Mammographic Breast Density IS a Breast Cancer Risk Factor

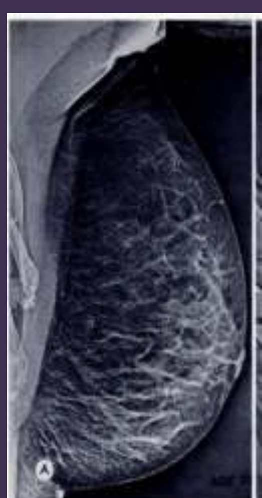
Jennifer A. Harvey, M.D., FACR, FSBI
Professor of Radiology
University of Virginia

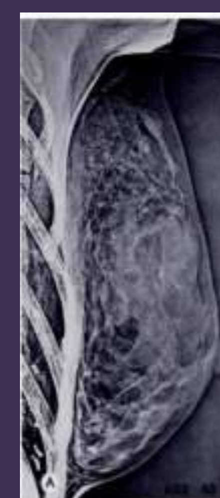
Disclosure

- Hologic, Inc. Shareholder and research agreement.
- Volpara Solutions, Ltd. Shareholder and research agreement.
- VuComp, Inc. Research agreement.

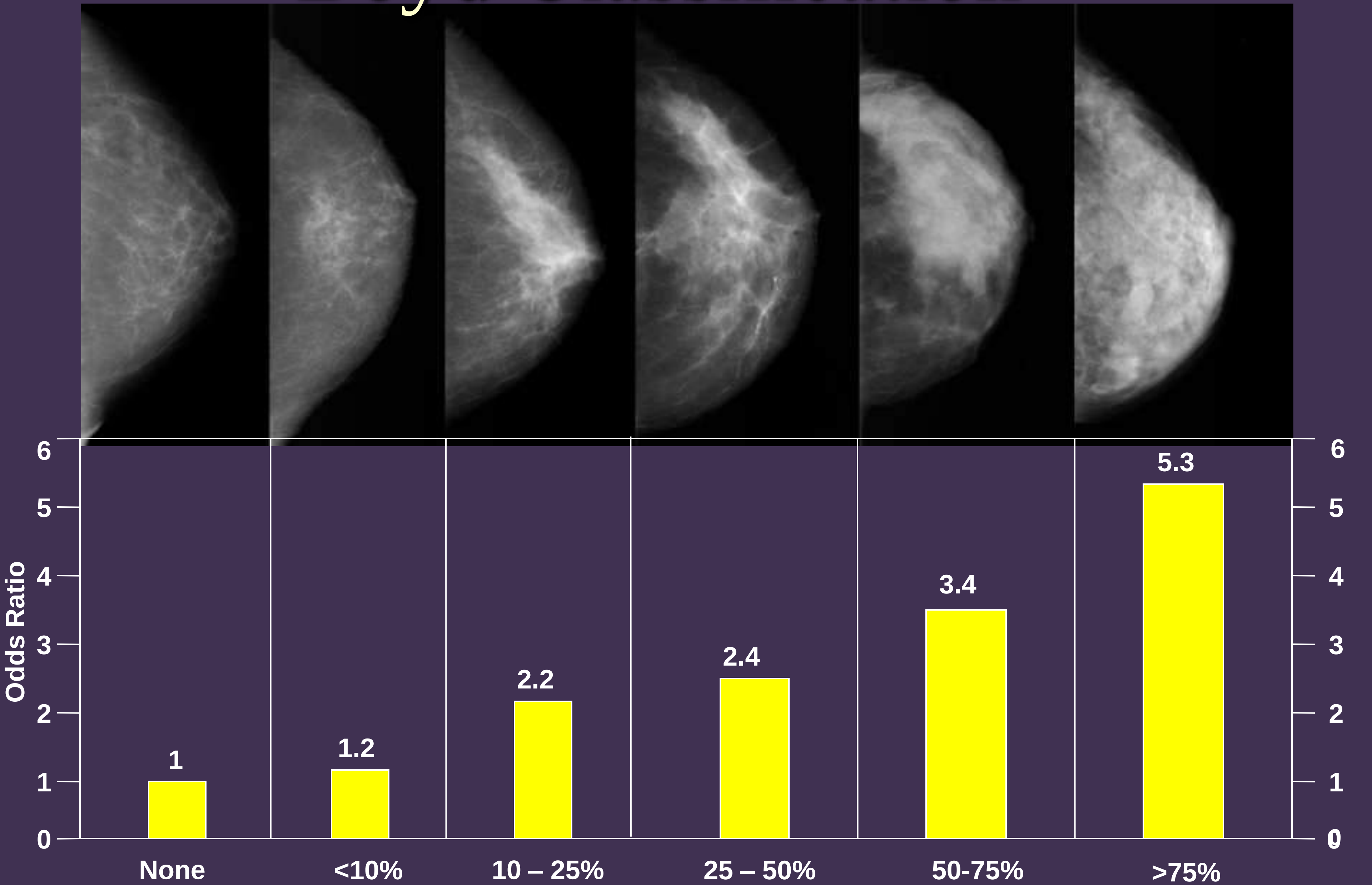
Wolfe JN, AJR 1976

- 7214 women
- N1,P1, P2, DY patterns
- RR 37 for developing breast cancer for P2/DY compared to N1/P1



Boyd Classification



Boyd, 1995

Quantitative Assessment of Breast Density and Breast Cancer Risk

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

	Method	Odds Ratio	95% C.I.
Boyd (1982)	Visual	2.8-6.0*	2.5-14.1
Brisson, Merletti (1984)	Visual	3.8-5.4**	2.5-11.4
Brisson, Morrison (1984)	Visual	2.0-4.4**	2.5-7.9
Wolfe (1987)	Manual Planimetry	4.3	1.8-10.4
Brisson, Verreault (1989)	Visual	5.5**	2.3-13.2
Saftas (1991)	Manual Planimetry	4.3	2.1-8.8
Boyd, Byng (1995)	Visual Computerized (Thresholding)	6.0 4.0	2.8-13.0 2.1-7.7
Kato (1995)	Manual Planimetry	3.6 (premeno) 2.1 (postmeno)	1.7-7.9 1.1-3.8
Byrne (1995)	Computerized Planimetry	4.3	3.1-6.1
Lam (2000)	BIRADS	4.5	1.9-10.6
VanGils (2000)	Computerized (automated)	3.3	1.5-7.2
Maskarinec (2000)	Computerized (thresholding)	1.8	1.1-3.0
Vacek (2004)	BI-RADS	4.0	2.8-5.7
Nagata (2005)	Computerized (thresholding)	4.4 (50-75%) Premeno 1.4 (>75%) Premeno 4.2 (>75%) Postmeno	1.2-15.4 0.3-6.06 1.3-13.2
Boyd (2007)	Computerized (thresholding)	4.7	3.0-7.4

Density and Breast Cancer Risk in 587,369 Women

Table 2. Association Between Breast Density and Breast Cancer Risk by Menopausal Status and HT Use

Variable	BIRADS Breast Density* 1 HR	1 95% CI	2	3 HR	3 95% CI	4 HR	4 95% CI
Premenopausal†	0.46	0.37 to 0.58	Reference	1.62	1.51 to 1.75	2.04	1.84 to 2.26
Postmenopausal no HT†	0.57	0.53 to 0.62	Reference	1.35	1.28 to 1.42	1.51	1.35 to 1.68
Postmenopausal HT†	0.50	0.44 to 0.57	Reference	1.59	1.51 to 1.69	2.02	1.83 to 2.22
Postmenopausal E use‡	0.61	0.48 to 0.78	Reference	1.60	1.42 to 1.80	1.99	1.61 to 2.46
Postmenopausal E + P‡	0.45	0.34 to 0.59	Reference	1.58	1.44 to 1.74	2.09	1.79 to 2.43

Abbreviations: HT, hormone therapy; BIRADS, Breast Imaging Reporting and Data System; HR, hazard ratio; E, estrogen; E + P, estrogen + progesterone; BMI, body mass index.

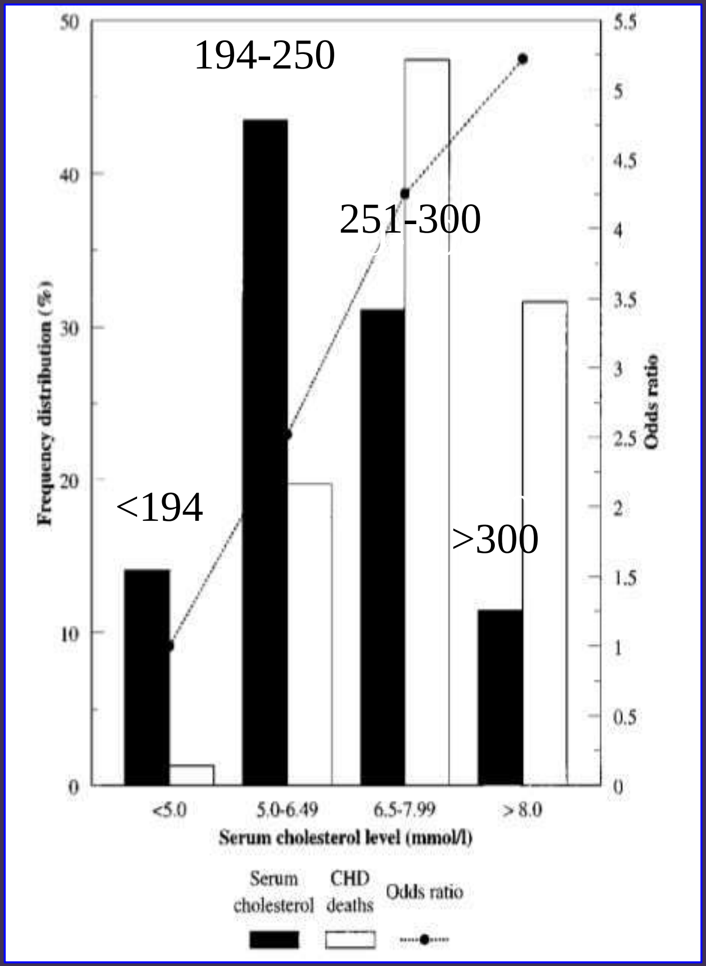
*BIRADS density 1 = almost entirely fat (low breast density); 2 = scattered fibroglandular densities (average breast density); 3 = heterogeneously dense (high breast density); 4 = extremely dense (very high breast density).

†HRs for entire cohort come from partly conditional Cox proportional hazards models assuming interactions between HT use, menopausal status, and breast density using robust sandwich variance estimates to account for multiple mammography estimations per woman adjusting for age category, BMI, BMI^2, interactions between BMI and BMI^2 with menopausal status (since they were significant $P = .001$ and $P = .025$, respectively) and registry. Interaction terms use a hierarchical algorithm in which all lower order main effects or interactions are included in the model regardless of statistical significance. Risk estimates were calculated for women with a BMI = 25 kg/m^2 (approximate average BMI in population) and average registry (proportions of mammography examinations from each registry).

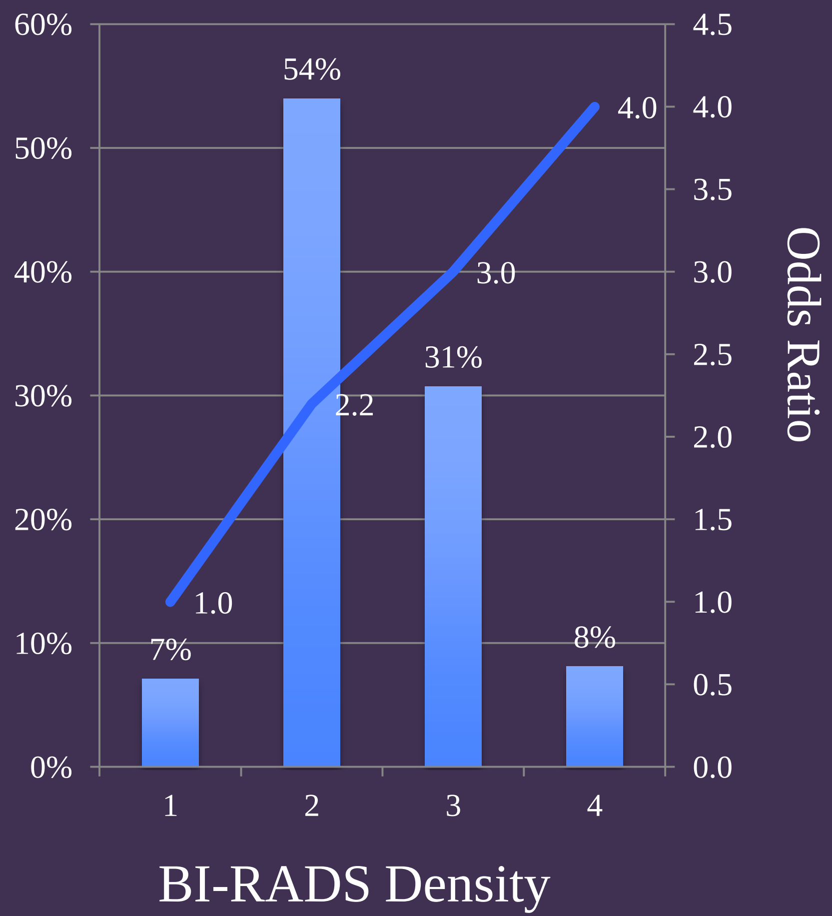
‡HRs for women with known hysterectomy status come from partly conditional Cox proportional hazards models assuming interactions between type of HT use, menopausal status, and breast density using robust sandwich variance estimates to account for multiple mammography estimations per woman adjusting for age category, BMI, BMI^2, interactions between BMI and BMI^2 with menopausal status (since they were significant ($P = .002$ and $P = .017$, respectively), E, E + P, and registry. Interaction terms use a hierarchical algorithm in which all lower order main effects or interactions are included in the model regardless of statistical significance. Risk estimates were calculated for women with a BMI = 25 kg/m^2 (approximate average BMI in population) and average registry (proportions of mammography examinations from each registry).

Kerlikowske K. J Clin Onc 2010

Cholesterol and CHD



Jousilahti P, et al. Circulation 1998



Vacek PM, Geller BM. CEBP 2004

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
Dense breast tissue	OR 4.0
Biopsy with atypia or LCIS	RR 5.0
Prior history of breast cancer	RR 7.0

Dr. Lewin …

Mammographic Breast Density is NOT a Risk Factor for Breast Cancer

John Lewin, M.D., FACR, FSBI
Diversified Radiology of Colorado

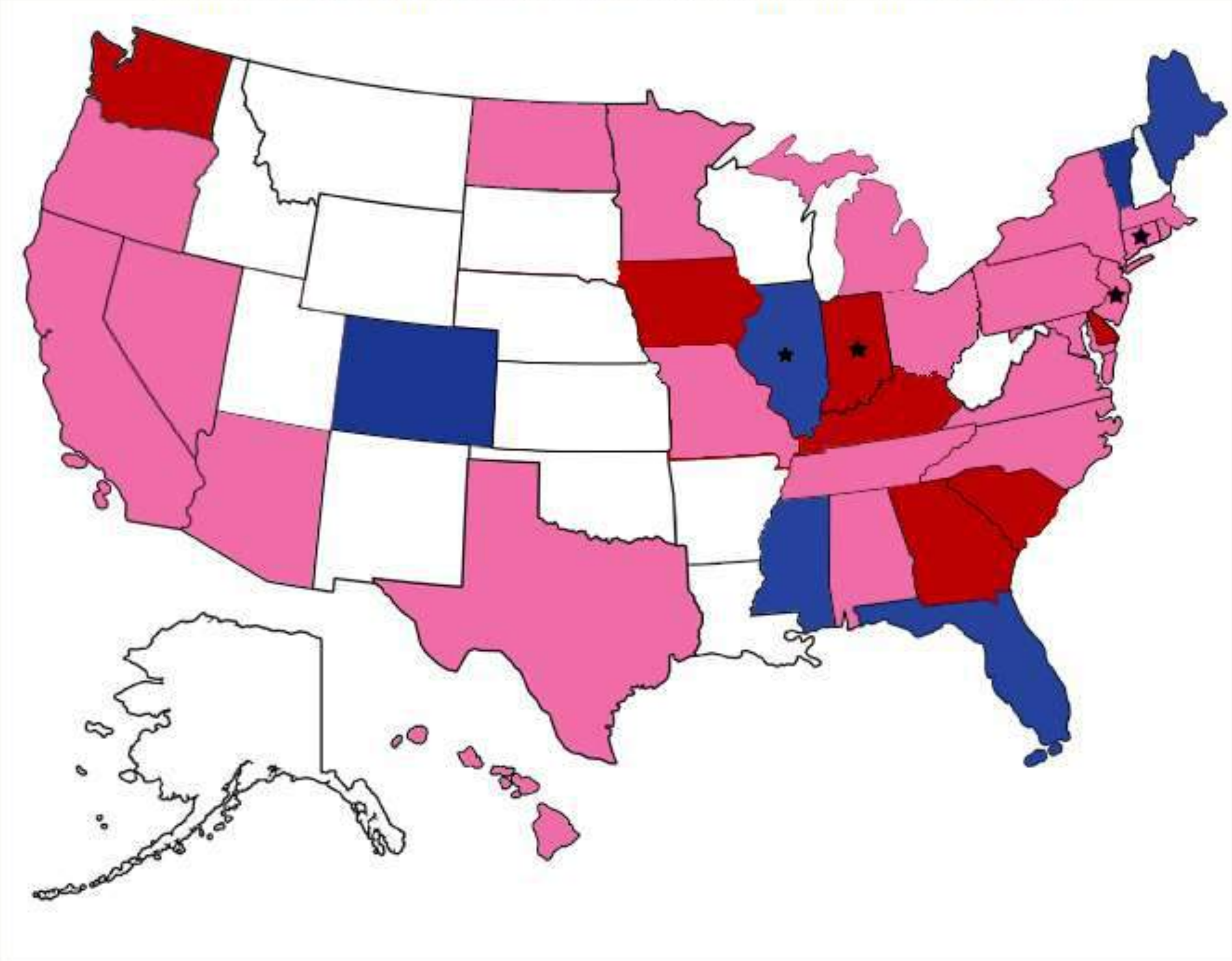
DIVERSIFIED Radiology

SOCIETY OF BREAST IMAGING SBI Since 1985

The Breast Density Industrial Complex

D.E.N.S.E.®
State Efforts

Click on your state to find information about "**mandatory breast density notification**" legislative efforts.



PINK: Enacted Law — RED: Introduced Bill — BLUE: Working on Bill — WHITE: No Action — BLACK ★ : Insurance Coverage Law

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DENSE™ BREAST-info — An Education Coalition

Get Smart About Being Dense™

For Patients | For Health Care Providers | Technology | Legislation

Dense Breast Fast Facts:

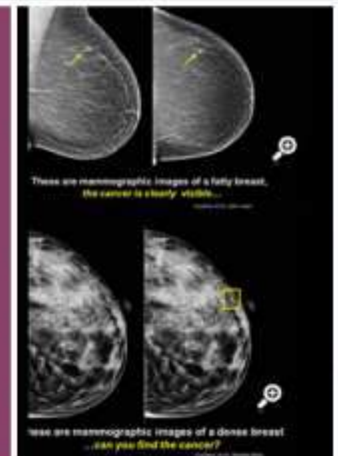
1. Breast density is determined through a woman's mammogram and described as one of four categories.

2. 40% of women age 40 and over have dense breasts.

3. Though mammograms find some cancers not seen on other screening tests, in dense breasts, mammograms will miss more than 50% of the cancers present.

4. Cancer is 4-6 times more likely in women with extremely dense breasts than in women with fatty breasts.

5. Other screening tests, such as ultrasound or MRI, in addition to mammography substantially increase detection of early stage breast cancers in dense breasts.



FOR PATIENTS

FOR HEALTH CARE PROVIDERS

TECHNOLOGY

LEGISLATION


Radiology

Basic Physics and Doubts about Relationship between Mammographically Determined Tissue Density and Breast Cancer Risk[1]

Daniel B. Kopans, MD

Numerous studies have suggested a link between breast tissue patterns, as defined with mammography, and risk for breast cancer. There may be a relationship, but the author believes all of these studies have methodological flaws. It is impossible, with the parameters used in these studies, to accurately measure the percentage of tissues by volume when two-dimensional x-ray mammographic images are used. Without exposure values, half-value layer information, and knowledge of the compressed thickness of the breast, an accurate volume of tissue cannot be calculated. The great variability in positioning the breast for a mammogram is also an uncontrollable factor in measuring tissue density. Computerized segmentation algorithms can accurately assess the percentage of the x-ray image that is "dense," but this does not accurately measure the true volume of tissue. Since the percentage of dense tissue is ultimately measured in relation to the complete volume of the breast, defining the true boundaries of the breast is also a problem. Studies that purport to show small percentage differences between groups are likely inaccurate. Future investigations need to use three-dimensional information.

[1] From the Department of Radiology, Breast Imaging Division, Massachusetts General Hospital, Ambulatory Care Bldg, Suite 219, 15 Parkman St, Boston, MA 02114. Received February 14, 2007; revision requested April 13; revision received June 13; accepted July 10; final version accepted August 15. **Address correspondence to the author.**

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Radiology

There is a broad spectrum of breast tissue patterns as demonstrated with mammography. There has long been an interest in understanding these patterns (1–13), measuring them, and linking them to an individual's risk for developing breast cancer. The authors

grams, is a major risk factor for breast cancer—perhaps the strongest risk factor (17). Although I personally suspect that there is a relationship between density and risk, the degree is far from clear, since I believe the studies that have been published provide analyses

lobules in various percentages. The relative percentages of these components are presently not measurable on two-dimensional (2D) mammographic images. Consequently, it is unclear which tissue compartment, if any, is related to breast cancer risk. Modern computer segmentation techniques that can measure the percentage of light gray to white areas (fibroglandular tissue) portrayed on the mammogram relative to the amount of dark gray to black areas (predominantly fat) on the image are no doubt highly reproducible (18). However, the true accuracy of the measurements in terms of a direct relationship

(not merely difficult, but impossible, in my opinion) to accurately measure the percentage of tissue volume that is dense on the basis of two-view mammograms. Since it is impossible, without additional information, to measure tissue percentages by using two projec-

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ments as accurate reflections of true volume ratios of the tissues. In my opinion, it is a failure of the peer review process that has permitted the publication of these articles and the perpetuation of this misinformation to achieve a status that is not supported by the science.

In the 1960s, Wolfe first suggested that tissue patterns, as defined with mammography, might be related to subsequent risk for the development of breast cancer (6,21). In the 1970s, interest increased and studies were performed to try to define the relationship (1,3,7). In 1984, Boyd et al (22) re-

(23), and, consequently, the American College of Radiology developed a rating system based on Wolfe's original four categories (6,21). These have been included in the American College of Radiology Breast Imaging Reporting and Data System, not as a means for establishing risks for developing breast cancer but as a way to alert referring physicians as to the likelihood that a cancer might be hidden on a mammogram.

In my experience, few radiologists have interest in tissue patterns as a marker of risk. Nevertheless, there has been a great deal of interest in the epidemiology community concerning tissue density and risk. Boyd continued his analyses, and, in 1992 he and colleagues published an article that suggested that women with dense breasts had five to nine times the risk of developing breast cancer, compared with those with fatty breasts (9). As was stated, this made tissue pattern one of the highest risks for breast cancer. Numerous articles have been written on the association, and most authors have concluded that there is some relationship between dense breast tissue and risk for breast cancer.

Most of the early studies of tissue pattern and cancer risk are based on the radiologist's subjective assessment of patterns by using both mediolateral oblique (MLO) and craniocaudal (CC) projections. By using both projections, the radiologist has some nonquantitative information about the three-dimensional (3D) distribution of the denser tissues. This is, nevertheless, a

Limitations of Breast Density Risk Studies
(Kopans)

- Impossibility of determining 3D volume of tissue from a 2D image
  - Irreproducibility due to effects of compression, positioning
- Effects on density of
  - Body habitus (BMI)
  - Menopausal status / stage of cycle
  - Hormone replacement therapy (HRT)
- Different types of tissue that contribute to density

Additional Limitations of Breast Density Risk Research

- Effects of other factors, e.g.
  - Parity, number and age of first childbirth
  - Age of menarche
  - Heredity/Genetics
- Retrospective analyses
  - Case – Control design used for smaller data sets
  - Large data sets far from perfect
  - Multiple degrees of freedom/corrections
    - Errors add up ; potential for manipulation

Measuring Dense Breast Tissue Volume from a Mammogram

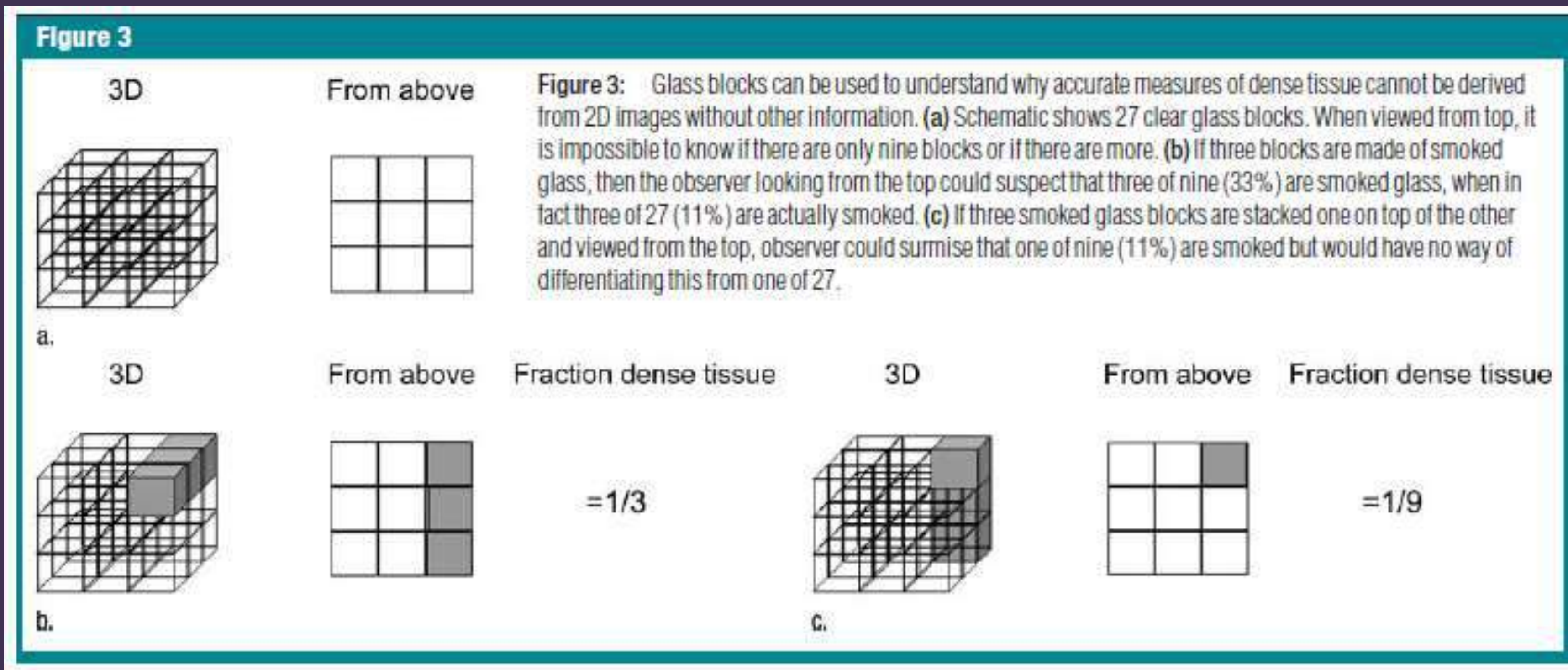
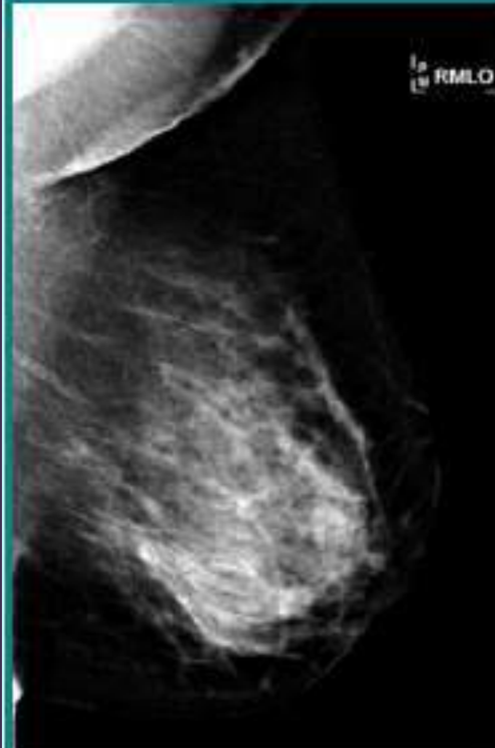
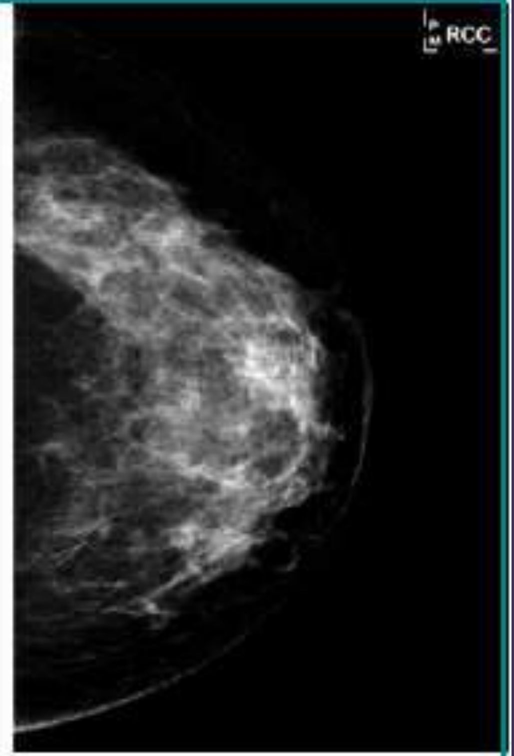


Figure 3: Glass blocks can be used to understand why accurate measures of dense tissue cannot be derived from 2D images without other information. **(a)** Schematic shows 27 clear glass blocks. When viewed from top, it is impossible to know if there are only nine blocks or if there are more. **(b)** If three blocks are made of smoked glass, then the observer looking from the top could suspect that three of nine (33%) are smoked glass, when in fact three of 27 (11%) are actually smoked. **(c)** If three smoked glass blocks are stacked one on top of the other and viewed from the top, observer could surmise that one of nine (11%) are smoked but would have no way of differentiating this from one of 27.

Figure 1



a.



b.

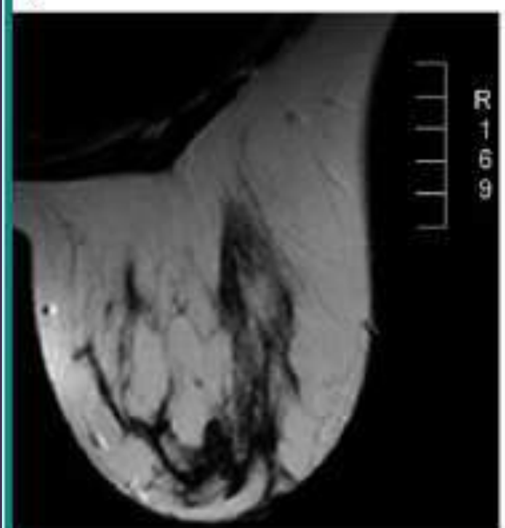


Figure 1: True volume of dense tissue cannot be accurately measured on 2D images without information on exposure values and breast thickness. Breast appears moderately dense on **(a)** MLO and **(b)** CC mammographic projections. **(c)** On transverse T2-weighted magnetic resonance (MR) image (repetition time, 5000 msec; echo time, 105 msec), fibroglandular tissue ("black" tissue) actually forms a shell around fat ("white" tissue) in center of right breast, and the breast is predominantly fat.

Correlated Variables -- Opposing

- BMI
  - As BMI goes up, risk goes up (postmenopausal) but breast density goes down
- Age
  - As age goes up, risk goes up but breast density goes down (a little)
- Ethnicity/Environment
  - Women in Asia are more likely to have dense breasts but have lower rates of breast cancer

Correlated Variables - Reinforcing

- HRT (increases density and risk)
- Parity (lowers density and risk)
- Height (increases density and risk)
- Genetics
  - BRCA mutations associated with increased density
  - Twin studies
  - Genome wide association studies (GWAS)
    - Shared genetic bases mediated through a large number of common (SNP) variants
      - Varghese, et al. Cancer Res. 2012

The Masking Effect

- In the case-control studies (e.g., Boyd), patients were “cancer-free” at time of enrollment/first mammo
  - If cancer is seen on the enrollment mammo, the patient was excluded
- Since it is harder to see cancers in denser breasts, more patients with pre-existing cancers are enrolled in the dense group

Regression Data in Density/Risk Studies are Corrected for Multiple Factors

Table 3. Mammographic Density and Risk of Breast Cancer According to Method of Detection.*

Mammographic Density	All Methods of Detection†			Detection by Screening			Detection <12 Mo after Negative Screening			Detection ≥12 Mo after Negative Screening		
	Case (N=1112)	Control (N=1112)	Odds Ratio (95% CI)	Case (N=717)	Control (N=717)	Odds Ratio (95% CI)	Case (N=124)	Control (N=124)	Odds Ratio (95% CI)	Case (N=262)	Control (N=262)	Odds Ratio (95% CI)
<10%	230	362	1.0	173	242	1.0	12	35	1.0	43	82	1.0
10 to <25%	272	270	1.8 (1.4–2.2)	171	162	1.6 (1.2–2.2)	22	29	2.1 (0.9–5.2)	79	79	2.0 (1.2–3.4)
25 to <50%	336	290	2.1 (1.6–2.6)	219	196	1.8 (1.3–2.4)	33	29	3.6 (1.5–8.7)	80	62	2.6 (1.5–4.6)
50 to <75%	178	144	2.4 (1.8–3.3)	102	88	2.0 (1.3–2.9)	32	23	5.6 (2.1–15.3)	42	30	3.1 (1.6–6.2)
≥75%	96	46	4.7 (3.0–7.4)	52	29	3.5 (2.0–6.2)	25	8	17.8 (4.8–65.9)	18	9	5.7 (2.1–15.5)
P value‡			<0.001			<0.001			<0.001			<0.001

* Odds ratios are adjusted for age, body-mass in… era-
py (ever or never), breast cancer in first-degree… -
notes confidence interval.
† Nine pairs were excluded from the group analy…
‡ P values are for the Cochran–Armitage test for…

Uncorrected:

	Case	Control	Ratio	Normalized
<10%	230	362	.635	**1.0**
10-25%	272	270	1.01	**1.6**
25-50%	336	290	1.16	**1.8**
50-75%	178	144	1.24	**1.9**
≥75%	96	46	2.08	**3.3**

Boyd NF, NEJM 2007

Large Data Sets (BCSC) Suffer from Missing Data

Exposure variables were associated with substantial missingness: 29% of observations were missing breast density, 43% were missing BMI, and 59% were missing one or both variables. To account for missing data, we used multiple-imputation by chained equations

Certain limitations must be considered in interpreting these results. In particular, there was considerable missing data in exposure and tumor marker variables. Differences between results from complete-case and multiple-imputation analyses illustrate that these missing data impact observed associations. Because breast density is known to vary with age (32), race/ethnicity (33), and BMI (4, 10), differences in the distribution of these factors in observations with known versus unknown breast density indicate that missingness was not completely random; the same was true for BMI. We used multiple-imputation to account for missing data (31). Simulation studies comparing multiple-imputation to complete-case analyses suggest that excluding observations with missing data can lead to considerable bias in regression coefficients if missingness is not completely random, and that such bias can be reduced via multiple-imputation (34). HRs based on a complete-case approach may be

From Phipps AI, et al. Breast density, body mass index and risk of tumor-marker defined subtypes of breast cancer. Ann Epidemiol 2012.

If Breast Density is Important it Should Correlate with Risk of Death from Breast Cancer – But it Doesn't

- 2012 BCSC study:

  "High mammographic breast density was not associated with risk of death from breast cancer or death from any cause after accounting for other patient and tumor characteristics."

Gierach GL, Ichikawa L, Kerlikowske K, et al. Relationship between mammographic density and breast cancer death in the Breast Cancer Surveillance Consortium. J Natl Cancer Inst. 2012 Aug 22;104(16):1218-27.

Bad Cancers and Cancer Deaths are More Likely in Fatty Breasts

- Mammographic breast density (MBD) inversely correlated with tumor grade and survival. Low and very low densities were more likely to have grade 3 tumors and poor prognosis.
  - “In patients with newly diagnosed breast cancer, very low MBD proved to be an independent prognostic feature, associated with higher tumour grade and predicted worse survival even after correcting for possible confounders.”

Masarwah A, Auvinen P, Sudah M, et al. Very low mammographic breast density predicts poorer outcome in patients with invasive breast cancer. Eur Radiol. 2015 Mar 4.

Dr. Harvey…

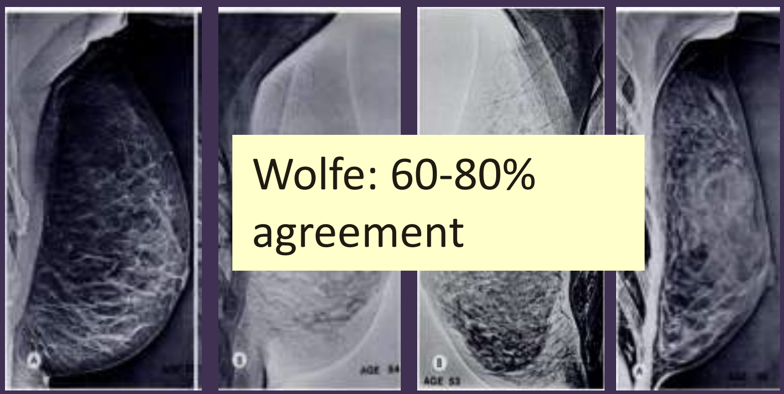
Controversies

- Density Measures
  - Reproducibility
  - Validity compared to reference standard (e.g. MRI)
  - Changes with weight/positioning
- Variation of density and risk by race
- Breast Cancer Types and Deaths

Accuracy of Density Measures

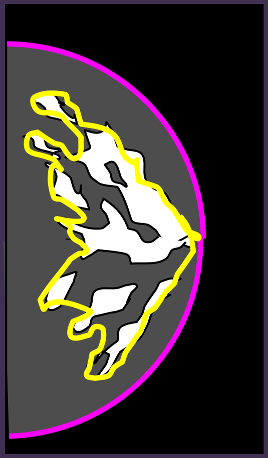
- Reliability
  - How close are repeated measures?
- Validity
  - How well do measures correspond to a reference standard?

Density Measurement Techniques: Inter-reader Agreement

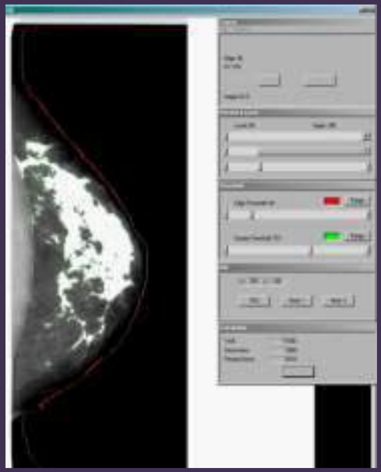


Wolfe: 60-80% agreement

BI-RADS: 60% agreement

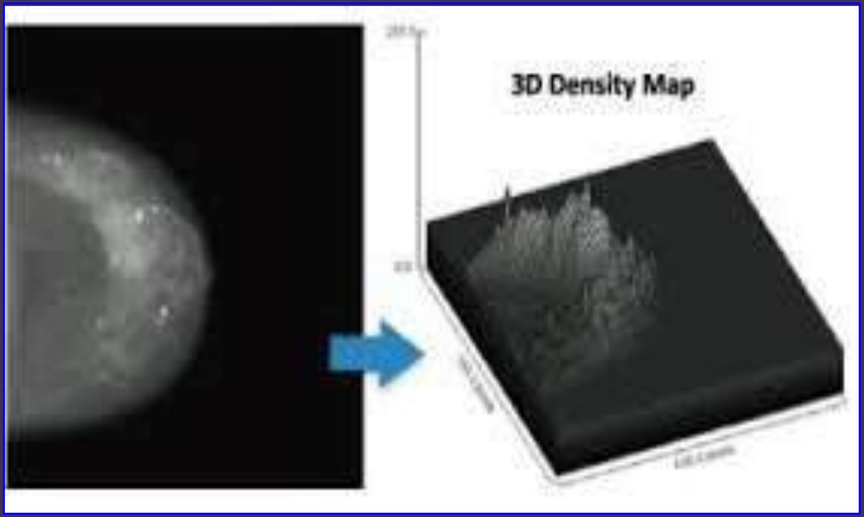


Planimetry: 85-90% agreement



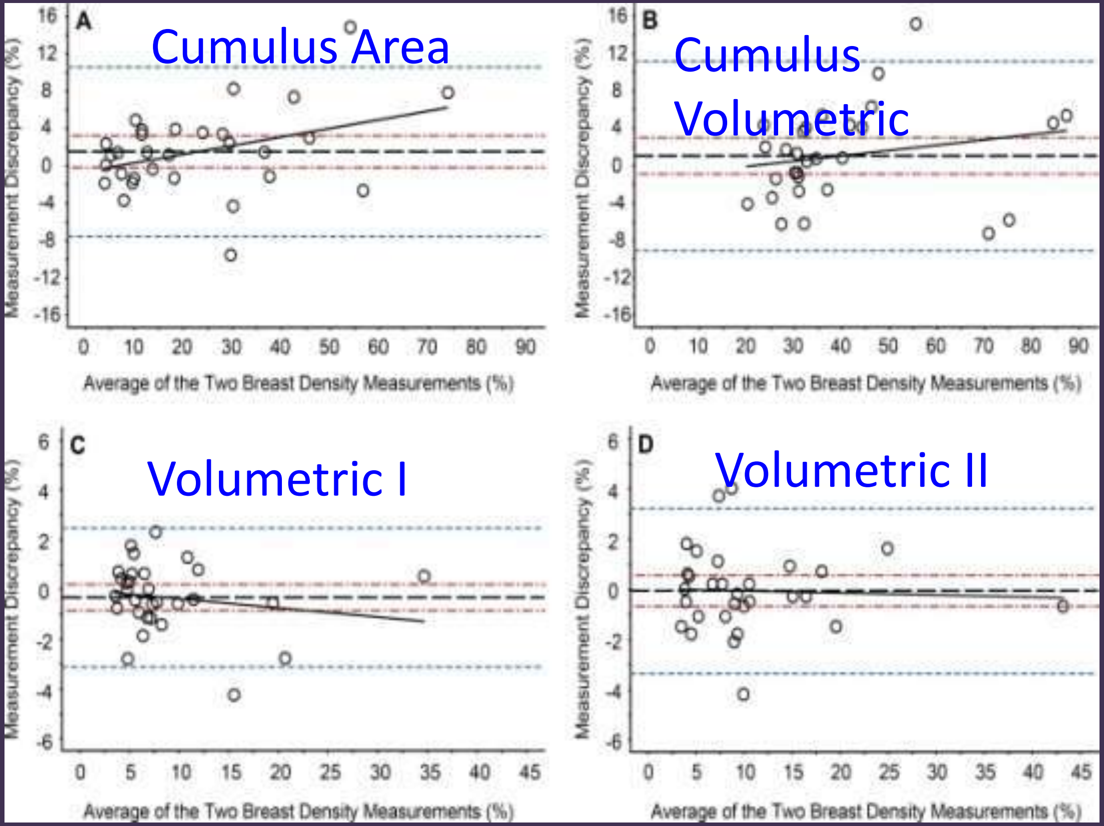
Cumulus: > 90% agreement

Automated Volumetric Breast Density



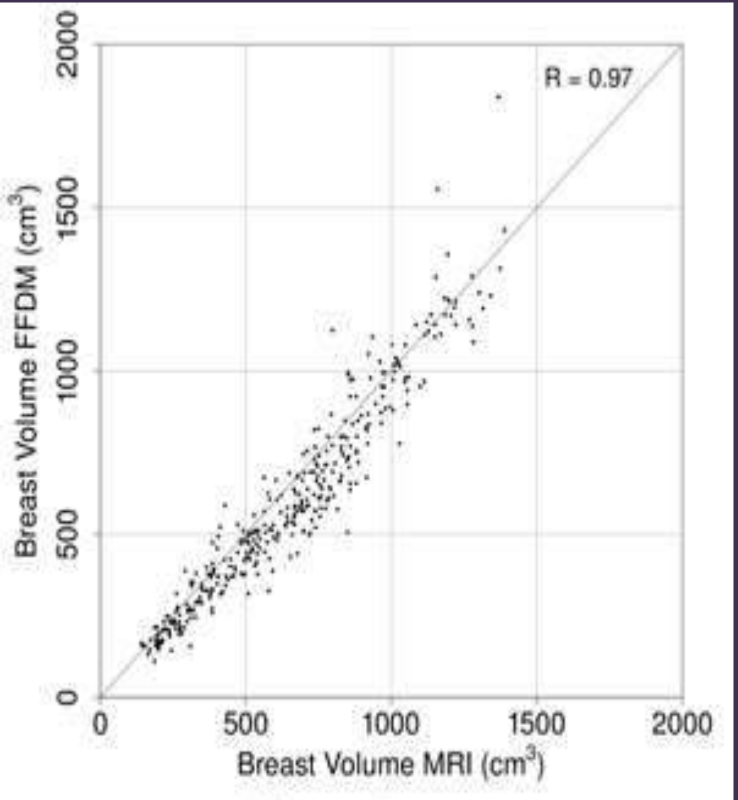
Reliability

- 30 women underwent a second left CC view by a different technologist on the same machine.

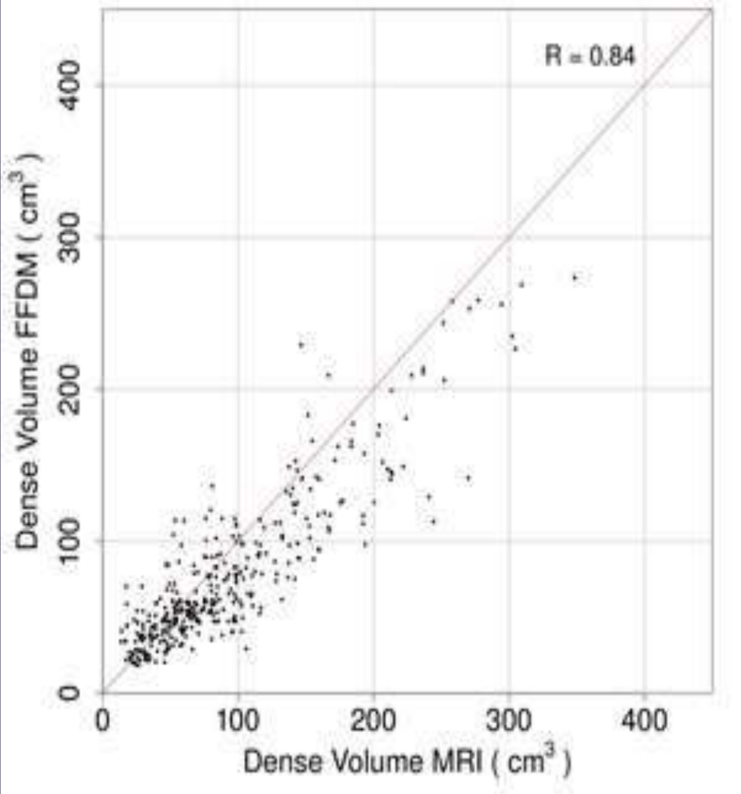


Alonzo-Proulx O. Radiology 2015

Validity Compared with MRI



(a) per breast



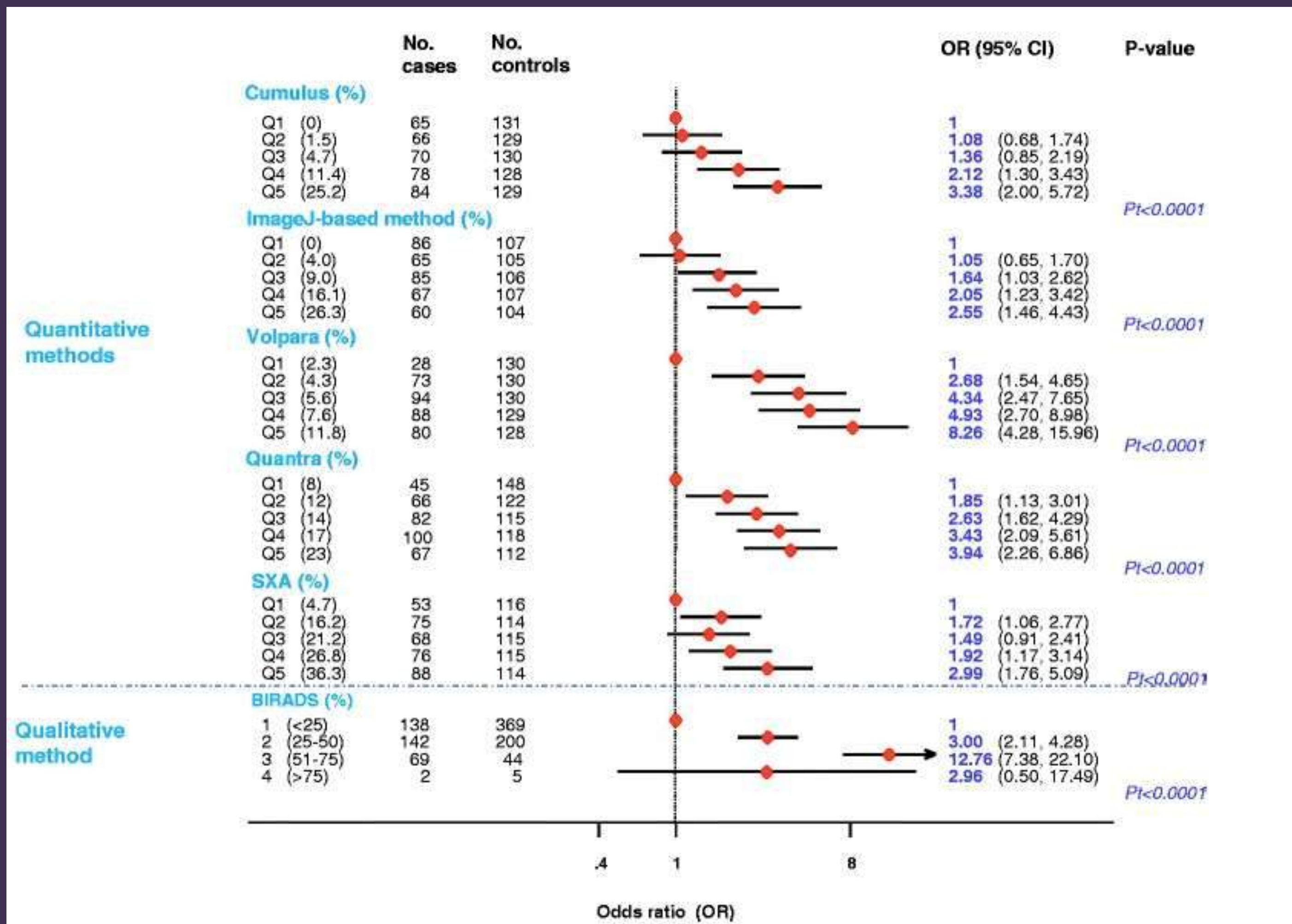
(a) per breast

Automated Volumetric Density, Correlation coeff for Percent Density: 0.93

Gubern-Merida A. PloS ONE 2014

Risk by Density Method

414 cases:685 controls



Eng A. Br Cancer Research; 2014

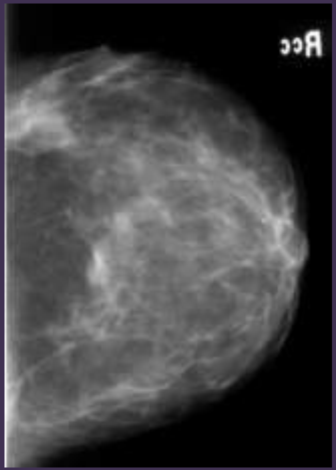
BMI and Density are Independent Risk Factors

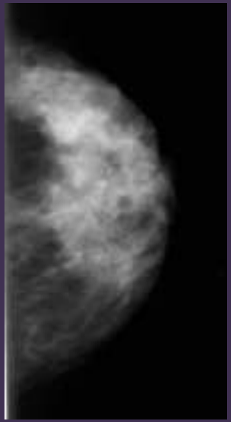
Associations of Weight, BMI, and Breast Density with Breast Carcinoma in Postmenopausal Women

Separate analyses	Unadjusted OR	(95% CI)	Adjusted[a] OR	(95% CI)
Weight (kg)				
≤ 63.0	1.0	—	1.0	—
63.1–70.0	1.5	(1.0–2.3)	1.6	(1.1–2.5)
70.1–81	1.6	(1.1–2.4)	1.9	(1.2–2.8)
> 81	1.7	(1.2–2.6)	2.1	(1.3–3.2)
BMI (kg/m^2)				
< 22.0	1.0	—	1.0	—
22.0–24.9	1.2	(0.8–2.0)	1.4	(0.9–2.3)
25.0–27.4	1.3	(0.8–2.2)	1.6	(0.9–2.7)
27.5–29.9	1.3	(0.7–2.1)	1.6	(0.9–2.7)
≥ 30.0	1.9	(1.2–3.0)	2.5	(1.6–4.1)
Density				
Entirely fat	1.0	—	1.0	—
Scattered	1.4	(0.8–2.5)	1.6	(0.9–2.8)
Heterogenous	1.9	(1.0–3.4)	2.3	(1.3–4.3)
Extremely	3.2	(1.4–7.4)	4.5	(1.9–10.6)

OR: odds ratio; CI: confidence interval; BMI: body mass index.

[a] Odds ratio for weight and BMI adjusted for breast density; odds ratio for breast density adjusted for weight.





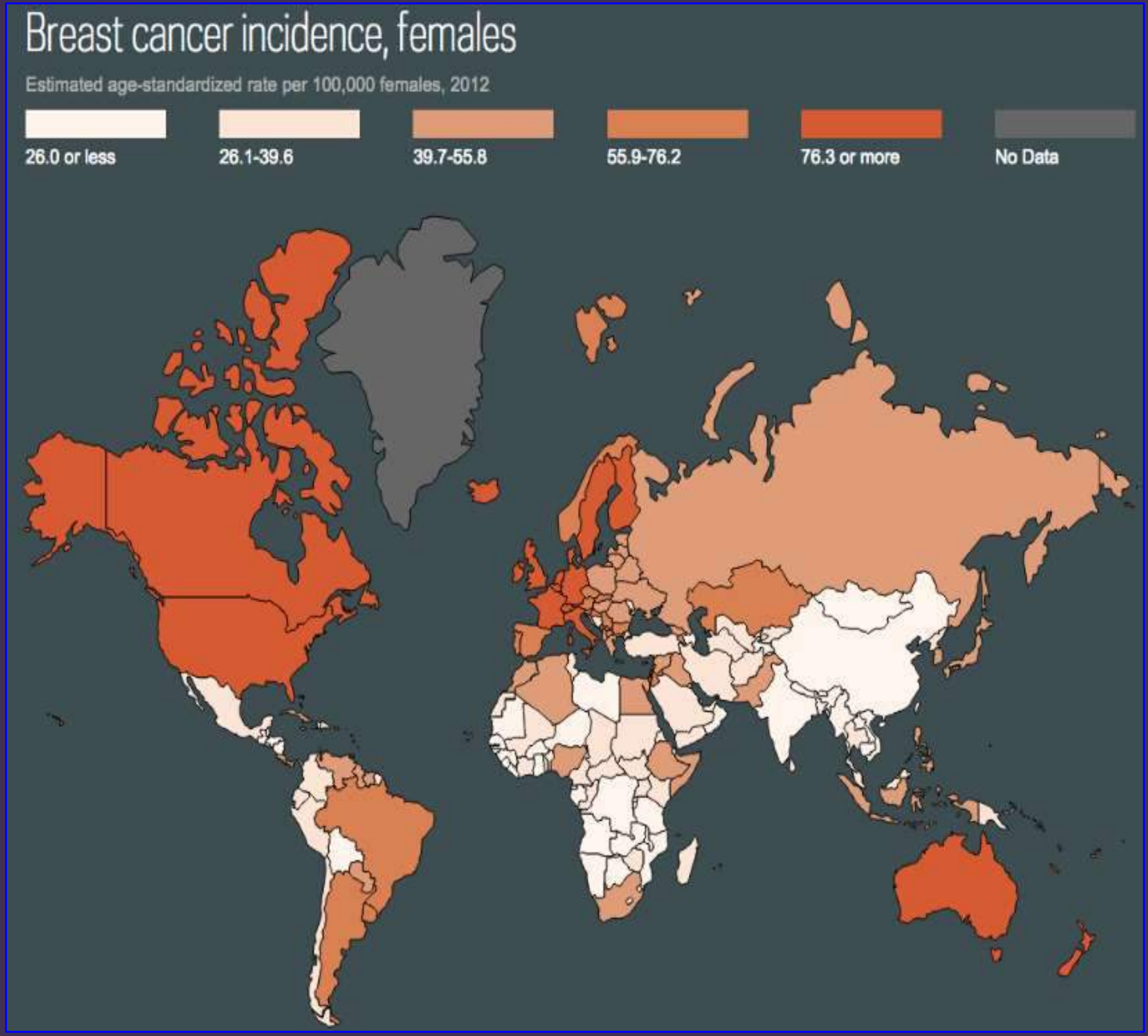
Lam PB. Cancer; 2000

Controversies

- Density Measures
  - Reproducibility
  - Validity compared to reference standard (e.g. MRI)
  - Changes with weight/positioning

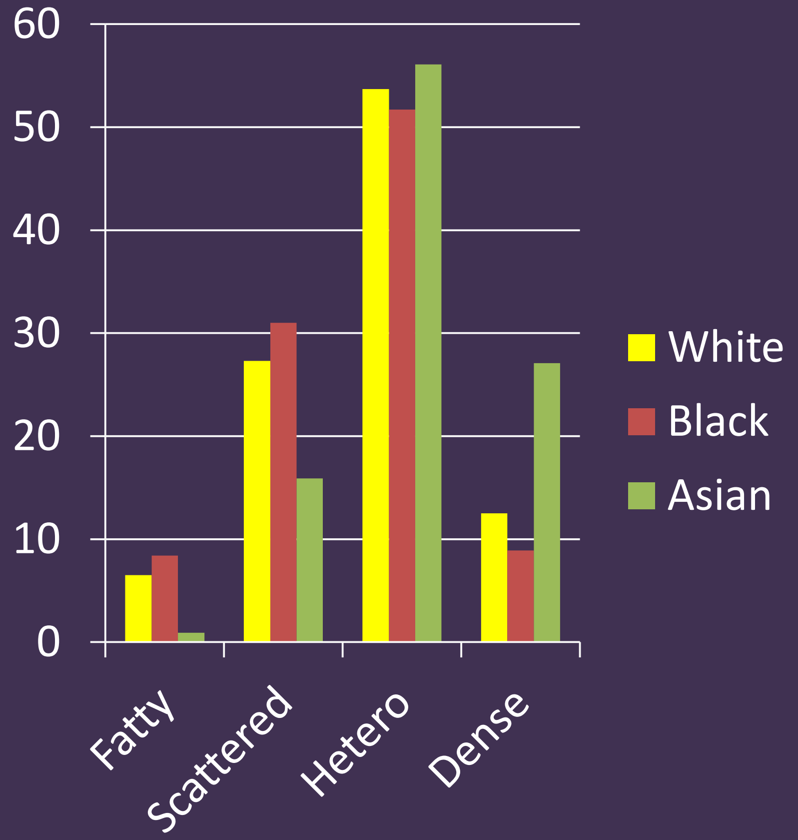
- Variation of density and risk by race

- Breast Cancer Types and Deaths



Breast cancer incidence, females
Estimated age-standardized rate per 100,000 females, 2012
26.0 or less
26.1-39.6
39.7-55.8
55.9-76.2
76.3 or more
No Data

BI-RADS Density by Race



- Asian significantly higher and Black significantly lower unadjusted density than White
- After adjustment for BMI and age, no difference in density except Asian.

del Carmen MG. AJR 2007

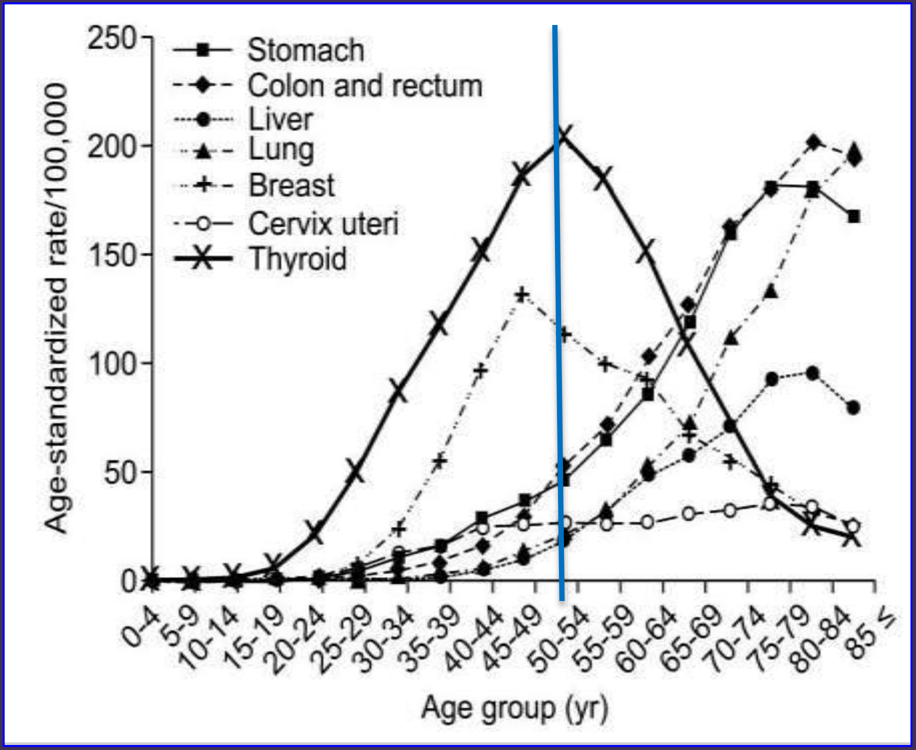
Risk of Breast Cancer

	White		Black		Asian	
Percent Density	Unadj	Adj	Unadj	Adj	Unadj	Adj
< 10%	1.00	1.00	1.00	1.00	1.00	1.00
10-59%	1.98	1.57	1.58	1.44	1.62	3.07
≥ 60%	3.62	2.56	1.82	1.66	2.53	6.42
Per 10% increase in density		15%		11%		30%

*Adjusted for age at mammo, BMI, age at menarche, FH, pregnancies, hormone use, age at menopause, age at first pregnancy

Urskin G. Cancer Epid Biomarkers Prev 2003

Breast Cancer Incidence in Korea



Jung KW. Cancer Res Treat 2011

Controversies

- Density Measures
  - Reproducibility
  - Validity compared to reference standard (e.g. MRI)
  - Changes with weight/positioning
- Variation of density and risk by race
- Breast Cancer Types and Deaths

Types of Cancers

- Metanalysis of six studies, 3414 women with breast cancer. Computerized thresholding used to obtain percent density.
- No association with specific histologic types
- Dense breasts associated with larger tumors (>2.1cm) and positive lymph nodes across all age groups
- Women < 55 years, stronger association with ER-negative breast cancer

Bertrand KA, Br Cancer Res 2013.

Cancer Characteristics

HR	ER/PR+	ER/PR-, HER-2+	Triple Negative
Age 40-64			
Fatty	0.45*	0.53	0.67
Scattered	1.0	1.0	1.0
Heterogeneous	1.63*	0.87	1.48*
Dense	2.04*	1.80	1.17
Age $\geq$65 years			
Fatty	0.61*	--	0.35
Scattered	1.0	1.0	1.0
Heterogeneous	1.31*	3.78*	0.99
Dense	1.51*	4.01	3.29*

Phipps AI. Ann Epidem 2012; 22:340.

Breast Cancer Mortality

- BCSC, 9232 women with invasive breast cancer, 1996-2005, mean follow-up 6.6 years
- 1795 deaths; 889 of breast cancer
- After adjustment for BMI, mode of detection, treatment and income, high density was not related to breast cancer death (HR 0.92, 95% CI 0.71-1.19) or death from all causes (HR 0.83, 95% CI 0.68-1.02)
- Increased risk of death from breast cancer among women with low density who were either obese (HR 2.02, CI 1.37-2.97) or with tumors at least 2 cm in size (HR 1.55, CI 1.14-2.09)

Gierach GL. JNCI 2012

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Gierach GL. JNCI 2012

Dense Breasts, 25 Yr F/U

	RR	95% CI
Incidence	1.57	1.23-2.01
Tumors > 2 cm	1.79	1.22-2.63
Node +	2.46	1.66-2.62
Grade 2-3 tumor	1.80	1.39-2.34
Death	1.91	1.26-1.91

Chiu SY et al. Cancer Epidemiol Biomarkers Prev 2010;19:1219-28

Dr. Lewin …

In Summary – Breast Density is Likely a Risk Factor, but…

- Situation is not has simple as it is made out to be (see above: cholesterol)
- Using density in your clinic may not be valid if you are not controlling for
  - Age
  - BMI
  - Age at menarche
  - Parity
  - Number of Live Births

  - Age at first birth
  - Menopausal status
  - Age at menopause
  - Hormone replacement therapy
  - Family history

- Also – The effect of breast density is purposely overstated by comparing extreme subgroups (e.g., <10% to >75%) rather than comparing each subgroup to the mean…

Boyd Data - again

	Case (N=1112)	Control (N=1112)	Odds Ratio (95% CI)
<10%	230	362	1.0
10 to <25%	272	270	1.8 (1.4–2.2)
25 to <50%	336	290	2.1 (1.6–2.6)
50 to <75%	178	144	2.4 (1.8–3.3)
≥75%	96	46	4.7 (3.0–7.4)

1.8
1.2
1.1
2.0

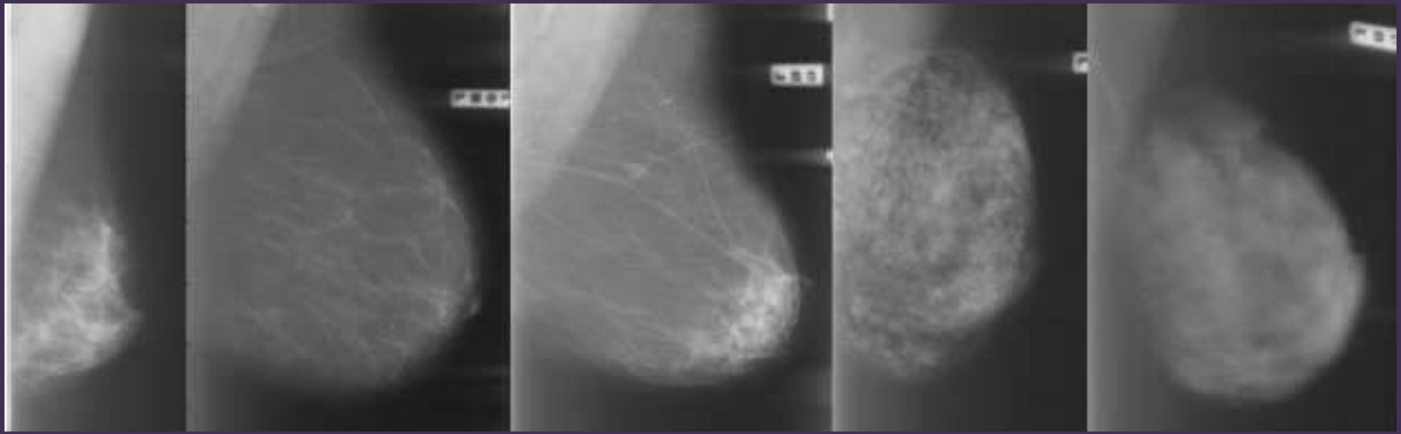
- Extremely dense vs very low density: RR= 4.7
- But … BIRADS c vs BIRADS b is only a RR of

  2.4/2.1 = 1.1

- Note:80% of patients are either BIRADS b or c
- Note that only 8.6% of cases were ≥75%

Density is a Poor Surrogate for Pattern Recognition

- Glands, Ducts, Connective Tissue, Cysts all contribute to breast density but likely have large differences in contribution to risk



- OR for Tabar (IV vs I) > Comp. % Density > BIRADS
  - Best Tabar reader OR = 7.7

Wolfe (DY vs N1) = 37!!

Cancer 2015

Thank you!