Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC)

- Prioritizes identification of periods of susceptibility throughout the life course
- Emphasizes understanding mechanisms of breast density and breast cancer
- Advocates an animal-to-human approach
Windows of Susceptibility to Environmental Breast Cancer

Breast tissue changes dynamically throughout life. Breast tissue responds to hormones. Hormonal fluctuation (e.g. puberty, postpartum, perimenopause) changes histology and mammographic density.
Histology and Aging

Age 23
- 6% Epithelium
- 82% Stroma
- 12% Adipose

Age 35
- 10% Epithelium
- 63% Stroma
- 27% Adipose
Histology and Aging

Age 49

12% Epithelium
38% Stroma
50% Adipose

Age 56

9% Epithelium
8% Stroma
83% Adipose

Age 61

3% Epithelium
8% Stroma
90% Adipose
Mammographic Density

• Among the strongest risk factors for breast cancer.

• Measure of ‘fibroglandular content’; mechanistically poorly understood.

• Mammographic density decreases with age.
Age-associated Gene Expression

A. Gene expression in whole tissue

Pirone, D’arcy et al. (2012) Cancer, Epidemiology Biomarkers & Prev
Age and Breast Cancer Risk

Pike et al. (1983) Nature
Windows of Susceptibility to Environmental Breast Cancer

Breast tissue changes dynamically throughout life. Breast tissue responds to hormones and environmental exposure. Hormonal fluctuation (e.g. puberty, postpartum, perimenopause) create windows of susceptibility to exposure.
The Normal Breast Study

• Women having breast surgery at UNC
  – Reduction mammoplasty, mastopexy
  – Excisional biopsy with benign diagnosis
  – Breast conserving surgery
  – Prophylactic mastectomy

• Medical records abstraction & telephone interview

• Blood and tissue specimens with detailed preanalytic data
  – Timed devascularization interval
  – Carefully measured distance to tumor (\(<1, 1-2, 2-4, >4\) cm)
  – Paired fresh, frozen and paraffin
Measurement of breast composition

Original H&E slide

Manual annotation
- Adiposity
- Epithelium
- Analysis area

Genie annotation
- Adiposity
- Epithelium
- Stroma
Measurement of breast composition

30% Stroma
63% Adipose
7% Epithelium

- Adipose Tissue
- Epithelium

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Breast Tissue Composition
Density of Nuclei within Regions

Figure 1

Sandhu et al. (2016) Hum Pathol
As age advances, the microenvironment shifts dramatically.

Sandhu et al. (2016) Hum Pathol
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Two Subtypes of Benign Breast Tissue

A

B

Two Subtypes of Benign Breast Tissue

Troester et al, TCGA normal breast committee (NPJ Breast Cancer 2016)
Histological Phenotypes of Density

Sun et al. (2013)
Clin Cancer Res
Hypothesis: Role for Microenvironment in ER+ Progression

- Presence of occult tumor cells or ‘field cancerization’ did not predict survival.

- Other evidence for microenvironment in ER+ progression from Rohan et al. (2014) JNCI, Tumor Microenvironment Metastasis (TMEM) score

Troester et al, TCGA normal breast committee (2016 NPJ Breast Cancer)
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Exposure-disease paradigm

CHALLENGE FOR BREAST CANCER BIOMARKER RESEARCH:
• Long induction and latency periods
• Multiple exposures
• Multiple outcomes
• Tissue-level biomarkers needed

Perera and Weinstein, J Chron Dis 35:581, 1982
Comparative Analysis: Humans vs. Rodent Models

Collaboration with Suzanne Fenton, NIEHS
Filgo et al. (2016) Toxicol Pathol 44 (7)
Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC)

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- Emphasizes understanding mechanisms of breast density and breast cancer
- Advocates an animal-to-human approach
- Intensify the study of environmental chemicals
Acknowledgments

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  – **UNC**: Bob Millikan, Andy Olshan, Chuck Perou, Keith Amos, Lisa Carey, Shelley Earp, Stephanie Cohen, Ryan Miller, Hazel Nichols, Carey Anders, Liza Makowski
  – **TCGA**: Chuck Perou, Katie Hoadley, Chris Benz, Andy Beck, Gordon Robertson, Andrew Cherniak, Peter Laird...

• Trainees
  – Emma Allott, Erin Kirk, Rupninder Sandhu, Patricia Casbas-Hernandez, Amy Sun, Lynn Chollet Hinton, Samantha Puvanesarajah, Ebonee Butler, Ashley Fuller, Lindsay Williams, Heather Ann Brauer, Jessica Rein, Tyisha Williams

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