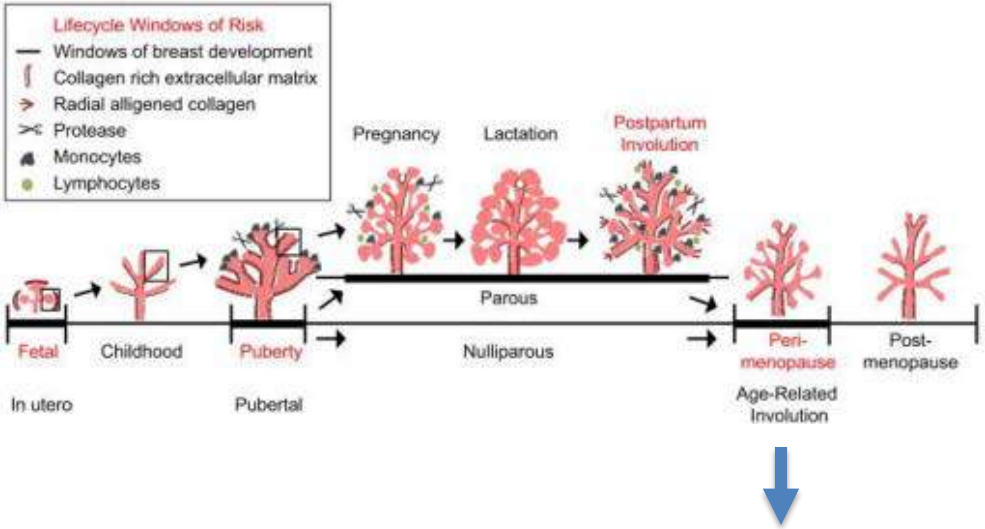
Age-related involution

Breast Tissue Aging: Involution of Terminal Duct Lobular Units (TDLU)



TDLUs change through the lifecourse





TDLU involution is a normal process of aging. During involution, the number and size of TDLU decrease in number and size.

Martinson, Exp Cell Res 2013; Guo, J Clin Med 2017

Age-related TDLU involution

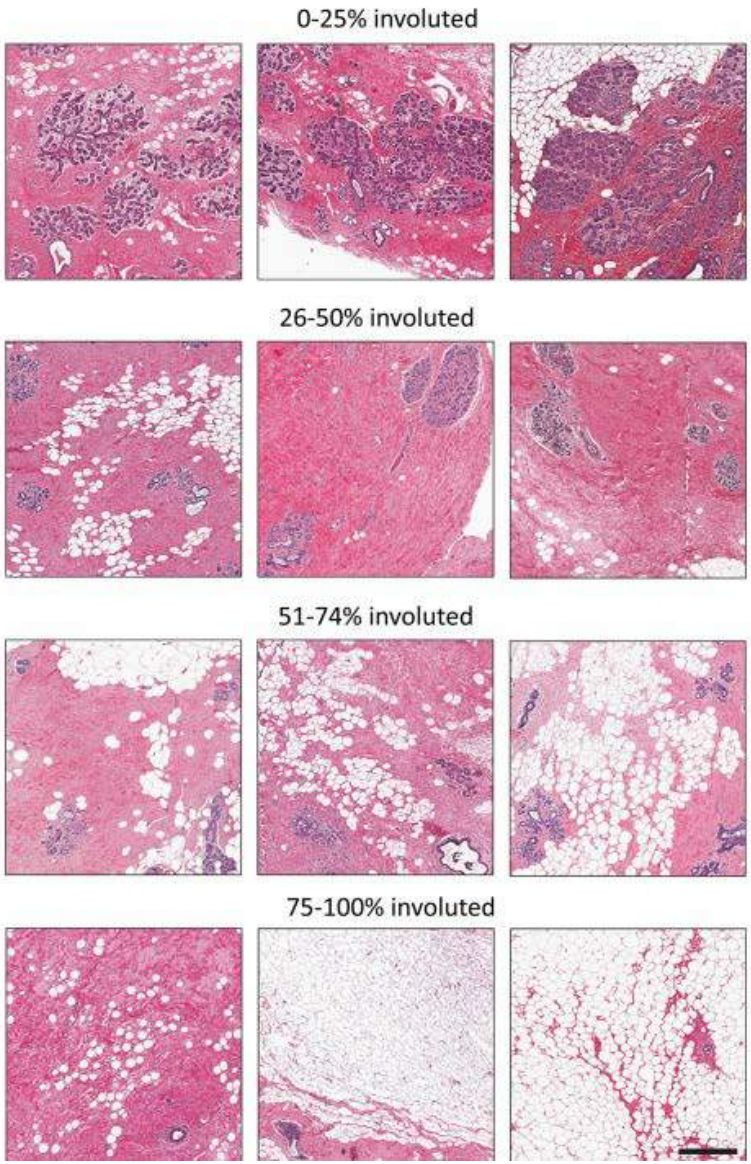
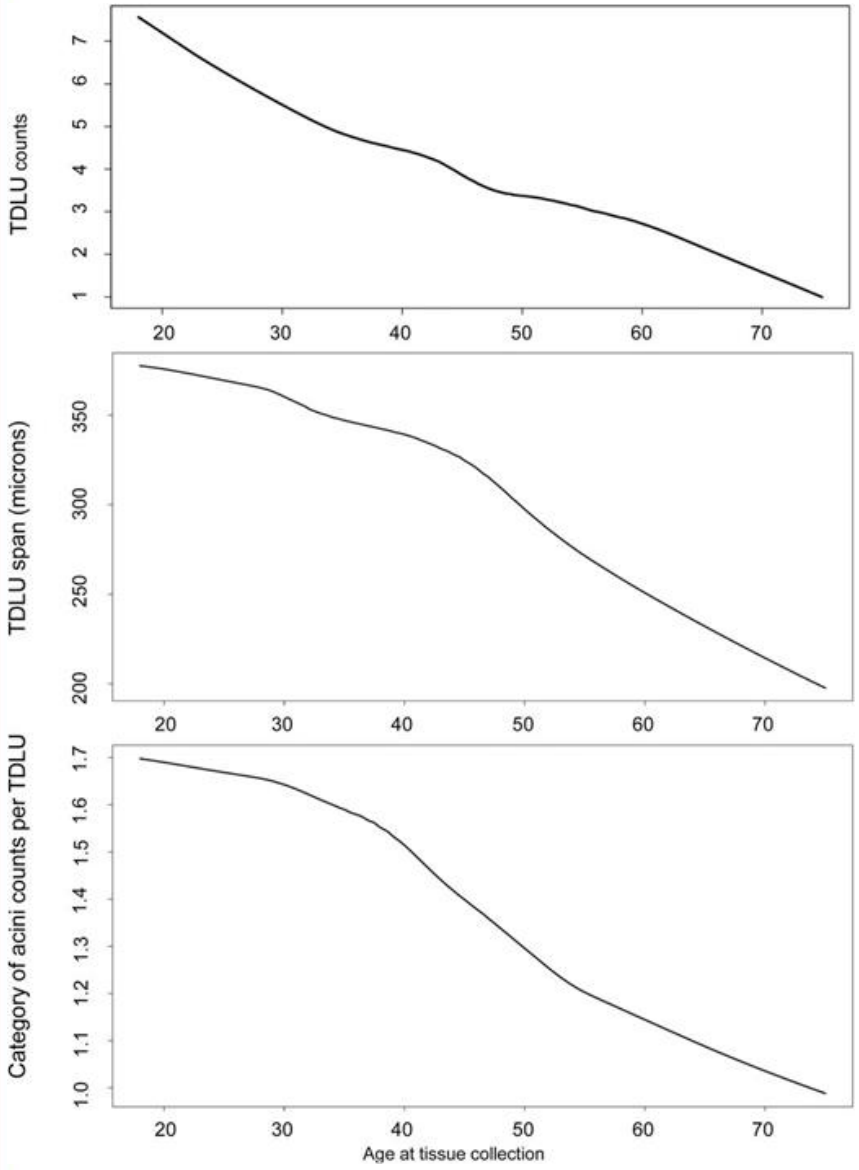
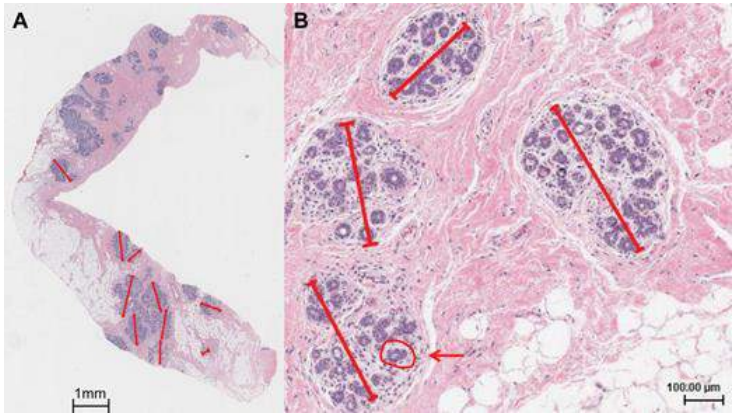


Fig. 1 Qualitative assessment of age-related lobular involution. All images are at the same magnification. *Scale bar* 500 μm

Radisky, BCRT 2016

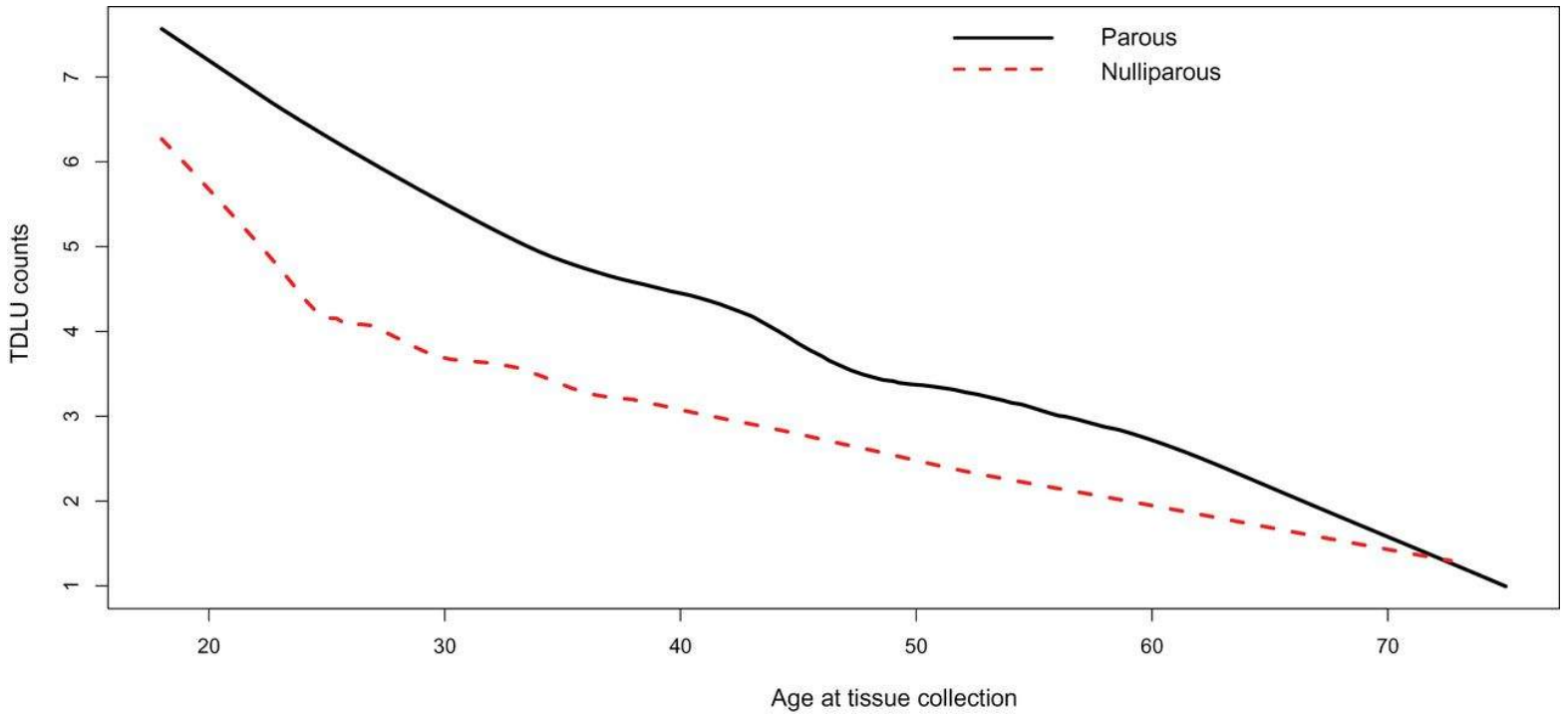
Quantifiable measures of TDLU involution related to age





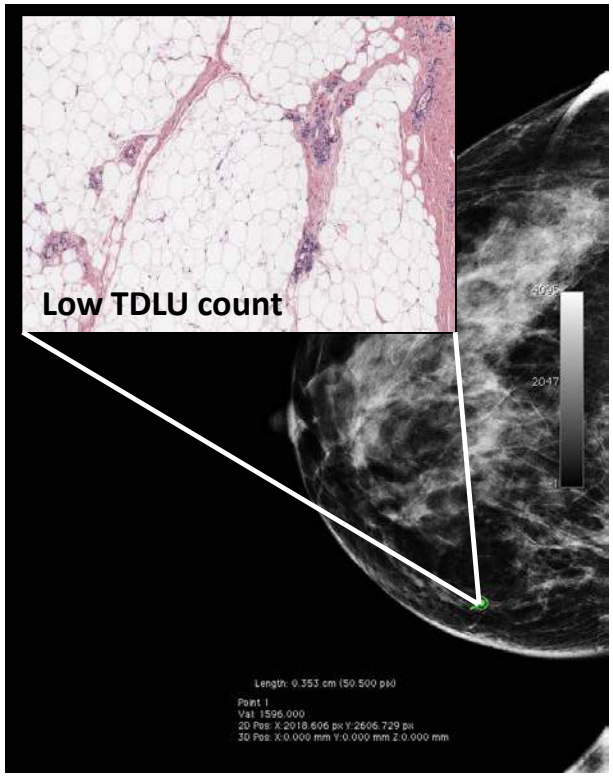
Figueroa, JNCI, 2014

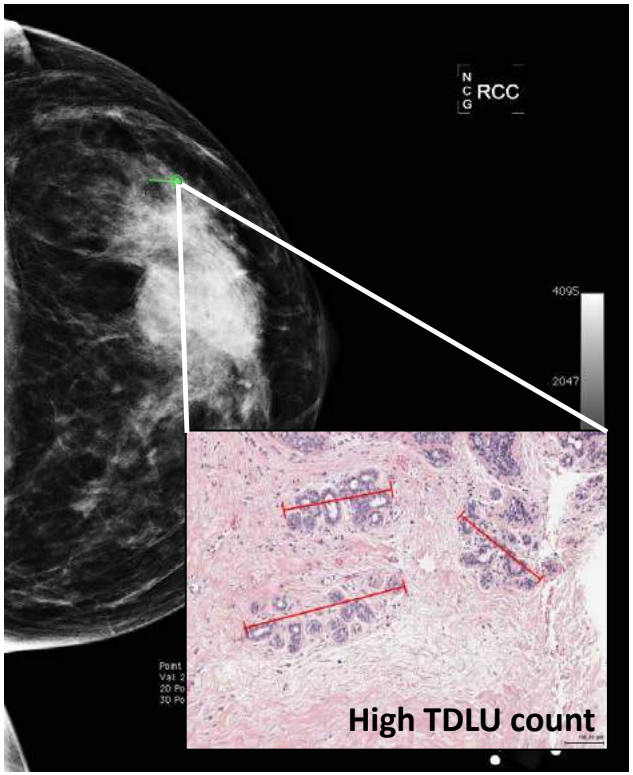
Parity related to TDLU counts by age



Figueroa, JNCI, 2014

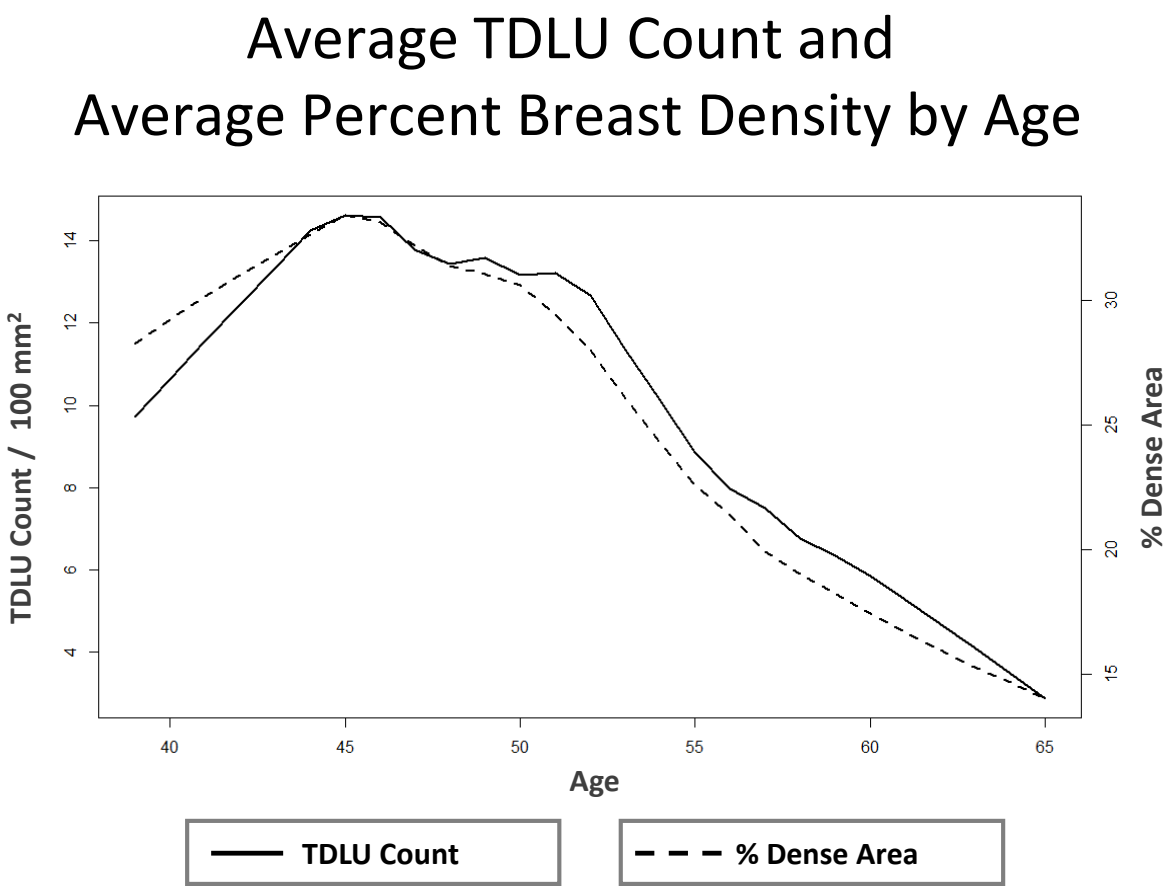
Epithelium and stroma responsible for radiological breast density





Gierach GL, et al. *Cancer Prev Res* 2015

After menopause, rapid decline in TDLU count and % dense area of the breast



More at-risk epithelium may partially explain risk associated with higher BD.

Gierach GL, et al. *Cancer Prev Res* 2015

Summary

Emerging concepts

- Breast tissue changes dynamically and continuously through perimenopause and early menopause
- Several modalities exist to query changes in breast composition as an intermediary of breast cancer
  - Mammographic density, used as breast cancer intermediary in BCERP studies
- Age-related TDLU involution reduces number of breast cells at risk of cancer
  - TDLU involution as an important intermediary endpoint for breast cancer
- Stroma plays an important role in breast development and carcinogenesis

Future directions

- Clarify robust measures of relevant characteristics of breast composition to identifying breast cancer risk factors
- Determine modifiable factors that increase rate of TDLU involution, epithelial nuclei density, and stromal proportion
- Use of other intermediate outcome for assessing role of environmental toxins

Take home points for our community: American Cancer Society Cancer Prevention Guidelines

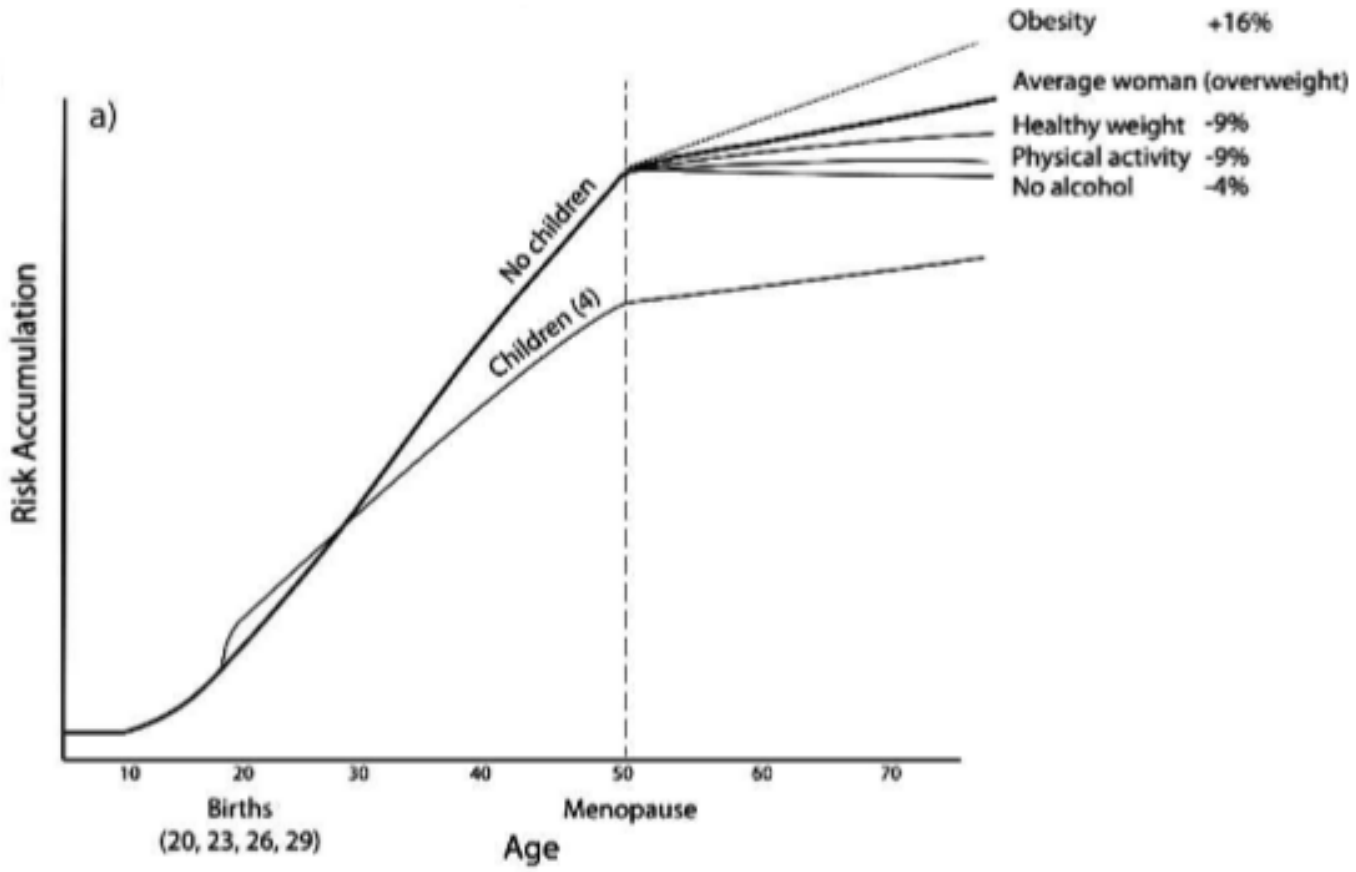
Consume lots of fruits and vegetables

Minimize alcohol intake, if at all

Walk an hour a day at a moderate pace

Maintain a healthy weight throughout life

Breast cancer risk reduction achievable changing modifiable factors after menopause



Colditz and Bohlke, CA Cancer J Clin, 2014

ACS recommendations for community action

Public, private, and community organizations should work together at national, state, and local levels to apply policy and environmental changes that:

- Increase access to affordable, healthy foods in communities, places of work, and schools, and decrease access to and marketing of foods and drinks of low nutritional value, particularly to youth.

- Provide safe, enjoyable, and accessible environments for physical activity in schools and workplaces, and for transportation and recreation in communities.

Q&A

Mammographic density also makes diagnosing breast cancer harder