



## Identification & Management of the Patient at High Risk for Breast Cancer: *The Role of Breast Density*

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## Objectives

- Describe the role of breast density in breast cancer risk assessment
- Describe the impact of hormonal compounds and lifestyle factors upon breast density
- Identify the potential role of breast density in breast cancer risk assessment models

## Handout

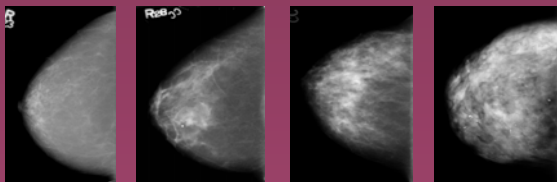
- Can be found at:

<http://www.healthsystem.virginia.edu/internet/radiology/mammography/RSNA2007handout.cfm>

## Disclosures

- Research agreements
  - General Electric Company
  - Wyeth Pharmaceuticals
  - Organon Pharmaceuticals

## Breast Density: Impact on Mammography



87%	→	63%
	Sensitivity	
97%	→	89%
	Specificity	

Carney PA. Ann Int Med 2003

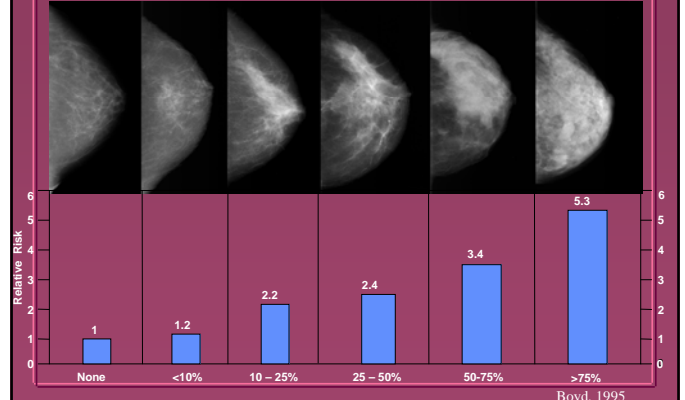
## Breast Cancer Risk Factors

Nulliparity/late parity	RR 1.3
Early menarche/late menopause	RR 1.3
Alcohol use	RR 1.3
Menopausal Hormone Therapy	RR 1.4
Obesity	RR 1.5
Female age 65	RR 1.7
Family History	RR 1.7
<b>Dense breast tissue</b>	<b>OR 4.3</b>
Biopsy with atypia or LCIS	RR 5.0
Prior history of breast cancer	RR 7.0

“Breast density is perhaps the most undervalued and underutilized risk factor in studies investigating the causes of breast cancer.”

Celia Byrne, Ph.D. 1997  
Brigham and Women’s Hospital

### Boyd Classification



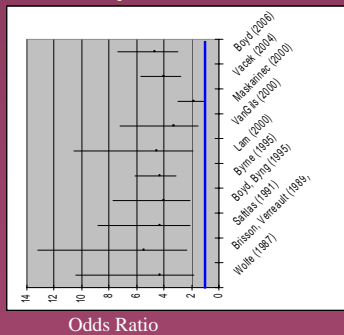
### Quantitative Assessment of Breast Density and Breast Cancer Risk

Type	Study Population	Cases: Controls
Boyd (1982)	Women’s College Hospital, Toronto, Canada	183:183
Brisson, Merletti (1984)	Two Boston hospitals (1972-1978)	408:1021
Brisson, Morrison (1984)	Three Boston hospitals (1978-1982)	362:686
Wolfe (1987)	Hutzel Hospital, Detroit MI (1979-1982)	160:160
Brisson, Verreault (1989)	Quebec City (1982-1984)	290:645
Saftas (1991)	BCDDP (1973-1975)	260:301
Boyd, Byng (1995)	NBSS	354:354
Kato (1995)	NYU Women’s Health Study (1985-1991)	197:521
Byrne (1995)	BCDDP (1973-1980)	1880:2152
Lam (2000)	VBCSS (1996-1997)	529:2116
VanGils (2000)	Nijmegen Br Cancer Scr Prog (1985-1994)	108:400
Maskarinec (2000)	Kaiser Permanente Hawaii (1991-1997)	647:647
Vacek (2004)	VBCSS (1996-2000)	61,844
Nagata (2005)	Gifu City (Japan) (2000-2002)	145:659
Boyd (2007)	NBSS, Ontario Breast SP, British Columbia	1112:1112

### Method Odds Ratio 95% C.I.

Method	Odds Ratio	95% C.I.
Boyd (1982)	Visual	2.8-6.0*
Brisson, Merletti (1984)	Visual	3.8-5.4**
Brisson, Morrison (1984)	Visual	2.0-4.4**
Wolfe (1987)	Manual Planimetry	4.3
Brisson, Verreault (1989)	Visual	5.5**
Saftas (1991)	Manual Planimetry	4.3
Boyd, Byng (1995)	Visual	6.0
	Computerized (Thresholding)	4.0
Kato (1995)	Manual Planimetry	3.6 (premeno)
		2.1 (postmeno)
Byrne (1995)	Computerized Planimetry	4.3
Lam (2000)	BIRADS	4.5
VanGils (2000)	Computerized (automated)	3.3
Maskarinec (2000)	Computerized (thresholding)	1.8
Vacek (2004)	BI-RADS	4.0
Nagata (2005)	Computerized (thresholding)	4.4 (50-75%) Premeno
		1.4 (>75%) Premeno
		4.2 (>75%) Postmeno
Boyd (2007)	Computerized (thresholding)	4.7

### Breast Density and Cancer Risk



### Density is an Independent Risk Factor

- Two studies controlled for weight, body mass index (BMI), age, menopausal status, age at first birth, nulliparity, family history, hormone use, and previous breast biopsy
- Still found a positive correlation with breast cancer risk

## Attributable Risk

- 50% of women 40-49 are >50% dense
- 30% of women 70-79 are >50% dense
- Two studies estimate attributable risk of breast density as 28-30% of all breast cancers

## Masking Hypothesis

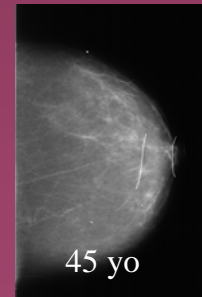
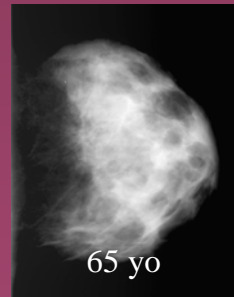
- Apparent association of density with cancer risk could be due to later detection of cancers missed on initial screen due to lower sensitivity of mammography in women with dense tissue



## Masking Hypothesis

	Time 1	1yr later	2yrs later	3yrs later	4yrs later
100 cancers	85	10	3	2	0
100 cancers	60	23	12	5	0

## Why do some women have dense breasts?



## Breast Density is Heritable

- Study of 571 monozygous and 380 dizygous twins
  - Heritability estimated to be 65%
- Family study in Minnesota
  - Chromosome 5p likely a locus of disease
  - May account for up to 22% of variation in breast density

Boyd NF. Cancer Epid Biomarkers & Prev 2006  
Vachon CM. Cancer Res 2007

## Genetics of Breast Cancer

- **Low prevalence**  
Account for about 5% of breast cancers
- **High prevalence**  
Account for 30-50% of breast cancers?
- **High penetrance**  
60-80% lifetime risk
  - BRCA 1
  - BRCA 2
  - Li-Fraumeni
- **Low penetrance**  
15-20% lifetime risk?
  - Related to breast density?
  - Estrogen metabolism?
  - Growth factor production?



## What is Breast Density?

- Ducts
- Lobules
- Stroma
  - Collagen
  - Fibroblasts
  - Blood vessels, etc.

Important!  
Produces growth factors

## Dense Breast Tissue

- Greater risk of benign breast disease
- RR 12.2 for usual hyperplasia
- RR 9.7 for ADH or DCIS

## Cancers in Dense Breasts

- Higher grade
- ER negative
- Larger size
  - Masking?
  - Growth factors?
  - More rapid tumor growth in dense tissue?

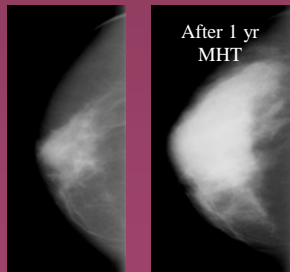
Roubidoux MA. Radiology; 2004

## Factors that Influence Density

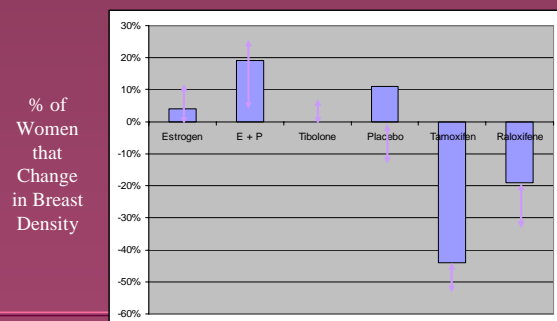
- Higher density
  - Menopausal hormone therapy
  - Nulliparity
- Lower density
  - Parity
  - Obesity
  - Menopause
  - Advancing age
- Weak or no assoc
  - Exercise
  - Diet
  - Alcohol
  - Smoking
  - Oral contraceptives

## Menopausal Hormone Therapy Increases Breast Density

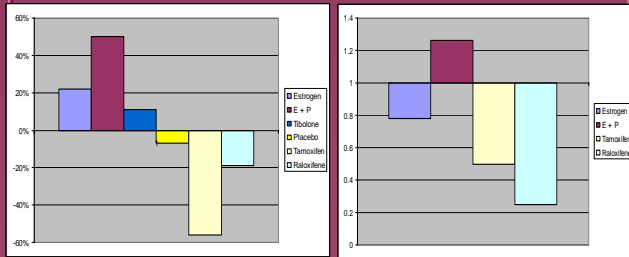
- 17-75% of women
- Usually bilateral and diffuse
- Greatest change occurs in the first year of use
- Associated with mastalgia



## Change in Breast Density



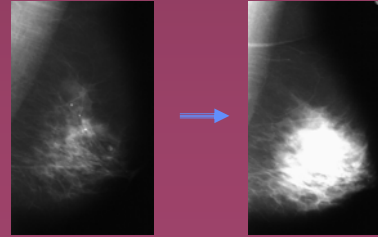
## Correlation of Breast Density and Breast Cancer Risk



% Women that Change in Density

RR of Breast Cancer

Does an increase (or decrease) in density increase (or decrease) individual risk?



## Current vs. Past Density?

Initial Density	3 yrs later	Odds Ratio
Fatty	Fatty	1.0
Fatty	Scattered	1.9
Fatty	Hetero	3.4

- Increasing breast density increases risk

Kerlikowski K.  
JNCI 2007

## Decreasing density may not lower risk

Initial Density	3 yrs later	Odds Ratio
Ext Dense	Ext Dense	1.0
Ext Dense	Hetero	1.1
Ext Dense	Scattered	0.72
Ext Dense	Fatty	0.96

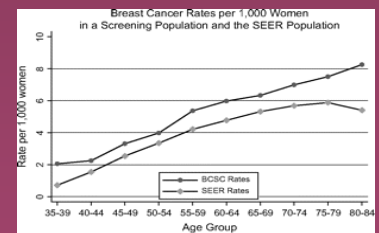
- Breast cancer risk remains elevated for 5-10 years after assessment

## Breast Cancer Risk Models

Model	Evaluates	Accuracy
Gail	Personal risk factors (age, parity, etc)	0.48
Claus/BRCA Pro	Family history	0.56
Tyrer-Cuzick	Personal risk factors & Family history	0.81

## Models that Incorporate Breast Density Improve Accuracy

- Breast Cancer Screening Consortium (BCSC) (Barlow WE. JNCI, 2006).
- BCDDP (Chen J. JNCI 2006)



## Managing Women with Dense Breast Tissue

- Annual mammography, age 40 and older
  - DMIST demonstrated small but significant increase in sensitivity with digital over film-screen for women with heterogeneous or extremely dense breasts
  - Lower sensitivity limits effectiveness
- MRI?
- Ultrasound?

## ACS Guidelines for Screening MRI

- *Insufficient evidence to recommend for or against MRI screening*
  - Lifetime risk 15-20% by BRCAPRO or other model based on family history
  - LCIS or ALH
  - ADH
  - **Heterogeneously or extremely dense breast tissue on mammography**
  - Personal history of breast cancer, including DCIS

## UVa Policy

- Currently do not offer screening US
- Women with heterogeneous or extremely dense breast tissue undergo MRI screening in addition to mammography IF there are additional breast cancer risk factors, such as LCIS, ADH, family history of breast cancer, etc, or if personal history of breast cancer that was not detected on screening mammogram.

## Conclusions

- Breast density is a moderate to strong independent risk factor for development of breast cancer, as demonstrated in studies with varied populations and settings
- Only genetic mutations, advancing age, prior breast cancer, or prior LCIS have a stronger association
- Management of women with dense breast tissue is currently annual mammography. Little data available on use of US or MRI in women with dense tissue and no other risk factors