Department of Radiology and Biomedical Imaging
University of California, San Francisco School of Medicine
presents

7th International Workshop on Breast Densitometry and Cancer Risk Assessment (Non-CME)

June 10-12, 2015
Hotel Kabuki
San Francisco, California

Course Chairs
Karla Kerlikowske, MD
John Shepherd, PhD
University of California, San Francisco

UCSF University of California, San Francisco School of Medicine

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Professor in the Medical Epidemiology and Biostatistics
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Overview:
A high amount of dense breast tissue has been shown to be one of the strongest risk factors for breast cancer, although the specific reason(s) for this is not known. Recent legislation in several states, including California, requires reporting of breast density to women with dense breasts undergoing mammography. Ideally, prior to enacting legislation, there would be guidelines on how best to measure breast density, what risk model to use that includes breast density to report breast cancer risk, as well as a standardized form to communicate this information. Research is ongoing to understand how different technologies that measure breast density relate to both breast cancer detection and breast cancer risk.

The 2015 Conference will feature three days of presentations consisting of approximately 15 internationally-recognized invited speakers, and 8 presentations selected from submitted abstracts. In addition, there will be a poster session on Thursday and Friday to highlight research from attendees.

Objectives:
The participants will leave the workshop having gained tangible understanding and insights to the clinical applications and research topics in breast density. Specifically, the participants will have a complete overview of the current trends, capabilities, and limitations of risk factors from mammographic imaging. Second, the participants will have a key understanding of how or if these imaging risk factors are independent from other clinical and genetic risk factors. Third, the participant will know the key needs and research breakthroughs needed to best identify women at high risk of breast cancer.

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UCSF University of California, San Francisco School of Medicine Presents

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Security

We urge caution with regard to your personal belongings and syllabus books. We are unable to replace these in the event of loss. Please do not leave any personal belongings unattended in the meeting room during lunch or breaks or overnight.

Exhibits

Industry exhibits will be available outside the ballroom in the Spring Room during breakfasts and breaks, and lunches.

Poster Sessions

The Poster Sessions will take place in the Sakura Ballroom on the lobby level of the hotel. Session 1 will be held on Thursday, and Session 2 will be held on Friday.

Final Presentations

A link to PDF versions of the final presentations will be sent via e-mail approximately 3 – 4 weeks post course. Only presentations that have been authorized for inclusion by the presenter will be included

Wednesday, June 10, 2015

7:30am	Registration and Continental Breakfast	

Clinical Aspects of Breast Density

8:30am	Introduction	John Shepherd
8:40am	Advocate Clinical Statement	Vivian Lee
8:50am	Breast Density Methods in Clinical Practice	Jennifer Harvey
9:40am	Breast Density and Other Risk Factors of Breast Cancer (Age, Genetics, Family History)	Giske Ursin
10:30am	Coffee Break	
11:00am	Identifying Women with Dense Breasts at High Risk of Interval Cancers	Karla Kerlikowske
11:50am	Luncheon Symposium- Sponsored by GE Healthcare and Volpara	
1:20pm	Reporting – Guidelines and Experience from CBDIG	Debra M. Ikeda
2:10pm	Non-mammographic Screening Strategies and Emerging Technologies for High Density Women	Wendie Berg
3:00pm	Coffee Break	
3:30pm	Examples	Debra M. Ikeda & Jennifer Harvey
4:30pm	Panel Discussion	
5:00pm	Adjourn	
5:00pm – 6:00pm	Networking Reception	

Thursday, June 11, 2015

8:00 am Continental Breakfast

Comparative Measures of Breast Density Moderator: Isabel Silva

8:30 am	Advocates Introduction	Vivian Lee
8:40 am	Masking Models and Breast Density	James Mainprize
9:15 am	Automated Clinical Breast Density Measures and Breast Cancer Risk	Celine Vachon
9:50 am	New Ultrasound Approaches for Identifying Women with High Breast Density and Screening them for Breast Cancer	Neb Duric
10:25 am	Coffee Break	
11:00 am	Multi-Modality Breast Imaging Radiomics of Tumors and Parenchymal Density & Texture	Maryellen Giger

Abstract Proffered Talk(s)

11:35 am	Fibroglandular tissue measured as mammographic density and texture (amount and distribution) can individually and jointly contribute to breast cancer risk assessment	Rikke Winkel
11:50 am	Early growth and breast-tissue composition at the end of breast development: exploring the pathways to breast cancer risk in prepubertal girls	Ana Pereira
12:05 pm	Lunch and Poster Session 1	

Afternoon Program - Breast Density and Biology and Genetics: Moderator: Per Hall

1:30 pm	Molecular Epidemiology and Biology of Mammographic Density in the BREAST Stamp Project	Gretchen Gierach
2:05 pm	Tissue Stiffness Can Contribute to Invasive Carcinoma	Ovijit Chaudhuri
2:40pm	Coffee Break	
3:10pm	Genetics of Breast Density and Breast Cancer	Rulla Tamimi
3:45pm	Adolescence and Breast Density	Karin Michels

Abstract Proffered Talk(s)

4:20 pm	Mammographic density and breast cancer intrinsic subtypes	Laurie Habel
4:35 pm	Functional assessment of breast fibroglandular tissue: correlations between MBI and MRI	Carrie Hruska

4:50 pm	Panel Discussion & Summary of Day One	Moderators: Karla Kerlikowske John Shepherd
7:00 pm	Group Dinner pre-registration required	

Friday, June 12, 2015

8:00am Continental Breakfast

Risk Modeling – Putting it All Together I - Moderator Celine Vachon

8:30 am	Mammographic Density Pooling Project – Insights from an International Perspective	Valerie McCormack
9:05 am	Benign Breast Disease, Mammographic Breast Density and Breast Cancer Risk	Jeff Tice
9:40 am	Tyrer/Cuzick Model with Density	Jack Cuzick
10:15 am	Coffee Break	

Threshold Probabilities for Clinical Recommendations - Moderator Karla Kerlikowske

10:35 am	Cost-Effectiveness and Harm-Benefit Analyses of Risk-Based Screening Strategies for Breast Cancer	Ester Vilaprinyo
11:10 am	Quantifying the Net Benefit of Mammography Screening Intervals Based on Screening Interval, Risk, Breast Density and Age	Anna Tosteson

Abstract Proffered Talk(s) - Celine Vachon

11:45 am	Combined Effect of Dense and Nondense Breast Volume on Breast Cancer Risk	Johanna Wanders
12:00 pm	Mammographic Density and breast cancer risk: A mediation analysis	Megan Rice
12:15 pm	Lunch and Poster Session 2	

Putting it All Together II Moderator – Karla Kerlikowske

1:45 pm	Assessing breast cancer masking risk in full field digital mammography with automated texture analysis	Mads Nielsen
2:00 pm	Density, Dose, and Digital Breast Tomosynthesis	Ralph Hinghnam
2:15 pm	Panel Discussion, Summary, and Closing	Moderators: Karla Kerlikowske John Shepherd
3:00 pm	Adjourn	

Clinical Aspects of Breast Density

Wednesday, June 10, 2015

Breast Density Methods in Clinical Practice

Jennifer Harvey, MD, FACR
Professor of Radiology, University of Virginia

Breast density in clinical practice is important due to its role in the masking of breast cancer as well as the association with breast cancer risk. Women with high breast density are up to 17 times more likely to present with an interval cancer and about 4 times more likely to be diagnosed with breast cancer. The best method of density measurement used may depend upon the role that the information conveys and the subsequent actions that may be taken depending upon the result. For masking, use of BI-RADS density categories may suffice. The latest edition (5th, 2013) changes the definitions slightly with an expected upshifting of density categories based on potential risk of masking. BI-RADS density categories potentially drive patient density notification results (now in 21 states) that may result in recommendations for additional screening, typically with ultrasound. The lack of reproducibility of BI-RADS categories could potentially drive use of automated methods of measuring breast density. Regarding breast cancer risk, little is currently communicated to the patient regarding her density. However, a comprehensive model that includes breast density may improve individual discrimination making risk-based screening more feasible. Risk models that include breast density would optimally use density as a continuous variable that has high reliability and validity. Measurement of density for purposes of predicting interval cancers may be very different than measurements optimized to predict breast cancer risk.

Breast density and other risk factors of breast cancer.

Giske Ursin

This presentation will review the association between mammographic breast density and other risk factors for breast cancer. Focus will be on both genetic and non-genetic risk factors.

Studies of twins have suggested that mammographic density is at least partially inherited. It seems likely that the genetic variants that predict mammographic density would partially, but not completely, overlap with genetic variants associated with breast cancer. Genetic studies of mammographic density have primarily focused on the role of candidate genes, or candidate pathways, but there have also been genome-wide association studies. Some genes or genetic variants have been found in several studies, but the consistency across studies has not been overwhelming. In addition to the uncertainty as to exactly which genetic variants are important for mammographic density, the role of gene-gene or gene-environmental interactions in mammographic density is largely unknown.

In terms of non-genetic factors, there is substantial evidence that reproductive factors and postmenopausal hormone therapy use are associated with mammographic density. For several of these hormonal exposures, only some women appear to be at higher or lower risk. Exactly what the determinants are for this individual variation is unknown.

The role of a number of other known or putative breast cancer risk factors have also been studied, including alcohol, diet, physical activity and this evidence will be discussed.

Identifying Women With Dense Breasts at High Risk for Interval Cancer

Karla Kerlikowske, MD; Weiwei Zhu, MS; Anna N.A. Tosteson, ScD; Brian L. Sprague, PhD; Jeffrey A. Tice, MD; Constance D. Lehman, MD, PhD; and Diana L. Miglioretti, PhD, for the US Breast Cancer Surveillance Consortium (BCSC)

Background: Twenty-two US states have laws requiring women with dense breasts be notified they have dense breasts and be advised to discuss supplemental imaging with their provider.

Objective: To determine which combinations of breast cancer risk and Breast Imaging Reporting and Data System (BI-RADS) breast density categories are associated with high interval cancer rates.

Methods; We included 831,455 digital screening mammography examinations among 365,426 women aged 40-74 years; 2696 developed invasive breast cancer. We examined BI-RADS breast density, BCSC 5-year breast cancer risk, and interval rate (invasive cancer $\leq$12 months after normal mammography result) per 1000 examinations. High interval rate was defined as >1 case/1000 examinations.

Results: High interval rates were observed for women with 5-year risk $\geq$1.67% and extremely dense breasts or 5-year risk $\geq$2.50% and heterogeneously dense breasts (24% of all women with dense breasts). The interval rate of advanced-stage disease was highest (>0.4/1000 examinations) among women with 5-year risk $\geq$2.50% and heterogeneously or extremely dense breasts (21% of women with dense breasts). Five-year risk was low to average (0%-1.66%) for 51.0% of women with heterogeneously dense breasts and 52.5% with extremely dense breasts, with interval rates of 0.58-0.63 and 0.72-0.89/1000 examinations, respectively.

Conclusion: Breast density should not be the sole criterion for deciding whether supplemental imaging is justified because not all women with dense breasts have high interval cancer rates. BCSC 5-year risk combined with BI-RADS breast density can identify women at high risk for interval cancer to inform patient–provider discussions about alternative screening strategies.

Breast Density Legislation and Reporting – Guidelines and Experience from the California Breast Density Information Group (CBDIG)

Debra M. Ikeda, M.D., FACR, FSBI

7th International Workshop on Breast Densitometry and Cancer Risk Assessment
San Francisco, CA June 10, 2015

Breast Density Notification laws, passed in 22 states as of April 2015, require that heterogeneously or extremely breast density information from mammograms be given to patients. Such legislation often is written without guidance on which supplemental screening modalities, if any, are recommended for women with dense breasts, which patients with dense breast tissue should be selected for supplemental screening nor is funding provided for supplemental screening. In 2012 the passage of the California SB 1539 breast density legislation impacted radiology practices across California. Since California was an early adopter of breast density legislation, there was little information nationally or on the web specifically to guide policy development in individual radiology practices on implementing the law or on supplemental screening studies. There was no discussion regarding breast cancer risk assessment and family history.

The U.S. Mammography Quality Standards Act (MQSA) requires that women receive a lay letter informing them of their mammogram result. California's breast density notification law required that the following statement be included in the letter for women determined to have heterogeneously or extremely dense breasts:

"*Your mammogram shows that your breast tissue is dense. Dense breast tissue is common and is not abnormal. However, dense breast tissue can make it harder to evaluate the results of your mammogram and may also be associated with an increased risk of breast cancer.*

This information about the results of your mammogram is given to you to raise your awareness and to inform your conversations with your doctor. Together, you can decide which screening options are right for you. A report of your results was sent to your physician."

In 2012, in response to California SB 1538 legislation, we formed a working group of breast imagers and breast cancer risk specialists called the California Breast Density Information Group (CBDIG), composed of academic and community-based specialists, to produce material that would be easily understood by and accessible to all stakeholders involved in the breast density question, including patients and providers alike. We recognized that institutions needed to respond individually and quickly to the law to develop policies in alignment with legislation, taking into consideration local concerns and available resources. We wished to leverage the expertise of our practitioners well known throughout California to develop evidence-based information that could be applied broadly. We expected that dissemination of our deliberative process

might provide a model and iterative process that radiologists and clinicians in other states could use to develop their own response to pending or already enacted legislation.

The result of our work was the website **"breastdensity.info"** which is unaffiliated with any academic or private practice institution, readily translatable into Spanish, Chinese, or other languages by Google Translate.

The key issues involved in breast density notification involve 1) the relative risk of breast cancer associated with dense breasts, 2) masking of cancers by overlying breast tissue on mammography and 3) the efficacy, benefits and harms of supplemental screening tests.

Breast density estimation is made by subjective visual assessment of the interpreting physician into 1 of 4 categories, as defined by the 2013 American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS), currently based on the probability of masking breast cancer rather than based on volume of glandular tissue. Computerized technologies provide quantitative density assessment, but computerized objective measures are not required. Based on large-scale population-based data from a representative sample of mammography practices in the United States, and listed in order of least dense to most dense, and based on the old BI-RADS density categories based on quartiles of density, the frequency distribution of the BI-RADS density categories is approximately: almost entirely fatty – 10%; scattered areas of fibroglandular density – 40%; heterogeneously dense – 40%; and extremely dense – 10% (as shown in the 2013 BI-RADS Atlas).

Given that approximately 50% of women in the USA are extremely dense or heterogeneously dense, CBDIG suggested an approach to stratify women for supplemental screening by using breast cancer risk assessment based on verified family history models, an approach that has been suggested also by other authors as recently as 2015 (Kerlikowske et al 2015).

First, mammography has been shown to decrease breast cancer mortality through randomized, controlled trials of invitation to screening, and any supplemental screening should be done in addition to mammography, unless the patient is very young and has a genetic predisposition to breast cancer. In this young population, some authors suggest screening MRI as the first test. In addition, tomosynthesis in addition to digital mammography detects breast cancer in both dense and non-dense breasts as shown in Scandinavian and European tomosynthesis screening trials.

Second, breast cancer risk assessment using validated models based on family history may help to select patients at highest risk and in whom supplemental screening in addition to standard screening mammography may maximize the benefit/harm ratio of supplemental screens. This trade-off involves early cancer detection compared to increased false positive examinations. Full breast cancer risk assessment requires detailed knowledge of mathematical models, such as Claus, modified Gail, BRCAPRO, Tyrer-Cuzick (IBIS Breast Cancer Risk Evaluation Tool), BOADICEA and others. A health care provider who is fully informed regarding the merits and weaknesses of these models best conducts risk assessment. Given the very large number of women who receive density notification letters, the demands for detailed risk assessment are likely to be

unmanageable. Therefore, it may be valuable for clinicians to elicit 'red flag' risk factors to rapidly triage patients to breast cancer risk assessment, or to have risk assessment done in their own clinics.

For individual patients at high risk and for known high-risk patient cohorts, supplemental screening is recommended. The National Comprehensive Cancer Network (NCCN), American Cancer Society, Society of Breast Imaging and American College of Radiology recommend screening breast MRI annually in addition to yearly mammography for high-risk patients. Although the California legislature did not mandate insurance coverage for any supplementary breast cancer screening tests, screening MRI is generally reimbursed for women who are at a lifetime risk of greater than 20%. Some states provided support for screening ultrasound for high-risk women, but only for those women with dense breasts who have no access to or cannot undergo MRI. If a woman has a screening MRI, screening ultrasound will provide no additional benefit. However, screening breast ultrasound is recommended if the patient cannot undergo breast MRI.

We have distributed a 20-question anonymous web-based survey to radiologists in the Society of Breast Imaging between August 2013 and March 2014. Our survey showed variations in available supplemental screening modalities and policy implementation at each facility. We will present this data at the conference.

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Title of Abstract: Non-mammographic Screening Strategies and Emerging Technologies for High Density Women

Presenting Authors Full Name: Wendie A. Berg, MD, PhD, FACR

Institution: Magee-Womens Hospital of UPMC; University of Pittsburgh School of Medicine

Additional Author's Names as to be Published:

Purpose: To compare and discuss rates of cancer detection and false positives using methods other than or in addition to mammography to screen for breast cancer in women with dense breasts.

Method: Review of the literature and case presentations

Results: Tomosynthesis provides slight improvement in cancer detection compared to standard mammography (averaging 1.3 per 1000), with reduction in recall rates, but performance is likely reduced in extremely dense breasts. Ultrasound (US) alone detects the same number of cancers as mammography but more of those cancers are invasive and node negative. When added to mammography, technologist-performed and automated US yield another 2-2.5 cancers per 1000 women screened, with physician-performed handheld US yielding 3-4 cancers per 1000 women screened, but another 5-6% of women will be recommended for biopsy because of US findings. Even in average risk women, MRI will depict another 10 cancers per 1000 women screened after mammography plus US, with substantial recall and biopsy rates but acceptable yield from biopsies. Fast MRI shows promise in reducing cost while maintaining cancer detection rates. Contrast-enhanced mammography and molecular breast imaging result in approximately 8 cancer detections per 1000 women with acceptable false positive rates, but direct biopsy methods are lacking.

Conclusion: Women with dense breasts should be informed of the expected outcomes from nonmammographic screening, including expected cancer detection and false positive rates.

Comparative Measures of Breast Density

Thursday, June 11, 2015

8:30am-11:00am

Title of Abstract:
Masking Models and Breast Density

Presenting Authors Full Name:
James G Mainprize, PhD

Institution:
Sunnybrook Research Institute

Additional Author's Names as to be Published:
Olivier Alonzo-Proulx, PhD, Martin J. Yaffe, PhD

Purpose:
Mortality reductions, as high as 40%, are attributable to earlier detection by screening mammography. However, mammography has reduced sensitivity and specificity for women with dense breasts due to “masking” of lesions or mimicking of nonexistent lesions by overlapping parenchymal tissue. While masking is most severe in very dense breasts, it also occurs in low or intermediate density breasts where local areas of density and the corresponding texture reduce lesion conspicuity. Ideally, if mammograms showing high masking potential could be identified, these women could be redirected to alternative screening. This could improve sensitivity while reducing recall rates and unnecessary biopsies. To do this, an objective, quantitative measure of masking is required.

Method:
Using a mathematical observer model, we estimated the detectability (SNR) of simulated lesions for small regions across the mammogram. In areas of high masking, caused by low contrast or complex tissue backgrounds, the detectability will be low. Fitted power spectra are extracted from small ROIs (256×256) throughout the mammogram, capturing both the quantum noise and the tissue texture characteristics. From these spectra and measured contrast of the lesion, a simple “localized” observer model is used to estimate the detectability, dL (SNR) of a potential lesion centred in each ROI.

Results:
Strong correlations are seen in a small study (n= 138 mammograms) between the average dL and both the volumetric breast density and the tissue texture parameter—the spectral power-law exponent, β. In a small study of 24 cancers, there was a significant (p=0.03) difference (38% change) in average dL between mammograms classified by an experienced radiologist as “easy” and “difficult” to interpret

Conclusion:
A masking index is being developed that correlates with reduced lesion conspicuity in mammograms. Future work will investigate use of this index to identify women who would benefit by being directed to an alternative screening modality.

New ultrasound approaches for identifying and screening women with high breast density

Nebojsa Duric

Karmanos Cancer Institute

Mark Sak, Gretchen Gierach, Mark Sherman, Norman Boyd, Heather Rone, Peter Littrup

Purpose:
For women with dense breast tissue, who are at higher risk for developing breast cancer, the performance of mammography is at its worst. Consequently some cancers are missed. Furthermore, reduction in breast density appears to be a marker of response for women taking tamoxifen in chemoprevention and adjuvant settings, but mammographic measurements of such response are typically taken 12 to 18 months post tamoxifen initiation. We investigate ultrasound tomography (UST) as a method that can quantify breast density to assess UST's potential for (i) personalized screening of women with dense breasts and (ii) frequent monitoring of treatment response.

Method:
(i) Major ultrasound breast screening studies were reviewed to provide the context for UST's role in detecting cancer in dense breasts. In a separate study, UST's diagnostic specificity was compared to that of hand-held ultrasound in a study of 162 lesions.
(ii) Asymptomatic women (N=139) were imaged with mammography and with UST. The mammographic percent density (MPD) and volume averaged sound speed (VASS) of the breast were determined for all participants and the results compared.
(iii)In an ongoing study, women who were prescribed tamoxifen for clinical indications (N=65) were imaged with UST at approximately 3 month intervals starting at baseline (just before administration of tamoxifen) and ending approximately 12 months later with VASS measurements made at each visit.

Results:
(i) Previous screening studies suggest that ultrasound finds an average of ~3.5 extra cancers per thousand for women in BI-RADS breast density categories of 3 and 4. However, the high recall rate has limited adoption. UST's tissue-specific imaging demonstrated increased diagnostic specificity relative to standard ultrasound.
(ii) UST measurements indicate that VASS has a strong positive association with MPD (r_s=0.703, $p<0.001$).
(iii) VASS declines from baseline to 12 months ($p < 0.003$) with declines discernable as early as 3 months after the start of tamoxifen use ($p<0.05$).

Conclusion:
If UST's higher diagnostic specificity translates to screening, adoption of screening ultrasound would be facilitated. Furthermore, UST provides a quantifiable method for assessing breast density which may prove useful in future risk stratification, personalized screening and density-based monitoring of risk-modulating treatment.

Multi-Modality Breast Imaging Radiomics of Tumors and Parenchymal Density & Texture

Maryellen L. Giger, Ph.D.
The University of Chicago

Radiomics – or Quantitative image analysis (QIA) and computer-aided diagnosis (CAD) methods (i.e., computerized methods of analyzing digital breast images: mammograms, ultrasound, and magnetic resonance images) -- can yield novel image-based tumor characteristics (i.e., signatures) that may ultimately contribute to the design of patient-specific breast cancer treatments. With computer-aided detection (CAD) of breast cancer, the aim was to provide a 'second opinion' to aid the radiologist in locating suspicious regions within screening mammograms. Today, the role of Radiomics/QIA/CAD is expanding beyond screening programs towards applications in risk assessment, diagnosis, prognosis, and response to therapy as well as in data mining to discover relationships of lesion characteristics as they apply to disease states.

Computerized methods are being developed to (a) quantitatively characterize the features of a suspicious region or tumor, e.g., those describing tumor morphology or function, (b) merge the relevant features into diagnostic, prognostic, or predictive image-based biomarkers, (c) estimate the probability of a particular disease state or molecular subtype, (d) assess breast cancer risk, (e) assess risk of recurrence, and (f) explore the complex relationships among image-based tumor characteristics across large populations and association studies between the image-based signatures (i.e, image-based phenotypes) and histological/genomic data for imaging genomics.

This presentation will first review our advances in mammographic 3CB (three compartmental breast) imaging and breast MRI HiSS imaging, along with their associated radiomics features, that allow us to "see" better the composition of the breast. Next presented will be our findings on the role of parenchymal texture pattern in breast cancer risk assessment and in cancer diagnosis. Finally, we will summarize our recent findings within the NCI TCGA/TCIS Breast Cancer Group on the association of breast MRI radiomics with molecular subtype, risk of recurrence, and genomics.

Abstract Proffered Talks

Thursday, June 11, 2015

11:35 am - 12:05 pm

Title of Abstract:
Fibroglandular Tissue Measured as Mammographic Density and Texture (Amount and Distribution) Can Individually and Jointly Contribute to Breast Cancer Risk Assessment

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Purpose:
Mammographic density is a well-established risk factor for breast cancer. Recently, measures of the textural/structural aspects of mammographic appearance have been shown to improve on risk segregation using density alone: both the (relative) amount of dense tissue and its distribution relates to risk. Our purpose was to investigate the risk segregation afforded, individually and in combination, by three measures of mammographic density and the corresponding density distribution using the BI-RADS classification, the Tabár classification, and a measure of mammographic texture.

Method:
The case/control study included 121 cases and 259 age-matched controls from a Danish 2007 screening cohort of all 14,736 women with negative screening mammograms. Cancer cases were diagnosed at later screening visits or as interval cancers whereas controls remained undiagnosed (per 2010). The screen-negative 2007 digitised mammograms were classified using 1) BI-RADS density classification (4th edition), 2) Tabár's classification on parenchymal patterns, and 3) an automated risk-specific texture quantification algorithm. The methods' individual and combined association with breast cancer were estimated using logistic regression to calculate age adjusted ORs and AUCs.

Results:
All three methods successfully segregated cancer cases from controls showing significant ORs for BI-RADS categories 3 and 4 (ORs: 2.37 and 3.93), for Tabár categories PIII and PIV (OR: 3.23 and 4.40), and for the highest quartile of texture (OR: 3.04). AUCs for BI-RADS, Tabár, and texture were 0.63, 0.65 and 0.63 (p<0.0001 for all), respectively. combining the three methods into one model improved (ns) the auc to 0.69 (p<0.0001).

Conclusion:
The results indicate that the amount of fibroglandular tissue (density) as well as the structural distribution individually and more so jointly contribute to mammography based breast cancer risk assessment and personalised screening. Results (not given) indicate that the high risk Tabár PIV category is strongly associated with elevated texture scores and thus more readily interpretable.

Title of Abstract:
Early Growth and Breast-tissue Composition at the End of Breast Development: Exploring the Pathways to Breast Cancer Risk in Prepubertal Girls

Presenting Authors Full Name:
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Purpose:
Breast Density(BD) is hypothesized to peak at the end of puberty and decreases thereafter. Little is known on the factors that define BD during childhood. Recently, dual-energy X-ray absorptiometry (DXA) has been validated as a safer and lower dose radiation tool than mammography to measure volumetric BD [fibroglandular volume(FGV) and percent FGV(%FGV)], in young women. Our objective is to assess the relationship between childhood adiposity and FGV and %FGV at the end of puberty onset.

Method:
This study was set up in a cohort of 400 Chileans girls born in 2002-2003 for whom we have detailed anthropometry from birth and serial Tanner breast development assessments. DXA(GE iDXA) BD was measured when the girls reached Tanner B4. Images were exported as low and high attenuation images and BD was measured using the UCSF DXA BD Software developed by one of the authors(Shepherd). Each girl received two dedicated scans of the left breast and one of the right. Linear regression models crude and adjusted by BMI at B4 were used to assess the relation between birth weight, childhood BMI growth, and FGV and %FGV at Tanner B4.

Results:
To date, 219 girls have completed the B4 study visit. The test-retest precision was 3.6% for %FGV. Mean %FGV was 49.3%(+/-15.5) and FGV of 79.9 cm3(+/-30.7 cm3). In the non-adjusted models BMI at birth, 2, 4 and 7 years were inversely associated with %FGV. In the adjusted models, BMI at birth(βadj=1.96; 95%CI:0.41,3.51), at 2(βadj=5.09; 95%CI:2.85,7.38), and at 4yrs(βadj=8.67; 95%CI:5.41,11.93) were positively associated with % FGV at B4 and BMI at age 7 was inversely related to %FGV(βadj=-7.22; 95%CI:-12.10,-2.33). FGV at B4 was not associated with the variables studied.

Conclusion:
BMI at birth, 2, 4 and 7 years are inversely related to %FGV, however childhood adiposity gain increased %FGV at the end of puberty. (Funding FONDECYT:3130532 WCRF2010/245)

POSTER SESSION 1

Thursday, June 11, 2015

12:05 pm – 1:30 pm

Poster #	Submission Title	Submitter Name
2	ASSOCIATION BETWEEN METABOLIC SYNDROME AND BREAST DENSITY IN PREMENOPAUSAL CHILEAN WOMEN	Andela Martinez
4	Measurement of mammographically dense and non-dense breast volume and cancer risk	Bo Fan
6	Predictors of Breast Density: Are there differences between Caucasian and African-American women?	Celia Byrne
8	LIBRA: The Laboratory for Individualized Breast Radiodensity Assessment	Despina Kontos
10	Breast Cancer Risk in Relation to Three Methods for Assessing Density Using Digital Mammograms	Daniel Rubin
12	Volumetric breast density assessment and mammographic sensitivity	Ariane Chan
14	Comparison of MRI Breast Density Protocols and Estimation Methods	John Hipwell
16	Volumetric breast density and the risk of screen detected and interval breast cancer	Johanna Wanders
18	Improve volumetric breast density assessment in dense breasts	Katharina Holland
20	Mammographic density and the risk of contralateral breast cancer (CBC) in the WECARE Study	Julia Knight
22	Recruitment Challenges in Clinical Trials for 3 Component Breast Imaging	Leila Kazemi
24	Mammographic density reduction during neoadjuvant endocrine therapy in hormone receptor positive breast cancer	Jisun Kim
26	Mammographic breast density decline as a marker of effectiveness among premenopausal breast cancer patients treated with tamoxifen	Maeve Mullooly
28	Volpara automated volumetric breast density software decreases radiologist overestimation of breast density by the second year of implementation	Miriam David
30	Mammographic density and histopathologic characteristics of screen-detected tumors in the Norwegian Breast Cancer Screening Program	Nataliia Moshina
32	Physical growth in childhood and adolescence and breast composition in young adulthood: findings from an English birth cohort	Rachel Denholm
34	Impact of Breast Density Information on Desire to Know Breast Density, Anxiety and Confusion, and Decisions Regarding Future Mammography and Supplemental Screening: Results of a National Survey	Deborah Rhodes
36	Reasons for (non-)participation in the Dense tissue and Early breast Neoplasm ScrEening (DENSE) trial	Stéphanie de Lange
38	Validation of Volumetric Breast Densities Derived by Statistical Model Approach	Serghei Malkov
40	Using visual and volumetric measures of mammographic density to identify women with high density breasts	Susan Astley
42	Birth weight, childhood BMI and height in relation to mammographic density and breast cancer: Danish Diet, Cancer and Cohort study	Zorana Andersen
44	Hormone replacement therapy, mammographic density, and breast cancer risk: a cohort study	Zorana Andersen
46	Association of Gail model breast cancer risk estimates and mammographic density in Asian women	Teo Soo Hwang PhD FASc

Title of Abstract:
ASSOCIATION BETWEEN METABOLIC SYNDROME AND BREAST DENSITY IN PREMENOPAUSAL CHILEAN WOMEN

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Purpose:
Metabolic syndrome (MS) has been previously associated with an increased risk of breast cancer (BC) in postmenopausal women. Mammographic density (MD) is a marker of BC risk. There is little evidence an association between MS and MD in premenopausal women. Our aim is to evaluate the relationship between MS and MD in premenopausal Chilean women of low-middle socioeconomic status.

Method:
A cross-sectional design within the DERCAM cohort was used, in which we studied 364 women (mean age 37.8 years, SD=4.2). We measured anthropometric characteristics, blood pressure and metabolic markers. Socio-demographic and gyneco-obstetrics variables were evaluated using a questionnaire. We estimated MD by dense volume (DV,cm3), non-dense volume (NDV,cm3) and volumetric breast density (%BD) through bilateral digital mammography (Hologic Selenia), with a fully automated commercial method (VOLPARA, St John, New Zealand). The MS was defined according to the NCEP ATPIII criteria. Linear regression models estimated the association between MS and MD.

Results:
The mean body mass index (BMI) was 28.1kg/mt2 (SD=5.5), 62.4% presented abdominal obesity and 80% had
high HDL-Cholesterol. One in four women showed MS. The mean DV in women without MS was 67.7 cm3 (SD=36.2), compared with 71.3 cm3 (SD=29.7) in women with MS (p=0.10). We found statistical differences: NDV 623.1 cm3 (SD=362.7) v/s 954.9 cm3 (SD=431.1) and %BD 11.2 (SD=5.5) v/s 7.5 (SD=2.7) in women without MS v/s with MS ($p<0.05$). MS was not associated with DV after adjusting by covariables (β=0.10;95%CI:-0.01;0.21), but it was directly associated with lower %BD
(β= -0.29;95%CI:-0.40;-0.19) and higher NDV (β=0.44; 95%CI:0.30;0.56) however, these associations were not significant after adjusting by BMI.

Conclusion:
Our results showed no association between MS and MD. The relationship between adiposity and NDV and how this might influence the future risk of BC should be further studied in depth.
(Fondecyt:11100238/3130532; Ellison Medical Foundation Fund, WCRF 2010/245)

Title of Abstract:
Measurement of mammographically dense and non-dense breast volume and cancer risk

Presenting Authors Full Name:
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Institution:
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Additional Author's Names as to be Published:
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Purpose:
Mammographic density (BD) is one of the strongest predictors of breast cancer risk. While increase BD is associated with increase of breast cancer risk, studies have found that non-dense area on film screening mammography is associated with a decrease in breast cancer risk. Our aim was to study how different approaches to measure volumetric non-dense breast volume and their association with breast cancer in digital full field mammography.

Method:
A total of 200 women with breast cancer were selected from the San Francisco Mammography Registry (SFMR) database. Participant's demographic and anthropomorphic information were also collected at time of mammography. Cancer cases as well as age, mammogram device and date of mammogram matched controls were analyzed using UCSF SXA version8 and version9 software. Two different approaches were used to calculate the non-dense volume. First: difference of total breast volume and SXA version9 dense volume. Second: difference of estimated nonperiphery and dense volume. Associations of density volume and non-dense volume with breast cancer risk were analyzed using conditional logistic adjusting BMI and family history.

Results:
We found that both version 8 and 9 dense volume were associated with increased breast cancer risk, the odds ratio and 95% CI of fourth quartile compare to the second quartile were 1.9 (1.1 – 3.2) and 2.6 (1.5 – 4.5) for version8 and version9 respectively. In contrary, odds ratio for non-dense volume version 8 had more protective than the two approaches of version 9, although none of them reached statistical significance. The odds ratio and 95% CI for fourth quartile compare to second quartile were 0.6 (0.3 – 1.2), 1.0 (0.5 – 1.9) and 0.9 (0.4 – 1.6) for version 8 and the two approaches of version 9, respectively.

Conclusion:
Our study show a similar trend as film data, however it did not reach statistical significance. Further investigation is warranted in a larger cohort study.

Title of Abstract:
Predictors of Breast Density: Are there differences between Caucasian and African-American women?

Presenting Authors Full Name:
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Purpose:
Mammographic breast density is one of the strongest predictors of both hormone receptor (HR) positive ( ) and HR negative (-) breast cancer. Furthermore, mammographic breast density predicts risk of both premenopausal and post-menopausal breast cancer. African-American women have higher rates of both HR- and premenopausal breast cancer. Studies have shown differences in associations between some traditional risk factors and breast cancer by race, however, only a few studies have evaluated differences in factors that predict mammographic breast density in both Caucasian and African-American women.

Method:
Between 2005 and 2011, we recruited over 1600 women coming to the Ourisman Breast Health Center at Georgetown University for screening mammography into a study of determinants of breast density. Women using exogenous hormones at the time were excluded. Of the women enrolled, 64% identified as Caucasian and 33% as African-Americans. Women completed a detailed questionnaire and provided a blood sample on the day of their mammogram. Breast density was measured using Cumulus computer-assisted methods. Linear regression models determined the predictors of percent breast density by race.

Results:
Preliminary analyses indicated age and body mass index (BMI) were both inversely associated with breast density for both Caucasian and African-American women (p<0.001). compared with nulliparous women the patterns of association between various ages at first birth and ages at last birth appeared to differ between caucasians and african-american women. in addition, lower income level was significantly associated with higher breast density in african-american women but not caucasian women.

Conclusion:
Age and BMI, were significantly inversely associated with breast density for both Caucasian and African-American women. The differences in associations between age at first birth and last birth with breast density by race suggest that reproductive factors have different influence on breast density and breast cancer risk by race.

Title of Abstract:
LIBRA: The Laboratory for Individualized Breast Radiodensity Assessment

Presenting Authors Full Name:
Despina Kontos PhD

Institution:
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Additional Author's Names as to be Published:
Brad Keller PhD, Meng-Kang Hsieh MS, Lauren Pantalone BS, Emily F. Conant MD, University of Pennsylvania

Purpose:
The amount of fibroglandular tissue in the breast as estimated mammographically, commonly referred to as percent density (PD%), is one of the most widely established risk factors for breast cancer. Here we present a new, publicly-available software package, the Laboratory for Individualized Breast Radiodensity Assessment (LIBRA), that allows for fully-automated breast density estimation from either raw (“FOR PROCESSING”) or post-processed (“FOR PRESENTATION”) digital mammography images from a variety of vendors.

Method:
Briefly, the LIBRA software first applies an edge-detection algorithm to delineate the boundary of the breast and the boundary of the pectoral muscle. Following the segmentation of the breast, an adaptive multi-class fuzzy c-means algorithm is applied to identify and partition the mammographic breast tissue area into multiple regions of similar x-ray attenuation. These clusters are then aggregated by a support-vector machine classifier into a final dense tissue area segmentation. The ratio of the segmented absolute dense area to the total breast area is then used to obtain a measure of breast percent density (PD%). LIBRA also generates quantitative estimates of absolute breast and dense tissue area as well as the corresponding breast and dense tissue area segmentations overlaid on the original mammographic image.

Results:
LIBRA has been validated against the widely used semi-automated Cumulus method and BIRADS density estimates, showing high agreement (r=0.85-0.89, k=0.62-0.64, p<0.001). to date, libra has been successfully applied to over 35,000 mammography screening exams and is increasingly utilized in larger studies looking at validating the method as a biomarker for breast cancer risk assessment.

Conclusion:
LIBRA is publicly available as open-source software that can be used freely for research purposes (http://www.cbica.upenn.edu/sbia/software/LIBRA/index.html). Given the increasing interest in automating density assessment, LIBRA could pave the way for larger clinical studies evaluating automated breast density measures in breast cancer risk assessment.

Title of Abstract:
Breast Cancer Risk in Relation to Three Methods for Assessing Density Using Digital Mammograms

Presenting Authors Full Name:
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Purpose:
The percentage of mammographic density (PD) on full field digital mammography (FFDM) is positively associated with breast cancer risk; however it is currently unknown how best to measure breast density from FFDM images. We compared PD assessed by BI-RADS density categories, quantitative 2D, and 3D measurements with respect to the strength of their associations with breast cancer risk.

Method:
Our study included 136 women with invasive breast cancer and 281 age- and race-matched controls who underwent screening mammography on a GE system during 2004-13. We extracted the BI-RADS density from the mammography report. We used the Cumulus 6 software for 2D assessment of PD, and Volpara v150 software for 3D assessment of Volpara percent density (VPD). We assessed intra-reader reproducibility of PD by computing Pearson's correlation coefficient (R) on blinded repeat measurements. We estimated the odds ratios (ORs) for breast cancer associated with BI-RADS density category, PD, and VPD using conditional logistic regression, stratified by age and race, and computed the area under receiver operating characteristic curve (AUC) for each method.

Results:
FFDM BI-RADS density was strongly associated with breast cancer risk; women with extremely dense vs. almost entirely fatty breasts had an OR=6.70 (95% confidence interval (CI) 5.67-7.72), AUC=0.68 (0.63-0.74). 2D PD assessment on processed FFDM images were highly reproducible (intra-reader R=0.90). Women in the highest vs. lowest quartiles of PD had OR=3.07 (2.32-3.81), AUC=0.66 (0.60-0.71), after adjusting for BMI, breast area, parity, menopausal status, and matching factors. The association between breast cancer risk and VPD was significant only for the highest quartile of VPD, AUC=0.63 (0.57-0.69), adjusting for matching factors.

Conclusion:
PD assessed on FFDM images was significantly associated with breast cancer risk, confirming prior results with film screen mammography. Associations with breast cancer risk were somewhat stronger for Cumulus 2D than for Volpara VPD measurements.

Title of Abstract:
Volumetric breast density assessment and mammographic sensitivity

Presenting Authors Full Name:
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Purpose:
Volumetric breast density (VBD) has previously been shown to correlate with the risk of developing breast cancer. In this study we wanted to investigate the relationship of VolparaDensity with mammographic sensitivity.

Method:
This study included histologically confirmed DCIS, invasive ductal or invasive lobular breast cancers detected at screening (SC; n = 574) or in the interval between screens (IC; n = 106), in women (aged over 40 y) diagnosed at a breast center in New York between January 2009 and December 2012. Women with bilateral cancer, a prior history of breast cancer or breast surgery, or missing raw digital images, were excluded from the analyses. Sensitivity (SC/[SC + IC]) was stratified by Volpara Density Grade (VDG) categories, which are determined using preset thresholds of VBD (i.e. <4.5, 4.5-7.5, 7.5-15.5, >15.5%) and are equivalent to BI-RADS 4th Edition density categories. To investigate sensitivity changes between women at the lower or higher end of each VDG category, additional thresholds were used using the mid-points of each VDG threshold (i.e. 3.75, 6, 11 and 25.5%, for VDG 1, 2, 3 and 4, respectively).

Results:
In a double-reading setting, the sensitivity of mammography screening by VDG categories 1 – 4 were 95%, 90%, 82%, and 69%, respectively. Further dichotomization of each VDG category using VBD cut-offs showed a fairly linear relationship between VBD and sensitivity (R2=0.959). Sensitivity was similar between low versus high VDG1 (100% and 94%, respectively) and low versus high VDG2 cases (90% and 90%, respectively). However, sensitivity decreased more dramatically between low versus high VDG3 and low versus high VDG4 cases (86% to 77% and 72% to 58%, respectively).

Conclusion:
Volumetric breast density is correlated with mammography sensitivity. The wide variation of sensitivity within some of the BI-RADS categories suggests that a continuous measure of density might be more appropriate.

Title of Abstract:
Comparison of MRI Breast Density Protocols and Estimation Methods

Presenting Authors Full Name:
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Purpose:
To compare a range of disparate automated, semi-automated and manual methods for MRI breast density estimation, and apply these to routinely acquired T1w and T2w data sets, and a dedicated water/fat Dixon MR protocol.

Method:
Each method consists of two components: (a) delineation of the whole breast region of interest (breast volume), over which the density estimation will subsequently be computed, and (b) segmentation of the internal breast tissue into two classes intended to represent dense and non-dense components. The automated methods include a rule-based method for whole breast volume computation, and fuzzy c-means clustering and expectation maximisation with Markov Random Field regularisation for density computation. The degree of manual interaction was varied, and ranged from fully automated to specification of the pectoral fascia boundary, lateral breast aspects or complete delineation of individual slices of the MRI. The methods were applied to MRI data sets acquired from 100 young women from the Avon Longitudinal Study of Parents and Children (ALSPAC) – a population-based birth cohort of children born in 1991-2 in Avon, UK.

Results:
High correlation values were obtained between the fully automated method applied to T2w images and the fully manual method applied to Dixon images, for both total breast volume (0.98) and fraction of dense tissue (0.93). The mean between-method difference (95% limits of agreement) for fraction of dense tissue was 0.07 (-0.04, 0.18), the T2w image estimates being lower compared to the Dixon method. Breast volume ranged from 358 to 4470.9 cm3, with mean between-method difference (95% limits of agreement) being -25.30cm3 (-402.2cm3, 452.7cm3).

Conclusion:
Automated methods applied to either routine clinical MRI acquisitions or dedicated Dixon fat/water measurements have the potential to replicate manual methods of breast density estimation. These methods could provide insight into the appearance and hence classification of dense breast tissue using different MRI protocols.

Title of Abstract:
Volumetric breast density and the risk of screen detected and interval breast cancer

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Purpose:
In light of the breast density legislation and discussions about supplemental screening it is important to know not only one's risk of breast cancer, but particularly the risk of a breast tumor that is not detected through mammographic screening. We investigated the relationship between volumetric breast density and the risk of screen detected and interval cancer within a full field digital mammographic (FFDM) screening program.

Method:
Mammographic density was automatically assessed with Volpara version 1.5.0 (Matakina, New Zealand) on the first available FFDM mammogram of 43,211 women (50-75 years) participating in the Dutch biennial breast cancer screening program (2003-2009). Screen-detected breast cancer information was obtained from the screening registration system and interval cancer information was obtained through linkage with the Netherlands Cancer Registry. We estimated risks of screen-detected and interval cancers in relation to breast density using multinomial logistic regression analysis (adjusted for age). No other confounders were available in this routine screening database.

Results:
413 screen-detected and 150 interval tumors were identified. Screen-detected breast cancer risk was significantly higher in the higher breast density categories compared to the lowest (OR: 1.65, 95% CI: 1.21-2.24, OR: 1.78, 95% CI: 1.29-2.47, OR: 1.69, 95% CI: 1.08-2.63, for density categories 2 to 4 respectively compared to category 1). Interval cancer risk increased with increasing breast density (OR: 2.45, 95% CI: 1.20-4.99, OR: 5.24, 95% CI: 2.59-10.59 and OR: 6.86, 95% CI: 3.12-15.11, for density categories 2 to 4 respectively compared to category 1). The relationship with interval cancers was statistically significantly stronger than with screen-detected cancers (p<0.01) for density categories 3 and 4.

Conclusion:
Although higher breast density is related to a higher risk of a screen-detected breast cancer, it is particularly strongly related to the risk of a breast cancer that is not detected through mammographic screening (interval cancer).

Title of Abstract:
Improve volumetric breast density assessment in dense breasts

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Purpose:
To personalize screening procedures, volumetric percent density (VPD) may be used to stratify risk groups. To obtain VPD, the glandular tissue volume (GTV) is estimated in unprocessed mammograms using a physics-based method which relies on an internal reference value (RV) representing the projection of fat only. However, pure fat pixels are rare in dense breasts, causing an underestimation of GTV and VPD. The purpose of this work is to improve the VPD estimate in dense breasts.

Method:
We collected 43 paired FFDM and MRI examinations. Mammographic VPD was estimated in different ways using three different reference values and compared to estimations based on MRI data. Pearson correlation coefficients were calculated with estimations averaged over both breasts and both mammographic views.
The first two RVs are percentiles (0.99) of the pixel value distribution in the breast interior (BI). RV1 was obtained with a small BI. For RV2, a larger BI was used. Especially in dense breasts this may facilitate the identification of a pure fat pixel, that may not be present in the small BI. RV3 was defined by estimating the proportion of dense tissue in the densest location in the larger BI, using the maximum fraction of dense tissue projected on a line crossing the BI. Additionally we investigated a combination of the three estimations, by taking estimations of RV1 for nondense breasts and a combination of the results of RV2 and RV3 for dense breasts, using the estimation with RV1 to determine if the breast is dense.

Results:
We found correlations of 0.89, 0.87 and 0.76 using RV1, RV2 and RV3 respectively. This improved to 0.91 when combining the three estimations.

Conclusion:
The reference value determination is crucial for calculation of VPD. The combination of three different methods yields the best result as different breasts density patterns require different approaches.

Title of Abstract:
Mammographic density and the risk of contralateral breast cancer (CBC) in the WECARE Study

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Purpose:
Mammographic density is a strong risk factor for unilateral breast cancer (UBC), but its association with the risk of subsequent CBC has not been established. Cancer treatment has been shown to alter density.

Method:
The WECARE Study is a multi-site case-control study of CBC with 1521 CBC cases and 2212 UBC controls. A subset of the cases and controls participated in the mammographic density study. We retrieved film mammograms of the unaffected breast within two years prior to the first diagnosis as well as at six months to two years after diagnosis. We digitized films and one reader measured percent density using Cumulus. Logistic regression was used for the analysis which included measurements from 134 CBC cases and 132 UBC controls pre-diagnosis and 161 CBC cases and 167 UBC controls post-diagnosis available at the time of this analysis. Detailed treatment data including chemotherapy, radiation, and hormone therapy were available on everyone.

Results:
Women with high density, ≥50% versus <25%, prior to or at first diagnosis had a non-significant increased risk of cbc (or=1.8, 95% ci 0.8-3.6, p-trend=0.12), adjusted for age, body mass index, menopausal status, and treatment. high density after diagnosis was associated with significantly increased risk (or=3.0, 95% ci 1.4-6.4, p-trend=0.003). in general, we observed similar patterns in most age (≤45 and >45) and menopausal subgroups, although data were sparse in some groups with wide confidence intervals. Density decreased 7.4% on average in women who received chemotherapy and 3.8% in women not treated with chemotherapy (p=0.02 unadjusted and 0.056 after adjustment).

Conclusion:
These findings suggest that density before and after first diagnosis is a risk factor for CBC and density following initial treatment may be a better predictor of risk than density at or prior to first diagnosis. We will further assess whether chemotherapy modifies this relationship.

Title of Abstract:
Recruitment Challenges in Clinical Trials for 3 Component Breast Imaging

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Purpose:
Breast cancer is the common form of cancer and leading cause of mortality among woman, especially in developed countries.(1) About 1 in 8 U.S. women (around 12%) will develop invasive breast cancer over the course of the lifetime. (2) Mammography is the current diagnostic method for early detection of breast cancer. (1) However mammography has been criticized for too many false positives. Patients with “suspicious” mammography result go on to have diagnostic mammograms and ultrasound studies that can lead to a breast biopsy as well. However, only 20 percent of breast biopsies are found to be invasive cancer. False positives increase anxiety, are inconvenient, and increase ember the overall cost of cancer screening. The purpose of this study is to decrease the number of unnecessary biopsies by improving the specificity of mammography. Our technique is called 3-composition breast mammography or 3CB, and describes suspicious lesions in terms of their fractional lipid, protein and water composition.

Method:
Women with an abnormal screening mammography, and who were going to have a breast biopsy (BIRADS diagnostic category 4), were recruited sequentially at two clinical sites [UCSF (San Francisco, CA) and Moffitt Cancer Center (Tampa Florida)]. After reviewing the radiology log book for patient eligibility and checking for permission to be contacted by research staff member, our recruiter qualified the participant on the phone and then scheduled the 3CB exam before the biopsy. At the 3CB visit, two dual-energy mammograms (CC and MLO views) were acquired followed by 6 to 9 phantom images. In addition, the following data was also collected: breast health questionnaire, clinical radiology findings form, a more complete study radiology finding form, clinical pathology form, study pathology form (extracted from clinical pathology result and second one based on reading the slides by the study pathologist). The images are then sent to the University of Chicago for further feature extraction, referred to as Quantitative Image Analysis), to better describe the morphology of the lesion. The information gathering included, but was not limited to, complete BIRADs information for breast density distribution, mass and calcification descriptions, also other findings (ex. asymmetry, architectural distortion, etc...) and sub-categories of tumor type for invasive cancer (ER/PR/HER2). However, our primary outcome is lesion type describe by the four following categories: invasive, DCIS, fibroadenoma, and other benign.

Results:
We have been approaching an average of 4 patients per week and being able to recruit 75% of them. To date, we recruited 257 patients. Our major findings and sub types are including:

Title of Abstract:
Mammographic density reduction during neoadjuvant endocrine therapy in hormone receptor positive breast cancer

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Purpose:
Mammographic density reduction(MDR) is suggested as a surrogate of reduced breast cancer risk during chemoprevention. Recently, greater MDR during adjuvant endocrine therapy have shown better prognosis. We aimed to assess the density during neoadjuvant endocrine therapy.

Method:
We analyzed mammographic density among 44 patients during 16-24 weeks of preoperative endocrine therapy. 26 premenopausal women undergone Tamoxifen(20mg/day)+GnRH agonist and 18 postmenopausal women undergone letrozole(1mg/day) diagnosed of ER and/or PR positive invasive breast cancer were included. Baseline and post-treatment mammographic density was measured using Cumulus by single observer(JY Woo) of the unaffected contralateral breast. Response was assessed 1)monthly by caliper, 2)sonography and breast MRI at pre/post-treatment. Absolute dense area (DA, cm2), DAR (DA reduction, preDA-postDA) and it’s association with overall clinical response, Ki67 level and prognosis were evaluated.

Results:
Mean age was 42.5yr±5.48 and 60.1yr±5.16 in premenopause and postmenopause women. Baseline density was higher in premenopause women(preDA; 45.78±25.36 vs 20.09±8.78, p<0.001) and greater density reduction was observed in this group(dar; 8.18±16.71 vs -1.95±5.86, p<0.001). 52.0%(13/25) among premenopause and 44.4%(8/10) among postmenopause women had clinical cr(complete response) or pr(partial response) by caliper and 80.8(21/26), 77.8%(14/18) by sonography. though not statistically significant, da reduction was greater in responder group(cr/pr) among premenopause women (11.68±21.19 vs 5.62±10.19). ki67 level in post-treatment specimen was significantly reduced in high dar group (29.55±28.85 vs 10.83±10.84, p=0.048). the preoperative endocrine prognostic index (pepi) score tended to be lower in high dar group in both pre and postmenopause women suggesting better prognosis in patients showing greater density reduction during neoadjuvant endocrine therapy (p=0.06).

Conclusion:
Significant density reduction was observed in premenopause women after 24 weeks of neoadjuvant tamoxifen+GnRH agonist while no significant change seen after letrozole. Greater density reduction during neoadjuvant endocrine therapy is strongly assumed to be associated with better clinical response, reduction of Ki67 and better prognosis.

Title of Abstract:
Mammographic breast density decline as a marker of effectiveness among premenopausal breast cancer patients treated with tamoxifen

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Purpose:
Mammographic breast density (MD) represents a putative biomarker of tamoxifen effectiveness. We and others have shown that MD decline after initiating tamoxifen portends improved outcomes in chemopreventive and adjuvant settings. Recent results from the Suppression of Ovarian Function Trial (SOFT) found that ER+ premenopausal breast cancer patients treated with adjuvant tamoxifen alone did not experience reduced disease free survival (DFS) compared to women treated with ovarian suppression and tamoxifen or exemestane. We used data from Nyante et al (J Natl Cancer Inst 2015) to explore anticipated outcomes that may have resulted among SOFT participants who received tamoxifen alone with a resultant decline in MD.

Method:
Data on 136 women <55 years with er+ breast cancer diagnosed at kaiser permanente northwest from 1990-2008 (nyante et al) were used to investigate whether decreased md (≥10%) following tamoxifen therapy was associated with dfs. follow-up time for the cox regression model was the interval from breast cancer diagnosis to recurrence, death or censoring events (oophorectomy, or last follow-up date through december 2010). data were also weighted to approximate characteristics of soft participants, and survival models adjusted for age, tumor size and nodal status.

Results:
Within our study population, ~36% experienced ≥10% decline in MD. There were 34 recurrences or deaths within 5 years and 50 overall. In unweighted analyses, patients with ≥10% decline in MD following tamoxifen initiation had improved DFS at 5 years compared to patients with <10% md decline, hazard ratio (hr)=0.79 (95% confidence intervals (ci): 0.38-1.67). in analyses weighted to soft participants, we observed a statistically significant improvement in 5-year dfs associated with ≥10% md decline, hr=0.12 (95%ci: 0.04-0.37). similar findings were observed for overall dfs, hr=0.13 (95%ci: 0.05-0.35).

Conclusion:
Our analysis suggests that tamoxifen monotherapy that is associated with ≥10% decline in MD suggests improved disease-free survival for ER+ premenopausal breast cancer patients.

Title of Abstract:
Volpara automated volumetric breast density software decreases radiologist overestimation of breast density by the second year of implementation

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Purpose:
We evaluated discordant readings between Volpara automated volumetric breast density software and radiologist assessment of breast density, comparing the first year to second year of Volpara implementation as an adjunct to evaluating density in clinical mammography interpretation setting.

Method:
200 women (37-85 years), the first 100 in April 2013 and in April 2014, were included. Volpara (v1.4.3 and v1.4.4) measurements stored in PACS were retrospectively compared with radiologist assessment in the final report. Radiologists had access to Volpara measurements displayed on their workstations during image interpretation. Readings were from three expert breast imagers. Data was analyzed to evaluate discordant readings using the four ACR BI-RADS density categories and a binary system (nondense A/B versus dense C/D).

Results:
In both years, 40% of cases had discordant assessments. In 2013, in 67.5% of cases, radiologists rated the mammogram more dense than Volpara using a four-point scale $\chi 2$ (9, N=100) = 70.28, p<.001 and in 58% using a binary system $\chi 2$ (9, N=100) = 58.9, p<.001. In 2014, in 32.5% of cases, radiologists gave a more dense assessment than Volpara using a four-point scale $\chi 2$ (9, N = 100) = 58.7, p<.001 and in 21% of cases using a binary system $\chi 2$ (9, N = 100) = 52.41, p<.001. Adjusting for age, the odds of an attending reporting lower scores in 2014 compared with 2013 increased by 70% (4-point system) and by 32% (binary-system), however, these were not statistically significant (OR=1.7, 95% CI:0.68-4.05, p=0.262) and (OR=0.72, 95% CI:0.39-1.33, p=0.293).

Conclusion:
Having Volpara automated density assessment available to the radiologist during mammogram interpretation may help the radiologist not overestimate breast density. Although not statistically significant, it seems a learning curve was observed, in that by the second year of Volpara implementation, the radiologist seemed to report a dense pattern less often

Title of Abstract:
Mammographic density and histopathologic characteristics of screen-detected tumors in the Norwegian Breast Cancer Screening Program

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Purpose:
High mammographic density (MD) is known to mask tumors which might lead to missed cancers and delayed diagnosis. To better understand the concept of masking, we aimed to investigate the association between histopathologic tumor characteristics and MD among women screened in the Norwegian Breast Cancer Screening Program.

Method:
In this case-only study, 968 cases of ductal carcinoma in situ (DCIS) and 4,214 cases of invasive breast cancer diagnosed among subsequently screened women 1996-2010, aged 50-69 years, were included. MD was classified according to the percentage of fibroglandular tissue, MD-1: <30%, md-2: 30-70%, and md-3: >70%, by the radiologists who performed the work-up examination. Histopathologic characteristics included tumor morphology, size, grade and lymph node status. Chi-square tests were used to compare the distribution of tumor characteristics across the MD categories. Logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (95%CI) for the association between tumor characteristics and MD, adjusting for screening mode (screen-film and full-field digital mammography) and age.

Results:
Mean tumor size was 13.2 mm (95% CI: 12.8-13.6) for MD-1 and 16.6 mm (95% CI: 15.4-17.8) for MD-3. DCIS and invasive lobular carcinoma were more common in women with MD-3 compared with MD-1 (22.1% and 11.8% versus 17.3% and 6.5%), while invasive ductal carcinoma was more common in women with MD-1 compared with MD-3 (70.8% versus 63.6%) (p<0.001 for all morphologies). the proportion of lymph node positive tumors was higher among md-3 compared with md-1 (27.8% versus 19.5%, p=0.001). md-2 and 3 was associated with a higher likelihood of tumor size ≥15 mm (or 1.37, 95% ci: 1.17-1.61), using md-1 as the reference.

Conclusion:
MD was positively associated with tumor size. Further investigation including survival and mortality from breast cancer by MD might be conducted to evaluate long-term consequences of masking by MD.

Title of Abstract:
Physical growth in childhood and adolescence and breast composition in young adulthood: findings from an English birth cohort

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Purpose:
To investigate the influence of early life growth and maturation on breast tissue composition in young women in a British birth cohort.

Method:
A nested study was conducted within the Avon Longitudinal Study of Parents and Children (ALSPAC) – a population-based birth cohort of children born in 1991-2 in Avon, UK. Repeated anthropometric measurements were collected from birth, including biannual clinical growth and developmental measurements taken from ages 5 to 17 years. Between June 2011 and November 2014, 504 nulliparous participants had an MRI scan to measure breast, water and fat volumes. Participants also completed a questionnaire, height and weight was measured, blood samples taken, and their mothers' mammograms retrieved. MRI water fraction (equivalent to percent density in mammography) was categorised into quartiles; quartile-specific z-scores for height and BMI were calculated to allow comparisons across ages.

Results:
Preliminary analyses revealed a positive association between MRI water fraction and birth weight, which persisted after adjustment for BMI at the time of the MRI examination (P for linear trend (Pt)<0.001). mri water fraction was inversely associated with age-specific bmi from age 5 to 21/22 years (pt<0.001 at each age) and with attained height between ages 5 and 15 years (pt<0.05 at each age). consequently, young women in the highest mri water fraction quartile had the lowest age-specific mean bmi throughout childhood, adolescence and young adulthood, and the lowest age-specific mean attained height during childhood and adolescence, albeit not in young adulthood. mri water fraction was positively associated with age at menarche after accounting for bmi at the time of the mri examination (pt<0.001).

Conclusion:
Preliminary findings in this unique cohort, with repeated clinical measurements of body size and maturation from birth up to age 21/22 years, indicate that early measures of physical development are associated with breast tissue composition in young adulthood.

Title of Abstract:
Impact of Breast Density Information on Desire to Know Breast Density, Anxiety and Confusion, and Decisions Regarding Future Mammography and Supplemental Screening: Results of a National Survey

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Purpose:
To assess impact of breast density (BD) information on women's desire to know BD, anxiety and confusion, likelihood of pursuing future mammography and supplemental screening (SS), and support for BD legislation.

Method:
Survey of U.S. women (ages 40-74) using probability-based web panel; analyses weighted to be representative of U.S. age-specific female population. Multivariate analyses were performed to identify associated factors.

Results:
Of 2,311 women surveyed, 65% responded. Sixty percent would still want to know their BD (vs. 8% would not vs. 32% unsure) after being told that BD increases breast cancer risk and reduces detection and there is no consensus on SS. Knowing their BD would cause anxiety in 45%, confusion in 43%, and feeling informed in 90%. If "told that the chance of your mammogram finding a cancer if present was 50%," 49% reported being "very likely" to get future mammograms (vs. 32% "somewhat likely"; 19% "unlikely"). In multivariate analyses, factors associated with wanting to know BD were age < 50, higher income, having insurance, 5+ prior mammograms; with anxiety was less education; with confusion were less education and income; with feeling informed were age <50 and prior mammogram; with likelihood of future mammogram were age < 50, non-white race, recent healthcare visit, prior mammogram (all p<0.05). eleven percent would not pursue ss; 33% would pursue if no cost; 46% would pursue even if "small cost to me"; 11% "even if large cost." factors significantly associated with pursuing ss regardless of expense include age <50, 5+ prior mammograms, and having insurance (all p<0.05). seventy-six percent supported federal bd legislation.

Conclusion:
Although breast density information would cause anxiety and confusion in 45%, the majority of women would feel informed, would still pursue mammography, and support federal BD legislation. Young and insured women are more likely to pursue supplemental screening.

Title of Abstract:
Reasons for (non-)participation in the Dense tissue and Early breast Neoplasm ScrEening (DENSE) trial

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Purpose:
To determine reasons for (non-)participation in a trial where women with extremely dense breasts are offered MRI examination after negative screening mammography.

Method:
We asked reasons for participation or non-participation of women invited for a multicenter randomized controlled trial investigating the additional value of MRI to detect breast cancer in women aged 50-75 years with extremely dense breasts (DENSE trial). The study, carried out in the Dutch biennial population-based screening program, has a prerandomization design which means that only women randomized to the MRI group are being invited for the trial.
In case women stated multiple reasons for (non-)participation, all mentioned reasons were used for analyses.

Results:
In total 65% (n=4314) of the current 6625 invitees were interested to participate (23% not interested, 12% non-response). Ninety-five percent (n=4078) of them actually participated, resulting in an ultimate participation rate of 62%. Of the interested invitees, 1% was ineligible for MRI. Participants were 54 years (IQR:51-59) compared to 55 years (IQR:51-66) in the general screening program for women with extremely dense breasts.
Most frequently stated reasons for participation were expected personal health benefit (43%) and contribution to science (31%).
Reasons stated most frequently for non-participation were MRI-related inconveniences and/or self-reported contraindications for MRI (26%), including claustrophobia or refusing the necessary intravenous injection. The anxiety that the MRI examination would cause, such as ‘too high emotional burden’ and concerns about false-positives, was stated in 18% of the reported reasons.
Other reasons for non-participation were practical reasons (16%), including time constraints or required travel for participation and personal reasons (13%), such as health complaints.

Conclusion:
Of 6625 women invited for MRI examination because of extremely dense breasts, 62% actually participated. The most frequently reported reason for participation was expected personal health benefit, and for non-participation MRI-related inconveniences and/or self-reported contraindications for MRI.

Title of Abstract:
Volumetric Breast Densities Derived by Statistical Model Approach

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Purpose:
The purpose of this study is to validate volumetric breast densities derived by a statistical model approach using clinical case control data set. Potentially, the designed approach could provide automated breast density similar to single energy absorptiometry (SXA) without using SXA phantom.

Method:
Using the San Francisco Mammography Registry, we created two training sets and one case-control set. One training set (model 1) contained 2000 full field digital mammograms (FFDM) obtained during 2.5 years at one facility. Another training set (model 2) consisted of 7000 FFDMs collected at 4 facilities for 6 years. The case-control set consisted of 201 breast cancer cases and 384 controls obtained at 4 facilities during 2.5 years. The percent fibroglandular volume (%FGV) for all mammograms were calculated using the SXA phantom method. The stepwise linear regression was used to estimate the %FGV outcomes on the two tests sets and case-control set using statistical model approach. Odds ratios (OR) were estimated by conditional logistic regression for calculated SXA phantom %FGV, model estimated %FGV and Volpara density comparing lowest to highest quartile adjusted by family history and body mass index.

Results:
The stepwise regression of the predicted outcome %FGV demonstrated R-square around 0.8 and 0.7 for model 1 and model 2 training sets, respectively. We found that odds to predict breast cancer for the four %FGV measures were similar; OR □ 3.5, 3, 3.2 and 3.8 for estimated %FGV model 1, estimated %FGV model 2, SXA phantom %FGV, and Volpara %FGV, respectively. The ORs for estimated %FGV model 1 and estimated %FGV model 2 are found to vary in dependence of a number of features selected.

Conclusion:
An automated SXA %FGV has similar ability to predict cancer as a commercial method. Results need to be validated in a larger population

Title of Abstract:
Using visual and volumetric measures of mammographic density to identify women with high density breasts

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Purpose:
High mammographic density is associated with both an increased risk of developing breast cancer, and a decrease in sensitivity of mammography. This study investigates the agreement of visual assessment recorded on Visual Analogue Scales (VAS), Volpara and Quantra in identifying women at increased risk of cancer (highest 10% of density) and of masking (highest 30%).

Method:
33658 women without a previous diagnosis of breast cancer were identified from the Predicting Risk Of Cancer At Screening (PROCAS) study in Greater Manchester, UK. Age ranged from 46 to 73 with a median of 58. Mammographic density from routine screening mammograms was assessed for each woman using VAS (average of 2 observers), Quantra and Volpara percent density.

Results:
5396 (16.0%) women were identified in the top 10% of densities by any method, of which 1648 (30.5%) were in the top 10% by all three methods, 2281 (42.3%) by one method and 2528 (46.8%) by both volumetric methods. 15380 (45.7%) women were identified in the top 30% of densities by any method, of which 5933 (38.6%) were in the top 30% by all three methods, 5695 (37.0%) by one method and 8008 (52.1%) by both volumetric methods. Dichotomising Volpara Density Grades (VDGs) and Quantra Quantized Density (QQD) according to risk of masking (BI-RADS equivalent 1/2 versus 3/4) there was 85.8% agreement, however 8.6% of those scoring 3/4 using QQD scored 1/2 using VDGs and 5.6% vice versa. The correlation between Quantra and Volpara was higher for gland volumes (Spearman’s correlation 0.873, p<0.01) than for percent density (spearman’s correlation 0.762, p<0.01).

Conclusion:
For women at high risk of developing breast cancer on the basis of increased mammographic density, and those at high risk of masking, the method used to assess density may have a significant influence on whether their risk is identified.

Title of Abstract:
Birth weight, childhood BMI and height in relation to mammographic density and breast cancer: Danish Diet, Cancer and Cohort study

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Purpose:
We have earlier reported that childhood body fatness was inversely associated to the breast cancer risk, possibly via a mechanism mediated by MD. Here, we examine whether associations of childhood anthropometry with mammographic density (MD) and breast cancer are independent of adult anthropometry.

Method:
2,481 women from Danish Diet, Cancer and Health cohort (with measured weight and height at age of 50-65 years) who participated in the Copenhagen mammography screening program (1993-2001) and had childhood anthropometric measurements in the Copenhagen School Health Records Register were followed for breast cancer diagnoses until 2013 in the Cancer Registry. Using logistic and Cox regression models we investigated associations of birth weight, height and BMI at ages 7 and 13 with MD (mixed/dense or fatty) and breast cancer, respectively, with and without adjustment for adult BMI (age 50-65).

Results:
54.6% women had mixed/dense breasts and 131 (5.3%) developed breast cancer. Significant inverse association between BMI at age 13 and odds of having mixed/dense breasts (odds ratio; 95% confidence interval (CI): 0.55; 0.50-0.61, per unit increase in z-score), attenuated but persisted after adjustment for adult BMI (0.69; 0.62-0.78). No associations were detected between birth weight or height and MD. Inverse, statistically non-significant association of BMI at age 13 with breast cancer (hazard ratio; 95 % CI: 0.84; 0.68-1.05) persisted after adjusting for adult BMI (0.85; 0.67-1.08), and attenuated after adjusting for MD (0.96; 0.77-1.20). Positive, non-significant associations of birth weight (1.22; 0.82-1.84) and height at age 13 (1.13; 0.94-1.35) with breast cancer remained unchanged when adjusting for BMI and MD.

Conclusion:
Inverse associations of early life body fatness with MD and the breast cancer risk are not explained by adult body fatness. MD seems to explain, at least in part, inverse association between childhood BMI and breast cancer risk.

Title of Abstract:
Hormone replacement therapy, mammographic density, and breast cancer risk: a cohort study

Presenting Authors Full Name:
Zorana Jovanovic Andersen, PhD (my student Shadi Azam will present, if we get funding for her travel)

Institution:
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Purpose:
High mammographic density (MD) is a strong predictor of breast cancer (BC) risk. Hormone replacement therapy (HRT) is an established risk factor for BC, and shown to increase MD. The purpose of this study is to examine whether MD mediates an association of HRT with the risk of BC.

Method:
For the 4,501 participants in the Danish Diet, Cancer and Health cohort (1993-1997) who attended mammographic screening in Copenhagen (1993-2001), MD were assessed at the first screening after cohort entry. MD was defined as mixed/dense or fatty. Use, duration, and type of HRT and potential confounders were assessed by questionnaire at the cohort baseline. BC diagnoses were obtained from Danish Cancer registry, until 2012. The association between HRT and MD, and HRT and BC were analysed with logistic and Cox's regression models, respectively with adjustment for potential confounders.

Results:
2,444 (54.3%) women had mixed/dense breasts and 229 (5.4%) developed BC during follow-up. Majority of women (51.5%) were ever users of HRT, 35.9% were current users at baseline. Ever users of HRT had significantly higher odds of having mixed/dense breasts (OR and 95% confidence interval (CI): 1.59; 1.33-1.91) than never HRT users. Having mixed/dense MD was significantly positively associated with the BC risk (Hazard Ratio (HR) and 95% CI: 1.74; 1.29-2.34). Ever users of HRT had significantly higher risk of BC than non-users (HR; 95% CI: 1.56; 1.19-2.04), and after adjustment for MD associations attenuated (1.48; 1.29-2.34). The BC risk related to HRT was higher in women with mixed/dense (1.79; 1.19-2.68), than with fatty breasts (1.34; 0.68-2.61), although the difference was not was no statistically significant (p-value for interaction 0.32).

Conclusion:
Positive association between HRT and BC was not mediated by MD. The adverse effect of HRT on BC seemed to be limited to women with dense breasts.

Title of Abstract:
Association of Gail model breast cancer risk estimates and mammographic density in Asian women

Presenting Authors Full Name:
Soo-Hwang Teo

Institution:
Cancer Research Initiatives Foundation, Sime Darby Medical Centre, Malaysia

Additional Author's Names as to be Published:
Shivaani Mariapun, Nurhashimah Hassan, Jingmei Li, Nadia Rajaram, Cheng Har Yip, Soo-Hwang Teo

Purpose:
Studies in high-risk populations have reported no correlation between the Gail model breast cancer risk estimates, which is based on non-modifiable breast cancer risk factors, and mammographic density, a strong and modifiable breast cancer risk factor. We sought to investigate this association in our moderate risk population where the discriminatory accuracy of risk prediction models are yet to be validated.

Method:
A total of 1,238 unrelated, asymptomatic Malay (138), Indian (199) and Chinese (901) women who attended a subsidized opportunistic screening mammography programme were eligible for analysis. Mammographic density was estimated using a fully-automated thresholding method for digital processed mammogram images. Breast cancer risk estimates were calculated using the Gail model. The association of mammographic density with risk estimates was assessed using linear regression analysis.

Results:
Women in this cohort had a mean of 0.78% (SD 0.43) 10-year risk of breast cancer, with the risk highest in Chinese (0.82%) compared to Indian (0.73%) and Malays (0.57%). After adjusting for age, body mass index, parity, menopausal status and ethnicity, we found that percent density and dense areas were not significantly associated with breast cancer risk scores. However, non-dense area was significantly decreased by 4.66 cm2 (SE 1.95) for every 1% increase in 10 year breast cancer risk ($p = 0.017$). Notably, non-dense areas and not percent density nor dense area, were also associated with breast cancer risk in the Chinese only analysis.

Conclusion:
Consistent with results in Caucasian populations, we report that percent density and dense area are not strongly associated with breast cancer risk scores which are based on lifestyle and hormonal risk factors. Our results suggest that mammographic density may be an important variable that could be added to improve the accuracy and reliability of risk assessment in Asians. Further analyses of the predictive value of the Gail model and mammographic density measures are required in the Asian population.

Invasive Carcinoma (IDC and ILC), DCIS, Fibroepethelial lesions (Fibroadenoma, FEL with cellular stroma, and Phyllodes), Papillary lesions (Intraductal papilloma, Papilloma with atypia, and Papillary carcinoma), and other Benign breast disease (Proliferative disease without atypia, Sclerosing lesions, Atypia hyperplasia, LCIS, and PASH). Merge of QIA method and 3CB phenotypes significantly improved the area of the curve from QIA or 3CB alone. We are two and half year into this study and the preliminary result can be found in table…. (Jennifer's New Table, preliminary findings- accumulation chart for all 4 findings). However, this study has its own unique challenges including being involved with extra radiation, scheduling crises, excluding participants with any kind of prior procedures or history of cancer on the same breast, as well as obscure masses or no correlation mammography results. We are on track to finish our recruitment on March of 2017

Conclusion:
Combining knowledge of the biologic composition of breast lesion and their periphery (3CB technique) with existing mammographic QIA method significantly improved the distinction between benign and malignant lesion and could help prevent unnecessary biopsies and improve diagnostic decision making.

Afternoon Program - Breast Density and Biology and Genetics

Thursday, June 11, 2015

1:30 pm - 4:20 pm

Molecular Epidemiology and Biology of Mammographic Density in the BREAST Stamp Project

Gretchen L. Gierach
National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Background: Mammographic density (MD), which reflects fibroglandular tissue content of the breast, is a strong breast cancer risk factor. However, the determinants of MD and mechanisms by which it increases breast cancer risk are poorly understood. In a study of women undergoing diagnostic breast biopsy, we aimed to explore the relationships of circulating growth factors, underlying tissue morphology and breast pathology with area and volume MD, measured throughout the breast and surrounding biopsy targets (peri-lesional).

Methods: Women aged 40-65 years were clinically referred for an image-guided breast biopsy and enrolled into the BREAST Stamp Project (n=1019), a molecular epidemiologic study of MD undertaken at the University of Vermont College of Medicine and the University of Vermont Medical Center from 2007-2010. Area MD was measured in pre-biopsy digital mammograms using thresholding software; volumetric MD was assessed using a density phantom (i.e., single X-ray absorptiometry). Peri-lesional MD was measured in increasing volumes surrounding a suspicious lesion detected on mammography and/or sonography. Risk factor data and breast tissues were collected; a subset of participants opted to donate blood. Digitized images of tissue sections from the biopsy target block were used for analysis of terminal duct lobular unit (TDLU) involution. Serum IGF-I, IGFBP-3 and the IGF-I:IGFBP-3 molar ratios were measured by ELISA.

Results: Among women diagnosed with benign breast disease, biopsy findings consistent with less extensive TDLU involution were significantly associated with higher area and volumetric MD (overall and peri-lesional). Higher levels of circulating growth factors (IGF-I and the ratio of IGF-I to IGFBP-3) were also associated with reduced TDLU involution, and this relationship was restricted to women with elevated volumetric and area MD measures. Among all study participants, we have preliminarily found support for the hypothesis that peri-lesional MD is increased around some malignant lesions relative to that of the entire breast.

Conclusions: Findings suggest that MD reflects underlying histologic and morphologic changes characterized by TDLU involution and that MD may moderate the relationship between circulating growth factors and involution. Some associations were stronger for peri-lesional MD, suggesting that evaluating local variation in MD may lend insight into etiological factors that contribute to MD and breast cancer risk. We are expanding the analysis of breast biopsy tissues from BREAST Stamp participants with a focus on epithelial and stromal markers, telomere lengths, and markers of microvessel density that may mediate MD-associated cancer risk. These studies may provide information about the microenvironment surrounding malignant vs. non-malignant lesions and could have value for improving radiological assessments of risk or early detection of cancer and its precursors.

Tissue Stiffness Can Contribute to Invasive Carcinoma

Ovijit Chaudhuri[1-3], Sandeep Koshy[1,2,4], Cristiana Branco da Cunha[1,2], Jae-Won Shin[1,2], Catia S Verbeke[1,2], Kimberly H Allison[5], and David J Mooney[1,2].

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The microenvironment of breast tumors exhibits striking differences from that of normal breast tissue, often featuring enhanced extracellular matrix (ECM) stiffness and altered ECM composition. *In vitro* models of normal mammary epithelium have correlated increased extracellular matrix (ECM) stiffness with malignant phenotypes. However, the role of increased stiffness in this transformation remains unclear because of difficulties in controlling ECM stiffness, composition, and architecture independently for 3D cell culture.

Here we demonstrate the use of interpenetrating networks (IPNs) of reconstituted basement membrane matrix and alginate to modulate matrix stiffness independent of composition and architecture. Using these IPNs, we find that increased ECM stiffness induces the transition to a highly malignant phenotype in non-transformed mammary epithelial cells. This malignant phenotype is characterized by un-arrested growth, collective cell invasion and migration into the matrix, and enhanced PI3K activity. Interestingly, the phenotypes observed resemble well-differentiated ER+ invasive ductal carcinomas. However, increased stiffness does not necessitate malignancy, as the effect of enhanced stiffness is completely abrogated when accompanied by an increase in basement membrane ligands. The combination of stiffness and composition is sensed through β4 integrin, Rac1, and PI3K activation, but not through Rho, FAK, or MAPK activation, presenting a previously unreported mechanism of mechanotransduction. Experiments suggest a mechanism in which an increase in ECM stiffness, without an increase in basement membrane ligands, prevents normal α6β4 integrin clustering into hemidesmosomes, leading to activation of PI3K and Rac1 through the cytoplasmic tail of β4 integrin.

Our work highlights the importance of ECM cues in epithelial biology, and suggests that ECM composition and stiffness together play an important role in regulating breast cancer invasion and malignancy.

Title of Abstract: Genetic predictors of mammographic density: Implications for breast cancer risk

Presenting Authors Full Name: Rulla M.Tamimi

Institution: Brigham and Women's Hospital, Harvard Medical School, Harvard T.H. Chan School of Public Health

Purpose: Mammographic density is one of the strongest risk factors for breast cancer. The biologic mechanisms by which mammographic density increases breast cancer risk are unclear. In addition, mammographic density is highly heritable. Understanding genetic predictors of mammographic density may have important implications for breast cancer etiology.

Method: I will present results from the DENSNP and Markers of Density (MODE) consortia, both of which examine genetic variation in relation to mammographic density.

Results: As part of MODE, we recently conducted GWAS of three mammographic density phenotypes: dense area, non-dense area and percent density in up to 7,916 women in stage 1 and an additional 10,379 women in stage 2. We identified genome-wide significant ($P<5x10^{-8}$) loci for dense area (*AREG, ESR1, ZNF365, LSP1/TNNT3, IGF1, TMEM184B, SGSM3/MKL1*), non-dense area (*8p11.23*) and percent density (*PRDM6, 8p11.23, TMEM184B*). Four of these regions are known breast cancer susceptibility loci, and four additional regions were found to be associated with breast cancer ($P<0.05$) in a large meta-analysis.

Conclusion: Our work demonstrates proof-of-principle that identification of genetic components of complex diseases can be enhanced through concentration on heritable risk factors for the disease. A GWAS of highly heritable, quantitative traits such as mammographic density is a powerful approach to identifying genes involved in breast density and breast carcinogenesis.

Adolescence and Breast Density

Karin B. Michels

Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, Boston Massachusetts
Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts

Over the past couple of decades the quest for identifying novel risk factors breast cancer has shifted towards earlier periods of a woman's life. As we are beginning to understand breast cancer as a disease developing over the life course rather than as a result of genetic predisposition interacting with adult lifestyle factors, periods of heightened susceptibility of mammary tissue to carcinogenic influences are of particular interest. Clearly, the period of breast development and growth, ranging from the intrauterine formation of ducts and mammary architecture to the fully developed breast at Tanner stage 5, deserves in-depth scrutiny. Several perinatal and pubertal factors have been associated with the risk of developing breast cancer later in life. With mammographic density being the strongest known predictor of breast cancer incidence, breast density during puberty is likely associated with later life breast cancer risk. We have therefore assembled a puberty cohort including about 500 Chilean girls in Santiago, Chile, born in 2002. Perinatal factors were assessed retrospectively in 2006 and the girls have been followed prospectively since then with at least annual in-person visits. Lifestyle and dietary habits, anthropometric measures, and developmental milestones have been assessed regularly and biospecimens have been collected. We aim to evaluate the importance of diet, exposure to endocrine-disrupting chemicals, inflammatory markers, and epigenetic marks for pubertal development and breast density at Tanner stage 4 (B4) in this unique cohort.

In preliminary analysis, we evaluated the impact of early life factors on Tanner staging and breast density at B4. Among the 466 girls that have reached B4, we assessed whether maternal pre-pregnancy BMI, maternal height, maternal weight, gestational weight gain, maternal age, maternal smoking during pregnancy, birth weight, or birth length were associated with the time to B4 onset. None of these characteristics were associated with B4 onset in either unadjusted or multivariable models adjusting for maternal age and smoking. In a subset of approximately 200 girls, we assessed whether these variables were associated with breast density, volume, or absolute fibroglandular volume (FGV) at B4, which were measured by breast DXA. A 1 kg/m^2 increase in maternal pre-pregnancy BMI was associated with 0.33% (95% CI: 0.02%, 0.64%) increase in breast density, adjusting for maternal age, smoking, and the girl's age at DXA and the girl's BMI. No other associations reached statistical significance. While not associated with the onset of B4 or breast density, we found that an 1 kg increase in birthweight was associated with a 2% faster time to menarche (AFT: 0.98 [95% CI: 0.98, 0.99]). A higher breast density and absolute FGV were found to accelerate the time to menarche. Our results suggest that variation in breast density associated with pre-pregnancy BMI is independent from the variation in density that is predictive of time to menarche. However, these findings are restricted to the girls that are more quickly progressing through puberty and should be interpreted prudently.

Abstract Proffered Talks

Thursday, June 11, 2015

4:20 pm - 4:50 pm

Title of Abstract:
Mammographic density and breast cancer intrinsic subtypes

Presenting Authors Full Name:
Laurel Habel, PhD

Institution:
Division of Research, Kaiser Permanente

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Purpose:
We examined the association between percent density (PD) and dense area (DA) and breast cancer intrinsic subtypes, as classified by the PAM50 assay. We also examined PD and expression levels of each of the individual genes within the PAM50 panel and the association of PD and tumor characteristics.

Method:
This case-cohort study included 881 breast cancer survivors from the Life After Cancer Epidemiology (LACE) and Pathways cohorts. The subcohort included a random sample of ER+/HER2- patients and all patients who were ER-, HER2+ or triple negative (by immunohistochemistry). Expression of the PAM50 genes was determined by RT-PCR. Analog mammograms taken at breast cancer diagnosis were digitized and density was measured using Cumulus. Linear regression modeling was used to examine differences in PD and DA across intrinsic subtypes and the association between PD and expression of individual genes and tumor characteristics, after adjustment for age, BMI and race/ethnicity.

Results:
Mean age at breast cancer diagnosis was 59.7 years. Participants were 76% non-Hispanic white, 5% African-American, 9% Hispanic, 8% Asian and 3% other race/ethnicity. There were 200 patients with Luminal-A tumors, 117 with Luminal-B tumors, 141 with Basal-like tumors and 164 with HER2 over-expressing (HER2-E) tumors. Although not statistically significantly different, PD and DA were highest for Luminal-A, then Luminal-B, then HER2-E and then Basal-like subtype. Higher PD was associated with higher gene expression for 23 of 50 genes – only one of these, FOXA1, was statistically significant. PD was highest for poorly differentiated tumors, and for those with 5+ vs 0 positive lymph nodes, although again differences were not statistically significant.

Conclusion:
Although PD differed across subtype and by tumor characteristics, differences were not statistically significant. We found only modest support for an association between PD and expression level of any of the genes included in the PAM50 panel.

Title of Abstract:
Functional Assessment of Breast Fibroglandular Tissue: Correlations Between MBI and MRI

Presenting Authors Full Name:
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Institution:
Mayo Clinic, Rochester, MN

Additional Author's Names as to be Published:
Katie Jones, MD; Kathleen Brandt, MD; Rickey Carter, PhD; Celine Vachon, PhD; all Mayo Clinic, Rochester, MN

Purpose:
Breast MRI depicts both the anatomy of normal fibroglandular tissue, similar to mammographic density, and its functional behavior through gadolinium-based contrast. This “background parenchymal enhancement” (BPE) has been shown associated with breast cancer risk, even after accounting for MR-depicted fibroglandular tissue. On molecular breast imaging (MBI), we have observed variation in functional uptake of Tc-99m sestamibi within normal fibroglandular tissue, termed “background parenchymal uptake” (BPU). Our objective was to assess correlation between BPU on MBI and BPE on MRI.

Method:
We reviewed examinations from all women who had MRI performed within +/-3 days of MBI over the years 2006-2013, excluding those with breast implants. One radiologist read the MBIs and assessed BPU per-breast as photopenic, minimal-mild, moderate, or marked according to a validated MBI lexicon. Another radiologist read the MRIs and assessed BPE per-breast on early post-contrast MR images as none-minimal, mild, moderate, or marked according to the BI-RADS MRI lexicon. Correlation in BPU and BPE assessments was examined by Spearman’s rank correlation coefficient (rs).

Results:
In 208 breasts (106 women), the 4-category BPU and BPE assessments were moderately positively correlated (rs = 0.57; P<0.0001). high bpe (moderate or marked) was observed in 65 breasts, of which 41 (63%) also had high bpu (moderate or marked). low bpe (none or minimal or mild) was observed in the other 143 breasts, of which 133 (93%) also had low bpu (photopenic or minimal-mild). overall, bpu and bpe were similar (high vs. low) in 84% of breasts examined (174/208), but discordant in 16% (34/208). when excluding 37 women with current breast cancer, results were unchanged.

Conclusion:
BPU on MBI and BPE on MRI are moderately correlated functional phenotypes, suggesting similar underlying physiology of the fibroglandular breast tissue. Future work will determine whether BPU has similar association with breast cancer as BPE.

Risk Modeling – Putting it All Together I

Friday, June 12, 2015

8:30 am - 10:15 am

Title of Abstract: Mammographic Density Pooling Project – Insights from an International Perspective

Presenting Authors Full Name: Valerie McCormack

Institution: Section of Environment and Radiation, International Agency for Research on Cancer, France

Additional Author's Names as to be Published: Anya Burton, Norman Boyd, Isabel dos Santos Silva, on behalf of the International Pooling Project of Mammographic Density

Purpose: To examine mammographic density (MD) and its determinants from an international perspective, in population groups from countries spanning low to high breast cancer incidence rates

Method: We contacted principle investigators of previously conducted studies of MD worldwide. Where possible, each study contributed comparable data on MD risk factors and mammographic images from a random sample of ~400 general population women, who had undergone screening mammography. Anonymized images, in digitized screen-film, full-field or computed radiography digital DICOM format (raw or processed), were read using the Cumulus 6 thresholding software, by 3 experienced readers who were blinded to study and individual-level factors. Percent MD (PMD) and dense areas were adjusted for reader and image type.

Results: 12,000 women were included, from 29 studies conducted in 22 countries. They represent 40 country, setting (time/place) and ethnicity-specific “population groups”. MD risk factors varied greatly across these populations, for example: mean age at menarche (in years) was 14.3 (95% CI 14.1-14.5) in Korean women and 12.6 (12.5-12.8) in Mexican women; mean parity was 3.8 (3.6-4.1) in Egyptian women and 1.3 (1.1-1.4) in those from Hong Kong; and mean BMI (in kg/m2) was 33.7 (33.1-34.3) in Egyptian women compared to 22.3 (21.6-22.9) in those from India. After adjusting for age and BMI, we found over 2-fold differences in age and BMI-adjusted mean PMD and mean dense area between populations groups.

Conclusion: The international perspective of this study has generated large risk factor and MD heterogeneity enabling a more extensive investigation of MD determinants, both within and between populations.

Title of Abstract:

Benign Breast Disease, Mammographic Breast Density and Breast Cancer Risk

Presenting Authors Full Name:

Jeffrey A. Tice, MD

Institution:

University of California San Francisco

Additional Author's Names as to be Published:

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Chin-Shang Li, PhD
Celine M.Vachon, PhD
Charlotte C. Gard, PhD
Karla Kerlikowske, MD

Purpose:

Women with proliferative breast lesions are candidates for primary prevention, but few risk models incorporate benign findings to assess breast cancer risk. We incorporated benign breast disease (BBD) diagnoses into the Breast Cancer Surveillance Consortium (BCSC) risk model, which is based on BI-RADS breast density.

Methods:

We developed and validated a competing-risk model using 2000-2010 Surveillance, Epidemiology and End Results for breast cancer incidence and 2010 vital statistics to adjust for the competing risk of death. We used Cox proportional hazards regression to estimate the relative hazards for age, race/ethnicity, family history of breast cancer, history of breast biopsy, BBD diagnoses, and breast density in the BCSC.

Results:

We included 1,135,977 women aged 35-74 years undergoing mammography with no history of breast cancer; 17% of the women had a prior breast biopsy. During a mean 6.9

years of follow-up, 17,908 women were diagnosed with invasive breast cancer. The BCSC BBD Model slightly over-predicted risk (expected to observed ratio 1.04, 95% CI 1.03-1.06) and had modest discriminatory accuracy (area under the receiver operator characteristic curve = 0.665). Among women with proliferative findings, adding BBD to the model increased the proportion of women with an estimated 5-year risk of 3% or higher from 9.3% to 27.8% ($p<0.0001$).

Conclusion:

The BCSC BBD Model accurately estimates women's risk for breast cancer using breast density and BBD diagnoses. Greater numbers of high-risk women eligible for primary prevention following BBD diagnosis are identified using the BCSC BBD model.

Adding mammographic density to the Tyrer-Cuzick (IBIS) model

Jack Cuzick and Adam Brentnall

Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, Charterhouse Square, EC1M 6BQ London, UK

There are a number of models currently available to assess the risk of breast cancer using classical risk factors. Of them the Tyrer-Cuzick model, which was originally developed to assess risk for women going through IBIS breast cancer prevention trials, is one of the more widely used and accurate models. The current version does not include breast density, and work is undergoing to do this. A major challenge is that breast density was originally assessed on film images and most risk estimates are based on that measure. Most mammograms are now digital and newer methods have been developed for that including volumetric measure such as the automated Volpara measure. However none of these have the clear predictive value and the original visual assessment. We briefly review these measures and discuss how they should be added to risk models using other well established factors. Longitudinal results from the IBIS-I trial in high risk women, and cross-section data from the PROCAS screening cohort will be presented.

Abstract Proffered Talks

Friday, June 12, 2015

11:45 am - 12:15 pm

Cost-Effectiveness and Harm-Benefit Analyses of Risk-Based Screening Strategies for Breast Cancer

Ester Vilaprinyo
Universitat de Lleida

The one-size-fits-all paradigm in organized screening of breast cancer is shifting towards a personalized approach. The present study has two objectives: 1) To perform an economic evaluation and to assess the harm-benefit ratios of screening strategies that vary in their intensity and interval ages based on breast cancer risk; and 2) To estimate the gain in terms of cost and harm reductions using risk-based screening with respect to the usual practice. We used a probabilistic model and input data from Spanish population registries and screening programs, as well as from clinical studies, to estimate the benefit, harm, and costs over time of 2,624 screening strategies, uniform or risk-based. We defined four risk groups, low, moderate-low, moderate-high and high, based on breast density, family history of breast cancer and personal history of breast biopsy. The risk-based strategies were obtained combining the exam periodicity (annual, biennial, triennial and quinquennial), the starting ages (40, 45 and 50 years) and the ending ages (69 and 74 years) in the four risk groups. Incremental cost-effectiveness and harm-benefit ratios were used to select the optimal strategies. Compared to risk-based strategies, the uniform ones result in a much lower benefit for a specific cost. Reductions close to 10% in costs and higher than 20% in false-positive results and overdiagnosed cases were obtained for risk-based strategies. Optimal screening is characterized by quinquennial or triennial periodicities for the low or moderate risk-groups and annual periodicity for the high-risk group. Risk-based strategies can reduce harm and costs. It is necessary to develop accurate measures of individual risk and to work on how to implement risk-based screening strategies

Title of Abstract:
Quantifying the net benefit of mammography screening based on risk, breast density, screening interval, and age

Presenting Authors Full Name: Anna N. A. Tosteson, ScD
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Additional Author's Names as to be Published: Amy Trentham-Dietz, Natasha Stout, Jeroen van den Broek, Clyde Schecter, Mehmet Ali Ergun, Oguzhan Alagoz, Brian Sprague, Ronald Gangnon, Aimee Near, Nicolien van Ravesteyn, Harry de Koning, Diana Miglioretti, Jeanne Mandelblatt, Karla Kerlikowske

Purpose: To evaluate the net benefits and cost-effectiveness of annual, biennial or triennial mammography screening intervals for women at ages 50 and 65 years within subgroups defined by risk level and breast density.

Method: Three calibrated simulation models were used to compare harms and benefits of alternative screening frequency scenarios (annual, biennial and triennial) among the 16 joint combinations of risk due to breast density (BI-RADS a, b, c, d) and other risk factors considered collectively (RR=1, 1.3, 2, 4).Outcomes included breast cancer deaths, quality-adjusted life-years (QALYs) gained, false-positive screens, and costs. Within each of the 16 subgroups, incremental cost-effectiveness ratios (ICER = change in cost/change in QALY) were estimated for scenarios ranked by increasing cost by each model. Comparisons of benefits and harms of triennial and annual screening were framed relative to those observed for biennial screening.

Results: ICERs within risk and density groups varied by model, but were highest for annual screening scenarios, which exceeded the commonly accepted $100,000 per QALY gained cost-effectiveness benchmark for all but the highest risk and density groups. Triennial screening was a cost-effective alternative for 2 of the 3 models for low density and risk. In contrast, biennial screening fell on the efficient frontier for all models. As screening frequency increased, deaths averted increased with risk levels and with increasing density. False-positives tended to decline with increasing risk without marked changes across density.

Conclusion: Model results provide support for risk and density-tailored screening. Quantifying the tradeoffs in harms and benefits when women either increase or decrease screening frequency from biennial schedules according to density and risk may help inform risk and density-tailored decision making for women and their healthcare providers.

Abstract Proffered Talks

Friday, June 12, 2015

11:45 am - 12:15 pm

Title of Abstract:
Combined Effect of Dense and Nondense Breast Volume on Breast Cancer Risk

Presenting Authors Full Name:
Johanna Wanders, MSc

Institution:
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Purpose:
The effect of nondense (fat) area on breast cancer risk was found to be not consistent across studies. Using a fully automatic volumetric breast density method we investigated the independent effects of dense and nondense volume and their combined effect in relation to breast cancer risk.

Method:
Dense and nondense volumes were assessed automatically with Volpara version 1.5.0 (Matakina, New Zealand) on the first available FFDM mammogram of 43,211 women (50-75 years) participating in the Dutch biennial breast cancer screening program (2003-2009). Breast cancer information was obtained from the screening registration system and through linkage with the Netherlands Cancer Registry. The independent effect of nondense volume and the combined effect of dense and nondense volume on breast cancer risk was determined using logistic regression analyses. Besides age, no other confounders were available in this routine screening database.

Results:
After a median follow-up of 2 years, 596 breast cancers were identified. After adjustment for age and dense volume, a large amount of nondense volume was associated with lower breast cancer risk. (quartile 4 versus quartile 1: OR: 0.66, 95% CI: 0.52-0.85). Women with the highest amount (tertile 3) of dense volume together with the lowest amount (tertile 1) of nondense volume showed the highest breast cancer risk, after adjustment for age. Compared to those in tertile 1 (T1) of both dense and nondense volume, those in T3 of dense and T1 of nondense volume showed an OR of 1.90 (95% CI: 1.35-2.67) and those in T3-dense and T3-nondense showed an OR of 1.28 (95% CI: 0.98-1.67). Those in T1-dense and T3-nondense showed the lowest risk (OR: 0.25, 95% CI: 0.08-0.80). The p-value for interaction was not statistically significant.

Conclusion:
In this largely postmenopausal population, dense and fatty volume are independently associated with breast cancer risk, in opposite directions.

Title of Abstract:
Mammographic Density and Breast Cancer Risk: A Mediation Analysis

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Purpose:
Purpose: To quantify the extent to which the associations between established risk factors and breast cancer (BC) risk is mediated by mammographic density (MD).

Method:
Methods: Our study population included 2062 BC cases and 4196 controls from the Nurses' Health Study (NHS)/NHSII nested case-control studies. We used statistical methods described by VanderWeele and Vansteelandt (2010) to estimate the odds ratios (OR) for the natural direct effects as well as the ORs for the natural indirect effects of the selected factors on BC risk as well as to estimate the proportion mediated (PM) by percent MD.

Results:
Results: For the associations that were mediated by percent MD, the PMs ranged from 1.3-99% in premenopausal and from 1.5-30% in postmenopausal women. In both pre- and postmenopausal women, the association between history of benign breast disease and BC risk was partially mediated by percent MD (PM=31% and 30%, respectively). In premenopausal women, the associations between early life body size (childhood somatotype, adolescent somatotype, and BMI at age 18) and BC risk were substantially mediated by percent MD (PM=71-99%). However, in postmenopausal women, the proportion of the associations for childhood somatotype and adolescent somatotype that were mediated by percent MD were substantially lower (PM=21-22%).

Conclusion:
Conclusion: Percent MD partially mediated some of the associations between risk factors and BC risk, though the magnitude varied by risk factor and menopausal status.

POSTER SESSION 2

Friday, June 12, 2015

12:15 pm – 1:45 pm

	Submission Title	Submitter Name
1	Effects of the peripheral part of the breast and finding the accurate reference spot on Volumetric Breast Density Assessment in raw Full Field Digital Mammography images	Amir Mahmoudzadeh
3	Bioimpedance to Assess Breast Density as a Risk Factor for Breast Cancer in Adult Women and Adolescent Girls	Gertraud Maskarinec
5	Joint modeling of longitudinal breast density and breast cancer risk	Carles Forne
7	Associations between Automated Breast Density Measures and Body Mass Index in a Large Cohort of Women Undergoing Screening with Digital Mammography	Despina Kontos
9	A Novel Automated Method to Estimate Breast Density in Digital Mammography: Associations with Breast Cancer Risk	Luis de Sisternes
11	Mammographic density fluctuations associated with interval breast cancer	Fredrik Strand
13	Association of breast cancer risk with background parenchymal uptake (BPU) at molecular breast imaging	Carrie Hruska
15	Effect of volumetric mammographic density on performance of a breast cancer screening program using full-field digital mammography	Johanna Wanders
17	Volumetric Breast Density of Japanese Women Using Adaptive Pattern Recognition-Based Calibrations	Jeff Wang
19	Circulating sex hormones and mammographic density in premenopausal women	Kimberly Bertrand
21	Case-control study of mammographic density and breast cancer risk using processed Hologic full-field digital mammograms	Laurel Habel
23	Combination of age/body mass index (BMI)-adjusted scores of percent density (PD) and dense area (DA) for assessing breast cancer risk	Jong Won Lee
25	Mammographic structure of dense tissue and its association to cancer detection and risk in the Copenhagen screening program	Mads Nielsen
27	Assessing impact of Volpara automated volumetric breast density software on radiologist evaluation of breast density in the clinical mammogram interpretation setting	Miriam David
29	Evidence of Bimodality in UST Breast Sound Speed Images	Mark Sak
31	Long-term ambient particulate matter exposure and mammographic density	Natalie DuPre
33	A descriptive analysis of mammographic breast density in patients with a history of breast malignancy in Iran	Reza Sirous
35	Predicted five-year Gail breast cancer risk in women with extremely dense breasts	Marje F. Bakker
37	Comparing mammographic density measures between an automated volumetric method and an area-based method in relation to circulating sex hormones and urinary estrogens in postmenopausal women	Hamed Samavat
39	Mammographic density and breast cancer: a case-control study	Susan Astley
41	Methods to improve the reproducibility of breast density measurements on processed digital mammograms using an operator-assisted program	Weiva Sieh
43	Diabetes, diabetes treatment and mammographic density in Danish Diet, Cancer, and Health cohort	Zorana Andersen
45	Long-term exposure to air pollution and mammographic density in the Danish Diet, Cancer and Health cohort	Zorana Andersen

Title of Abstract:
Further Improvement of Single X-ray absorptiometry Approach called Version 9.0 to Assess Volumetric Breast Density in raw Full Field Digital Mammography images

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Purpose:
Volumetric breast density (VBD) is one of the significant breast cancer risk factors, but the technique that most accurately measures the quantity of breast fibroglandular tissue is not known. Single X-ray absorptiometry (SXA) has been developed over 15 years and the previous versions of SXA (version 6.5, version 7.1 and Version 8.0) have been frequently referenced in many journals [1-3]. In version 6.5, the grayscale values for the pixels in the breast image were calibrated by comparing with the grayscale values in the SXA phantom with a known fibroglandular volume (FGV) composition and thickness. The difference between version 6.5 and 7 is the stability of SXA measures over time, in version 7, calibration images were taken on each machine and serial scans of a quality control phantom were acquired every week to provide absolute breast tissue composition accuracy in clinical conditions for the long term [4]. In version 8, we developed 52 image texture features into our breast density analysis program. SXA is now in its 9th developmental stage and we found the removal of the peripheral part of the breast and finding the good reference spot has direct effects on VBD assessment. SXA version9.0 takes into account these two entities. We evaluated percent volumetric breast density and dense volume, using volumetric approaches (SXA (version8.0 and version9.0) and Volpara (Version 2.0.3)) previously validated as predictive of breast cancer risk.

Method:
We prospectively acquired the mammograms as part of the Breast Cancer Surveillance Consortium, a collection of mammograms, serum, and breast health questions collected by the San Francisco Mammography Registry and Vermont Breast Cancer Surveillance System from 2009-2013. Only CC-view images were analyzed for this study. Two fully-automated volumetric methods (Volpara and SXA) were assessed in 585 FFDM images from 201 cases and 384 controls, ages 33-91 and body mass index (BMI) 14.6-54.9 kg/m2. Women were primarily Caucaisan (72%) or Asian (20%) or Black (2%) or other (6%). Conditional logistic regression was used to assess density-breast cancer risk associations, adjusted for family history, biopsy history, and body mass index.

Results:
VBD in two methods was positively associated with breast cancer risk. Women in the top VBD quartile had odds ratios (OR) 2.1 (95% CI: 1.2- 3.5), 2.6 (95% CI: 1.5- 4.5), 2.5 (95% CI: 1.4- 4.4) times the risk of those in the bottom one, respectively, for SXA version 8.0, SXA version 9.0 and Volpara. The SXA Version 9.0 method had a slightly higher ability to discriminate between

Title of Abstract:
Bioimpedance to Assess Breast Density as a Risk Factor for Breast Cancer in Adult Women and Adolescent Girls

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Purpose:
Although high mammographic density is one of the strongest predictors of breast cancer risk, due to the relatively high radiation dose, mammography cannot be performed before the recommended screening age. Development of non-radiation methods is desirable to measure breast density in young women and girls as a predictor of future breast cancer risk.

Method:
This study in Guam and Hawaii evaluated a radiation-free, bioimpedance device called Electrical Breast Densitometer™ (EBD) by SenoSENSE Medical Systems Inc., Ontario, Canada, in 95 women aged 31-82 years and 41 girls aged 8-18 years who answered a brief questionnaire and completed anthropometric and EBD measurements. In girls, Tanner stages of breast development were also clinically assessed. Percent density (PD) was estimated in the women's most recent mammograms using a computer-assisted method (Cumulus). Correlation coefficients and linear regression were applied for statistical analysis.

Results:
Based on self-declared primary ethnicity, the study population was 30% Asian, 46% Native Hawaiian/Chamorro/Pacific Islander, 19% white, and 5% others. In adult women, mean EBD and PD values of the left and right breasts were 230±52 and 226±50 Ω and 23.7±15.1 and 24.2±15.2%, respectively. The EBD measurements were inversely correlated with PD (rs=-0.52, p<0.0001); the correlation was stronger in whites (rs=-0.70, p<0.0001) than asians (rs=-0.54, p<0.01) and native hawaiian/chamorro/pacific islanders (rs=-0.34, p=0.06). using 4 categories of increasing pd (<10, 10-25, 26-50, 51-75%), the respective mean ebd values were 256±32, 249±41, 202±46, and 178±43 Ω (p<0.0001). among girls, the mean ebd values in the left and right breast were 148±40 and 155±54 Ω; ebd values decreased from tanner stages 1 to 4 (204±14, 154±79, 136±43, and 119±16 Ω for stages 1-4, respectively) but were higher at stage 5 (165±30 Ω).

Conclusion:
With further development, this bioimpedance method may allow for assessment of breast cancer risk early in life and in populations without access to mammography.

Title of Abstract:
Joint modeling of longitudinal breast density and breast cancer risk

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Purpose:
Several studies have shown that breast density (BD) is one of the strongest predictors of breast cancer (BC). A few studies have assessed the association between longitudinal changes of BD and BC diagnosis. Our goal is to describe the longitudinal trajectories of BD in women attending a screening program and obtain risk profiles based on density level and longitudinal profile.

Method:
This is an observational prospective study including 13,760 women that participated for the first time in the BC early-detection program in the Vallès Occidental Est (BCEDP-VOE) area in Catalonia (Spain), between October 1995 and June 1998, and followed for vital status or possible diagnosis of BC until December 2013. The BCEDP-VOE invites women aged 50-69 years with no personal history of BC for a biennial mammographic exam. Of the initial cohort, 458 were diagnosed with BC. BD was prospectively collected at each mammography examination according to the BI-RADS ordinal scale with categories 1 (entirely fatty) to 4 (extremely dense).
Our joint model consists of two processes: (1) a cumulative logit model for the longitudinal ordinal measures of BD based on the idea of a continuous latent variable, and (2) a left-truncated Cox proportional-hazards model for the time to diagnosis of BC, which incorporates information from the longitudinal process. Inferences were obtained under the Bayesian approach using Markov Chain Monte Carlo methods.

Results:
Preliminary results show: (1) a population-based reduction of BD over time, (2) a higher BD at baseline is positively associated with an increased BC risk, and (3) trends in BD over time seem to be associated with BC risk.

Conclusion:
Our results are consistent with those showing association between BD trajectories over time and BC risk. Adding BD longitudinal profile to the current risk models could provide more accurate individual risk estimates and facilitate personalized screening.

Title of Abstract:
Associations between Automated Breast Density Measures and Body Mass Index in a Large Cohort of Women Undergoing Screening with Digital Mammography

Presenting Authors Full Name:
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Purpose:
We investigate the association between automated measures of area and volumetric breast density and body mass index (BMI) in a large cohort of women screened with digital mammography. Understanding the association between these risk factors could help understand their joint role in breast cancer risk assessment.

Method:
We retrospectively analyzed digital mammograms from 10,537 women (age 56.9y±11.0y) who had BMI and raw (‘For Processing’) digital mammograms available from a total of 11,141 consecutive women screened for breast cancer over the course of one year at our institution (2012-2013). A previously-validated and publicly available fully-automated algorithm developed at our institution (LIBRA) was used to generate per-woman estimates of absolute dense area and percent density (PD%). Volumetric estimates of absolute and percent dense tissue (VD%) were obtained using FDA-cleared software (Quantra™, Hologic, Inc). The Pearson correlation (r) and linear regression was used to assess associations between the breast density measures and BMI, after also adjusting for age and race.

Results:
BMI has a moderate negative association with PD% (r=-0.53, p<0.001) and vd% (r=-0.31, p<0.001), a weak association with absolute dense area (r=-0.11, p<0.001), and a moderate positive association with absolute dense tissue volume (r=0.46, p<0.001). after adjusting for age and race, the strongest associations remained between bmi and pd% (r-squared=0.34; p <0.001); and between bmi and absolute dense tissue volume (r-squared=0.25; p<0.001).

Conclusion:
Breast density is significantly associated with BMI. However, only up to 34% of the observed variation in PD% can be attributed to BMI, age, and race. Given the negative association between PD% and BMI, yet their established positive associations with risk, failure to consider both BMI and PD% could lead to an underestimation of the risk for breast cancer. Further investigation is warranted to understand the implications of BMI for risk assessment using volumetric density measures.

Title of Abstract:
A Novel Automated Method to Estimate Breast Density in Digital Mammography: Associations with Breast Cancer Risk

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Purpose:
We present a novel, fully automated method (PXA) to estimate dense volume and dense-to-adipose tissue ratio directly on digital mammograms. We evaluated its ability to predict breast cancer risk compared with Cumulus and Volpara density measures.

Method:
Our PXA method relies on multiple-energy X-ray absorptiometry, nonlinear programming and image processing techniques to estimate dense and adipose volume on a pixel-by-pixel basis, yielding absolute dense volume (DV) and volumetric percent density (VPD) measurements. We processed mammograms from healthy breasts of 130 women subsequently diagnosed with cancer in the contralateral breast (cases) and 239 age- and race-matched control women. We computed DV and VPD using PXA and Volpara, and dense area (DA) and percent dense area (PD) using Cumulus. We compared the odds-ratios (ORs) for breast cancer associated with each technique, adjusting for age, race, body-mass index, and menopausal status. We also computed the area under the receiver operating characteristic curves (AUC) for discriminating between cases and controls.

Results:
Our PXA measurements showed the strongest association with breast cancer risk: OR of 1.51 (1.18, 1.94) for each PXA-VPD SD increment (compared to 1.25 (0.94, 1.67) and 1.39 (1.04, 1.86) for Volpara-VPD and Cumulus-PD, respectively), and OR of 2.90 (1.33, 6.34) for the highest vs. lowest PXA-DV quartiles (compared to 1.40 (0,68, 2.89) and 2.40 (1.04, 5.56) for Volpara-DV and Cumulus-DA, respectively). PXA-VPD measurements also showed a slightly greater ability to discriminate between cases and controls than any of the other methods evaluated, with AUC = 0.63 (0.57, 0.69).

Conclusion:
Our breast density estimation method yielded stronger associations with breast cancer risk than two current quantitative techniques, and it may be a superior automated alternative when raw FFDM images are available for analysis. Its estimations might be useful to stratify women according to breast cancer risk and enable tailored screening and management.

Title of Abstract:
Mammographic density fluctuations associated with interval breast cancer

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Purpose:
Since it is known that interval breast cancer has a worse prognosis than screen-detected cancer it is important to identify risk factors for interval cancer. Mammographic density measured on a single occasion is one such risk factor. In this study, we investigate whether the magnitude of the fluctuations around the long-term trend in mammographic density may be an additional risk factor for interval cancer.

Method:
Using an automated method for mammographic density estimation, we analyzed all available pre-diagnostic mammograms for postmenopausal breast cancer cases in two independent Swedish cohorts. We used mixed effects modeling to separate the slope of the long-term trend from the fluctuations around that trend. We analyzed a potential association between the fluctuations and interval vs. screen-detected breast cancer using logistic regression. Potential associations between the fluctuations and tumor characteristics were also examined.

Results:
We found that large fluctuations in mammographic density were significantly associated with interval cancer (vs. screen-detected cancer) with an odds ratio of 1.18 per standard deviation in one cohort ($p=0.026$) and 1.15 in the other ($p=0.017$), after adjustments for percent density at last pre-diagnostic mammography, the long-term change in mammographic density, age at diagnosis, BMI and hormone replacement therapy. We found that the higher fluctuations were associated with an increased proportion of ER negative tumors in one of the cohorts.

Conclusion:
We identified fluctuations in percent density as a novel risk factor for postmenopausal interval vs. screen-detected breast cancer.

Title of Abstract:
Association of breast cancer risk with background parenchymal uptake (BPU) at molecular breast imaging

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Purpose:
In prior evaluations of molecular breast imaging (MBI) for supplemental screening in dense breasts, we observed wide variability in background parenchymal uptake (BPU), which refers to the relative uptake of Tc-99m sestamibi within normal fibroglandular tissue compared to fat. In women with similar mammographic density, BPU varied from photopenic (fibroglandular uptake less intense than fat uptake) to marked (fibroglandular uptake >2 times as intense as fat uptake). Here, we investigated whether BPU is associated with subsequent breast cancer development.

Method:
We conducted a nested case-control study among women with MBI examinations performed at Mayo Clinic between 2005-2014. Women with breast cancer history or diagnosis within 60 days after MBI were excluded. A total of 77 incident breast cancer cases were identified through linkage with the Mayo Clinic tumor registry; 225 controls were matched to cases on age, MBI date, menopausal status, and follow-up. While blinded to case-control status, BPU was assessed by an expert reader according to a validated MBI lexicon into one of 4 categories: photopenic, minimal-mild, moderate, or marked. Conditional logistic analysis was performed.

Results:
Women with high BPU at MBI (moderate or marked) had a greater risk of breast cancer compared to women with low BPU (photopenic or minimal-mild); odds ratio (OR (95% CI), 5.5 (2.6,11.6)). Results were unchanged with adjustment for BI-RADS density (OR=5.5 (2.6, 11.6) and BMI (OR, 5.4 (2.6, 11.4)). The association of BPU and breast cancer was stronger for cases diagnosed <3 years (or=10.6) compared to cases diagnosed ≥3 years (or=4.2), although power was limited.

Conclusion:
BPU provides a functional assessment of fibroglandular tissue that is associated with breast cancer risk. For women with dense breasts, who are now increasingly undergoing low-radiation-dose MBI, this additional risk factor may help identify the subset most likely to benefit from supplemental screening and risk-reduction options.

Title of Abstract:
Effect of volumetric mammographic density on performance of a breast cancer screening program using full-field digital mammography

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Purpose:
Film screen mammography (FSM) showed reduced screening performance in women with mammographically dense breasts. We examined to what extent mammographic density is still a problem for screening performance when using full field digital mammography (FFDM).

Method:
We collected a consecutive series of 69,840 FFDM examinations (2003-2009) from one screening unit of the Dutch biennial screening program (50-75 years). Volumetric mammographic density was automatically assessed with Volpara version 1.5.0 (Matakina, New Zealand). Recall and breast cancer detection information was obtained from the screening registration system. Interval cancers were identified through linkage with the Netherlands Cancer Registry. Within four breast density categories, comparable to ACR breast density categories, we assessed screening performance measures and linear trends with a Chi Square linear trend test.

Results:
19.7% of the examinations was categorized as density category 1 (‘almost entirely fatty’), 43.1% as category 2, 29.4% as category 3 and 7.7% as category 4 (‘extremely dense’). In total 413 screen-detected and 150 interval tumors (diagnosed within 2 years after the last screening mammogram) were identified. Cancer detection rates were 3.7‰, 6.4‰, 6.6‰ and 6.3‰ in breast density categories 1 to 4 respectively (p-trend=0.005). Interval cancer rates increased with increasing density categories: 0.7‰, 1.9‰, 3.0‰ and 4.5‰, respectively (p-trend<0.001). as a result, the sensitivity (proportion of screen-detected tumors of screen-detected and interval tumors) was lower in higher density categories: 85.0%, 77.6%, 69.0% and 58.6% respectively (p-trend<0.001). the number of false-positives was higher in women with dense breasts: 11.4‰, 14.1‰, 18.3‰ and 28.6‰ for categories 1 to 4, respectively (p-trend<0.001). the positive predictive value of screening mammography was 24.5%, 31.4%, 26.5% and 18.1% in categories 1 to 4, respectively (p-trend=0.034).

Conclusion:
Also when FFDM is used in breast cancer screening, higher interval cancer and false-positive rates are observed in women with mammographically dense compared to non-dense breasts.

Title of Abstract:
Volumetric Breast Density of Japanese Women Using Adaptive Pattern Recognition-Based Calibrations

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Purpose:
Mammographic density is a strong breast cancer risk factor and has significant influence over screening sensitivity. Artificial neural networks (ANN) are suitable for performing pattern-to-pattern recognition. Their adaptive nature are potentially useful for calibrating Full-Field Digital Mammography (FFDM) for quantitative analysis. This study uses ANN modeling to estimate volumetric breast density (VBD) from mammography on a population of Japanese women with and without breast cancer.

Method:
A “GEN III” VBD quality control phantom, consisting of 9 steps of radiographically breast-equivalent materials at varying thicknesses and fibroglandular densities was imaged repeatedly on one Fujifilm Amulet f FFDM system across a broad range of imaging parameters. Feedforward ANN were trained using the parameters and resulting appearance of the phantom image to construct flexible models with which VBD could be quantified from parameters and appearance of standard patient mammograms. Mammograms acquired between February 2012 and 2013 of 46 women, subsequently diagnosed with invasive carcinoma, were included in the study and their cranial-caudal (CC) images contralateral to the tumor were analyzed with the ANN models. Additionally, screening CC mammograms acquired in June 2014 of 53 women with negative findings were also analyzed.

Results:
Results of the 2 groups are reported as mean and standard deviations below:

	Cancer	Non-cancer	p-value (Wilcoxon)
Age	58.8 (11.0)	60.3 (11.9)	0.483
Breast volume, cm3	416.1 (224.2)	439.0 (243.5)	0.705
Dense volume, cm3	177.5 (102.9)	171.4 (106.8)	0.537
Volumetric breast density, %	44.6 (13.8)	38.9 (12.5)	0.046

VBD was inversely correlated with age in both group as expected.

In the non-cancer group, left and right breast volumes were correlated with R2=0.91, dense volumes with R2=0.90, and VBD with R2=0.79.

Conclusion:
ANN calibrated models appear to produce reasonable values of mammographic density. VBD appears to be significantly higher in Japanese women with cancer in comparison to those without.

Title of Abstract:
Circulating sex hormones and mammographic density in premenopausal women

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Purpose:
Prior research suggests that endogenous sex steroids are associated with breast cancer risk, particularly in postmenopausal women, while mammographic density (MD) may reflect cumulative exposure to estrogens. A few studies, but not all, have reported positive associations between estrogens and MD, primarily among postmenopausal women, suggesting at least one possible biological mechanism of action. However, there have been few studies among premenopausal women, and results are inconsistent.

Method:
To test the hypothesis that plasma sex hormones are associated with MD, we conducted a cross-sectional study among 630 cancer-free premenopausal women in the Nurses' Health Study II. We measured percent MD from screening mammograms using a computer-assisted method. We assayed estradiol, estrone, estrone sulfate, testosterone, androstenedione, progesterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and sex hormone-binding globulin (SHBG) in blood samples timed in early follicular and mid-luteal phases of the menstrual cycle (for estrogens) or untimed (for androgens and SHBG). We used multivariable linear regression to quantify the association of %MD with quartiles of each hormone, adjusting for age, body mass index, age at menarche, parity/age at first birth, family history of breast cancer, alcohol intake, and luteal day of blood draw.

Results:
In these preliminary analyses, %MD was significantly higher among women in the highest quartile of follicular estradiol levels compared to those in the lowest quartile (difference: 7.0; 95% confidence interval: 2.3, 11.7; p-trend <0.001). similar associations were observed for follicular free estradiol but not luteal-phase estradiol. in addition, women in the top (vs. bottom) quartile of free testosterone had significantly lower %md (difference: -6.1; 95% ci: -11.0, -1.3; p-trend <0.01). percent md was not strongly associated with any of the other measured hormones.

Conclusion:
Our findings suggest that follicular estradiol may play an important role in mammographic density.

Title of Abstract:
Case-control study of mammographic density and breast cancer risk using processed Hologic full-field digital mammograms

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Purpose:
While breast density assessed from film mammograms has been strongly associated with breast cancer risk, data are limited for breast density assessed from full-field digital mammograms (FFDM). Information is especially limited for processed digital images from Hologic machines, the most prevalent type in the US.

Method:
We conducted a case-control study nested within a cohort of 34,386 women participating in the Research Program in Genes, Environment and Health (RPGEH). Cases (n=224) and controls (n=224) were ages 40 to 74 years with a screening FFDM acquired from Hologic machines. Cases had a first primary invasive breast cancer. Controls were women without a history of breast cancer, matched to cases on age at FFDM. Percent density (PD) and dense area (DA) were assessed by a breast imaging specialist trained in the Cumulus method. A random subset of 46 images was re-assessed blindly for PD and DA. Conditional logistic regression was used to estimate odds ratios (ORs) for breast cancer associated with PD and DA, modeled continuously in standard deviation (SD) increments and categorically in quintiles, after adjusting for body mass index and menopausal hormone use.

Results:
Intra-reader reproducibility was high (Pearson’s r= 0.93 for both PD and DA). The adjusted ORs for breast cancer associated with each SD increment were 1.39 (95% confidence interval, 1.07-1.80) for PD, and 1.23 (0.99-1.52) for DA. The adjusted ORs for each quintile were: 1.00 (ref.), 1.06 (0.53-2.16), 1.86 (0.95-3.67), 1.90 (0.93-3.88), 2.66 (1.19-5.92) for PD, and 1.00 (ref.), 1.20 (0.64-2.27), 2.02 (1.00-4.06), 1.79 (0.89-3.59), 1.92 (1.00-3.67) for DA.

Conclusion:
We found that PD and DA measured using Cumulus on processed FFDM images are reproducible and positively associated with breast cancer risk. These results indicate that processed FFDMs acquired for routine clinical care in a general practice setting are suitable for use in breast cancer research.

Title of Abstract:
Combination of age/body mass index (BMI)-adjusted scores of percent density (PD) and dense area (DA) for assessing breast cancer risk

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Purpose:
The aim of this study was to evaluate the usefulness of integrating the scores of PD and DA to predict breast cancer risk.

Method:
Mammographic density of 1441 non-affected healthy women (control group) and 701 breast cancer patients (case group) aged between 40 and 59 were analyzed. Mammographic density was assessed by CumulusTM from digital mammogram. at times when mammograms were taken were collected from all subjects and clinicopathologic factors in breast cancer patients were reviewed. Through adjustment of age and BMI by generalized additive model for location, scale and shape (GAMLSS), standardized breast density scores (percentile) were calculated and analyzed

Results:
PD (%) and DA (pixel) by CumulusTM and their standardized scores (GAMLSS ZPD percentile and GAMLSS ZlnDA percentile) were significant risk factors for breast cancer, respectively. With the cutoff of 60 percentile, PD dominant dense breast (discordant group 1: GAMLSS ZPD percentile≥60 and GAMLSS ZlnDA percentile<60) and da dominant dense breast (discordant group 2: gamlss zpd percentile<60 and gamlss zlnda percentile≥60) could be defined respectively. along with conventional dense breast (accordant group 1: gamlss zpd percentile≥60 and gamlss zlnda percentile≥60), pd or da dominant dense breast had higher risks for breast cancer compared with non-dense breast (accordant group 2: gamlss zpd percentile<60 and gamlss zlnda percentile<60): or of conventional dense breast = 7.73 [95% confidence interval (ci) = 5.99 – 9.98], or of pd dominant dense breast = 4.97 (95% ci = 3.59 – 6.90), and or of da dominant dense breast = 3.99 (95% ci = 2.84 – 5.60). breast cancers developed in the da dominant dense breasts (discordant group 2) were characteristic of older onset age and hormone receptor negativity.

Conclusion:
In addition to conventional dense breast, PD or DA dominant dense breast is a risk factor for breast cancer. Particularly, DA dominant dense breast may be associated with hormone receptor negative breast cancer.

Title of Abstract:
Mammographic structure of dense tissue and its association to cancer detection and risk in the Copenhagen screening program

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Purpose:
In several case-control studies and some epidemiological cohorts, the relation between volumetric breast density and breast cancer risk and risk of non-detection in screening have been reported. We examine not just the relation of breast density, but also the structure of the dense tissue as recorded by its texture, to the detection of breast cancer in the screening program, and the occurrence of interval cancers.

Method:
The Capitol Region of Denmark screening program offers biannual screening to all women aged 50-69. For women attending the screening program in the period November 1st 2012 to December 31st 2013 raw mammograms were saved for post hoc analysis. They were scored for density by radiologist's BI-RADS (version 4) categorization by two trained radiologists, by volumetric breast density by Volpara, and texture scored by the mammographic texture resemblance score as computed by deep learning. Cancer status as detected by the screening program was recorded. Interval cancers were recorded 15 months after screening for the individual.
Association of density measures and age to cancer status was analyzed by logistic regression including interaction terms between density and structure. Only terms contributing significantly to the model were retained.

Results:
In the study period, approximately 87.000 women were eligible for screening. Approximately 60.000 attended the program. Of these 600 are expected to have been diagnosed with a screen-detected cancer and 200 diagnosed with an interval cancer.
ORs according to models are reported.

Conclusion:
ORs of density, texture and interactions relation to risk of breast cancer and risk of interval cancer are concluded upon. Special attention is given to whether women of low density but high texture scoring are at increased risk of cancer or at risk of interval cancer.

Title of Abstract:
Assessing impact of Volpara automated volumetric breast density software on radiologist evaluation of breast density in the clinical mammogram interpretation setting

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Purpose:
This project evaluates radiologist's use of Volpara automated volumetric breast density software as an adjunct to evaluating density in the clinical mammography interpretation setting.

Method:
200 women (aged 37-85) who underwent screening mammography, the first 100 in April 2013 and the first 100 in April 2014, were included in this study. Breast density evaluations as calculated by Volpara automated breast density software (v1.4.3 and v1.4.4) and recorded in PACS were retrospectively compared to the radiologist's assessment as recorded in the report. Radiologists had access to the Volpara measurements which were displayed on their workstations during image interpretation. Readings were from three expert breast imagers. Data was compared using four grades from ACR BI-RADS density categories and binary grading system (nondense A and B versus dense C and D), facilitating analysis of the impact recommending screening breast ultrasound. Additionally, cases with potential for technical failure of automated Volpara system, such as lumpectomy, catheter, pacemaker, and or implant, were noted

Results:
The agreement between the Volpara estimation and the radiologist's evaluation of breast density in both 2013 and 2014 was fair ($k= 0.386$, $p<0.001$ and $k=0.346$, $p<0.001$) when using a four grade BI-RADS system, and substantial ($k= 0.720$, $p<0.001$ $k=0.681$, $p<0.001$) when using the binary scale. Too few cases had a lumpectomy or implant to see a significant effect

Conclusion:
The impact of seeing the Volpara density measurement during clinical interpretation on radiology decision making cannot be directly measured. In clinical practice, when radiologists have access to the Volpara data during their mammography interpretation, there is substantial agreement on breast density assessment when using the binary classification. Substantial agreement between Volpara and the radiologist is noteworthy, particularly in the binary setting, as this measurement determines recommendation for screening ultrasound

Title of Abstract:
Evidence of Bimodality in UST Breast Sound Speed Images

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Purpose:
Ultrasound tomography (UST) sound speed images produce a quantitative distribution of sound speed voxels that represent the acoustic sound speed and heterogeneity of breast tissue density. Sound speed is a direct and quantitative measure of both whole-breast and regional tissue density. The new BI-RADS breast category for heterogeneous density also includes more regional density which may obscure cancers. Denser tissue regions amidst non-dense fatty tissue should then present as bimodal distributions for whole-breast sound speed.

Method:
A total of 164 healthy women with negative mammographic screens underwent UST scans. The kurtosis, k, and the skewness, s, of their distribution of sound speeds were measured. The kurtosis along with the value k – s2 are both measures of bimodality with the most bimodal distributions having values that approach 1. These measures of bimodality were compared to the volume averaged sound speed of a randomly selected breast from each woman.

Results:
Plots of the average sound speed versus the two bimodality measures and the corresponding Spearman correlation coefficients were produced. Results show a strong and inverse correlation between the sound speed measures of breast density and measures of bimodality ($r_s = -0.729$, $r_s = -0.539$). This indicates that as breast density increases, the distribution of the density becomes more bimodal, reflecting the fibroglandular and adipose tissue components. Fatty breasts appear to have a homogeneous unimodal sound speed distribution, whereas denser breasts seem to have more heterogeneous tissue composition as demonstrated by the bimodal sound speed distribution.

Conclusion:
Whole breast averages of UST sound speed images show a bimodal density distribution particularly for women with higher breast density. The bimodality indicates that different types of tissue can be detected using UST imaging and suggests that further work may also help quantitate the new grouping of women with more regional heterogeneous density.

Title of Abstract:
Long-term ambient particulate matter exposure and mammographic density

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Purpose:
Mammographic density is a strong risk factor for breast cancer. Studies suggest that air pollutants may be associated with breast cancer incidence, though no studies have assessed the relationship of air pollutants and normal breast tissue composition. We assessed whether particulate matter size fractions (PM2.5, PM2.5-10, and PM10) are associated with mammographic density in women without breast cancer.

Method:
The Nurses' Health Study II (NHSII) is an ongoing prospective cohort study with detailed longitudinal data. PM2.5, PM2.5-10, and PM10 were estimated using GIS-based spatio-temporal prediction models linked to residential addresses throughout follow-up. Screening film mammograms were collected for participants in the breast cancer case-control study and evaluated for percent mammographic density. Among 1800 controls, we performed multivariable linear regression to assess associations of annual average PM2.5, PM2.5-10, and PM10 in 1991 and the cumulative average from 1991 until the mammogram (average follow-up = 8.4 years) with percent mammographic density after adjusting for breast density predictors. Analyses were stratified by menopause status at mammogram and region of residence.

Results:
PM 2.5, PM2.5-10, and PM10 were not associated with mammographic density overall or after stratification by menopausal status. However, there was some evidence that among postmenopausal women in the Northeast (n=171), every 10 µg/m3 increase in cumulative average PM2.5 was associated with 21.1% higher percent mammographic density (cumulative average PM2.5: 21.1% 95% CI 10.7, 31.5%, p-value <0.05). in contrast, there was no association among 406 premenopausal women in the northeast.

Conclusion:
There was no association between particulate matter and mammographic density overall. Additional work is necessary to confirm suggestive associations in postmenopausal women living the Northeast.

Acknowledgements: This research was supported by the National Institutes of Health Cancer Epidemiology Educational Program (NIH T32 CA09001) and a grant from the Susan G. Komen for the Cure ® (IIR13264020).

Title of Abstract:
A descriptive analysis of mammographic breast density in patients with a history of breast malignancy in Iran

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Purpose:
Among different risk factors for breast cancer, breast density(BD) is considered as a moderate independent risk factor. BD is highly heritable, thus it differs according to ethnicity. Other factors such as age, BMI, hormonal status of women, parity, breast feeding have influence over BD. Iran as a Middle Eastern country has a low incidence of breast cancer (with an ASR of 23.65 in 2006) but the incidence has been increased steadily during the last decades.
Till now there have been few studies conducted on BD and it’s distribution in Iran. In this article we've studied BD distribution among those with a history of breast malignancy.

Method:
This was a cross sectional study, conducted in 4 major mammographic screening centers of Isfahan, Iran between 2012-2014. During this period every women who has been referred to one of these centers were included in the study .We conducted a questionnaire based survey assessing different risk factors of breast cancer alongside with demographic features and BD. The final sample size was 7807 with 1187 malignant cases. For malignant cases, a second mammogram within the past 5 years has been obtained. The mammographies were reported according to BIRADS 4th edition standards.

Results:
The mean age of our malignant patients was 48.3(±8.3) years. From 1187 malignant cases, 38.8 % had fatty BD(< 25%), 38 % had scattered fibroglandular bd(25-50%), 11.2 % had heterogeneously dense bd(50-75%), 12 % had extremely dense(>75%). Furthermore, during a 5 year period, 0.5 % and 1.4 % of those with a fatty and scattered BD have turned into extremely dense.

Conclusion:
It seems that in comparison to western studies, the frequency of extremely dense breasts are higher in our population. This may be due to younger age of onset of breast cancer in Iran, however other environmental factors may play a role.

Title of Abstract:
Predicted five-year Gail breast cancer risk in women with extremely dense breasts

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Purpose:
To investigate five-year Gail breast cancer risk for participants in a trial where women with extremely dense breasts are offered MRI examination after negative screening mammography.

Method:
We investigated breast cancer risk and presence of breast cancer risk factors among women participating in a multicenter randomized controlled trial investigating the additional value of MRI to detect breast cancer in women aged 50-75 years with extremely dense breasts (DENSE trial). The study was carried out in the Dutch biennial population-based screening program. Information on breast cancer risk factors was obtained through questionnaires. Five-year Gail breast cancer risk (breast density not included) was computed and the percentage of women with an elevated risk (five-year risk ≥1.67%) was calculated. Results were compared to available Dutch data or to U.S. data on white women if Dutch data were not available.

Results:
Participants were 54 years of age (IQR:51-59) and their median five-year breast cancer risk was 1.50% (IQR:1.20-1.94). Of the participants 39% had a five-year Gail breast cancer risk ≥1.67%. The five-year Gail risk was elevated in 28.8% of participants aged 50-59 years respectively 73.6% of participants aged 60-69 years. This was respectively 15.5% (50-59 years) and 39.1% (60-69 years) in a white U.S. population.[1]
Of the participants 33% (n=731) was ≥30 years of age at first live birth, compared to 23% of a representative general Dutch population.
Of the participants aged 50-54 years 1.3% (n=16) had a BMI≥30, compared to 12.0% in the general Dutch population. Of participants aged 55-64 years, this was 1.1% (n=8) compared to 16.2% in the general Dutch population.

[1]Graubard et al. CEBP 2010;19:2430-6

Conclusion:
The majority of the participants was <60 years and their median five-year gail breast cancer risk was 1.50%. five-year gail breast cancer risk was elevated in 39% of the women with extremely dense breasts participating in dense.

Title of Abstract:
Comparing mammographic density measures between an automated volumetric method and an area-based method in relation to circulating sex hormones and urinary estrogens in postmenopausal women

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Purpose:
To investigate the associations between mammographic density (MD) and blood reproductive hormones and urinary estrogens and estrogen metabolites using both automated volumetric software (Volpara) and a threshold, computer assisted area-based method (Madena).

Method:
The Minnesota Green Tea Study is a randomized placebo-controlled, double-blinded trial assessing the effects of green tea catechin intake on breast cancer biomarkers in postmenopausal women with dense breasts. Baseline left craniocausal mammogram were evaluated in a subgroup of 101 women (age = 60.2 ± 5.1 years, BMI=24.9 ± 3.7 kg/m2). Volumetric breast density (VBD) including fibroglandular volume (cm3) and %VBD were measured using Volpara software, and percent MD (%MD) and absolute dense area (cm2) were estimated by the Madena method. Fasting circulating sex hormones and 24-hour urinary estrogens and estrogen metabolites were quantified by liquid chromatography-tandem mass spectrometry.

Results:
Percent VBD was significantly correlated with %MD, and fibroglandular volume was significantly correlated with absolute dense area (r = 0.65, P<0.0001, for both correlations). percent vbd and %md were inversely associated with bmi (p trend =0.001) and age (p trend =0.008 and 0.10, respectively). after adjustment for age and bmi, %vmd was inversely associated with circulating testosterone (p trend =0.005) and androstenedione (p trend =0.08). both %vbd and %md were inversely associated with urinary estrone (p trend =0.004 and 0.03, respectively), and estriol (p trend =0.0006 and 0.04, respectively). %vbd was inversely associated with urinary estradiol (p trend =0.053) and 2-hydroxyestrone (p trend =0.03). fibroglandular volume, but not absolute dense area, was inversely associated with circulating testosterone (p trend =0.03) and urinary 2-hydroxyestrone and 2-hydroxyestradiol (p trend for both= 0.02).

Conclusion:
Mammographic density was significantly correlated between Volpara and Madena methods. Our results show that specific blood sex hormones and urinary estrogens are both inversely associated with mammographic density and associations are stronger for volumetric method.

Title of Abstract:
Mammographic density and breast cancer: a case-control study

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Purpose:
High mammographic density is associated with an increased risk of developing breast cancer. The aim of this study was to compare the ability of two-dimensional and volumetric measurements of mammographic density to predict case-control status based on the density of the contralateral breast of screen-detected cancers.

Method:
We conducted a case control study in women from Predicting Risk Of Cancer At Screening (PROCAS), a prospective study of over 50,000 women attending mammographic screening in Greater Manchester, UK. Cases were identified as women with their first diagnosis of breast cancer at entry to the study (n=318) and matched to three controls using age, menopausal status, HRT use and BMI group (n=952). Mammographic density was assessed for the contralateral breast for cases and matched breast for controls from digital mammograms using visual assessment recorded on Visual Analogue Scales (VAS), CUMULUS, Quantra™ and Volpara™. Conditional logistic regression was used to examine the relationship between density and the risk of breast cancer.

Results:
VAS, Volpara gland volume, Volpara percent density, CUMULUS dense area and CUMULUS percent density were all associated with an increased risk of breast cancer. The strongest association was for VAS, with those in the highest quintile having four times the odds of breast cancer compared to those in the lowest quintile (OR 4.1, 95% CI 2.5-6.6). Corresponding odds ratios for Quantra, Volpara and CUMULUS were 0.9 (95% CI 0.6-1.3), 1.7 (95% CI 1.1-2.7) and 2.0 (95% CI 1.3-3.3) respectively for gland volume/area, and 1.0 (95% CI 0.7-1.6), 2.5 (95% CI 1.5-4.1) and 2.0 (95% CI 1.3-3.3) for percent density.

Conclusion:
Whilst this analysis suggests that VAS is a better predictor of breast cancer status than volumetric methods, it is impractical on a large scale and suffers from observer variability. Volpara percent density provided the best automated alternative.

Title of Abstract:
Methods to improve the reproducibility of breast density measurements on processed digital mammograms using an operator-assisted program

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Purpose:
In the past decade, full-field digital mammography has replaced conventional film mammography as the most common modality for screening mammography. Several automated methods have been developed to estimate breast density from raw digital mammograms. However, most health care facilities store only the processed images for presentation to the radiologist, and not the raw images. It is currently unknown how best to quantify breast density from processed digital images that are routinely archived for clinical care. We evaluated application of Cumulus, an operator-assisted method widely used for film mammograms, to measure density on processed digital mammograms.

Method:
We found that the reproducibility of density measurements on processed digital mammograms using Cumulus was generally lower than standard for film mammography. We hypothesized that relatively high variability of pixel intensities, or image noise, at the boundary of dense and non-dense tissues, perhaps increased by proprietary processing algorithms that enhance local contrast, may decrease the reproducibility of density measurements. To test our hypothesis, we applied median filtering, a standard noise reduction algorithm, to processed digital images acquired on Hologic and GE mammography units in community-based clinics and a large academic hospital.

Results:
We found that the intra-reader reproducibility was significantly higher for denoised vs. unaltered processed Hologic images (Pearson R of 0.970 vs. 0.892; p <0.0001), and similar results for processed ge images. furthermore, density measured with cumulus on the denoised processed images was significantly associated with breast cancer risk for both hologic (habel et al, submitted abstract) and ge (jeffers et al, submitted abstract) mammograms.

Conclusion:
Our findings suggest that denoising improves the reproducibility of density measurements using Cumulus on processed digital mammograms routinely archived for clinical care, and that these image repositories are suitable for research on breast density and cancer risk.

Title of Abstract:
Diabetes, diabetes treatment and mammographic density in Danish Diet, Cancer, and Health cohort

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Purpose:
Diabetes is associated with increased risk of breast cancer, but exact mechanisms are unknown. The role of insulin has been debated. High mammographic density (MD) is one of the strongest predictors and a biomarker of breast cancer risk. Few studies have linked diabetes to MD, finding none or weak inverse associations, but none had data on diabetes treatment. We examined whether diabetes and diabetes treatment are associated with MD in a prospective cohort study of Danish women above age of 50 years.

Method:
Study cohort consisted of 5,703 women (4,501 postmenopausal) who participated in the Danish Diet, Cancer and Health cohort (1993-1997) and subsequently attended mammographic screening in Copenhagen (1993-2001). We used MD assessed at the first screening after the cohort entry. MD was defined as mixed/dense or fatty. Diabetes diagnoses, and diabetes treatments (diet, insulin, pills) were self-reported at recruitment (1993-1997). The association between MD and diabetes was analyzed by logistic regression adjusted for potential confounders. Effect modification by menopausal status and body mass index (BMI) was performed by introducing an interaction term into the model and tested by Wald test.

Results:
Of 5,703 women with mean age of 56 years, 137 (2.4%) had diabetes and 3,212 (56.3%) had mixed/dense breasts. Having diabetes was significantly inversely associated with having mixed/dense breasts, in both, the crude model (odds ratio; 95% confidence interval: 0.33; 0.23-0.48), and after adjustment for adiposity and other risk factors (0.61; 0.40-0.92). Similar inverse associations were observed for 44 women who controlled diabetes by diet only and didn’t receive any medication (0.63; 0.29-1.36), and 62 who took pills only for diabetes (0.59; 0.32-1.09), while diabetic women taking insulin seemed to have increased odds of mixed/dense breasts (2.08; 0.68-6.35). There was no effect modification of these associations by menopause or BMI.

Conclusion:
Among women 50 years and older, having diabetes controlled by diet or pills decreases MD, whereas taking insulin may increase MD.

Title of Abstract:
Long-term exposure to air pollution and mammographic density in the Danish Diet, Cancer and Health cohort

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Purpose:
Growing evidence suggests that air pollution may be a risk factor for breast cancer, but the biological mechanism remains unknown. High mammographic density (MD) is one of the strongest predictors and biomarkers of breast cancer risk, but it has yet to be linked to air pollution. We investigated the association between long-term exposure to traffic-related air pollution and MD in a prospective cohort of women 50 years and older.

Method:
For the 4,769 women (3,930 postmenopausal) participants in the Danish Diet, Cancer and Health cohort (1993-1997) who attended mammographic screening in Copenhagen (1993-2001), we used MD assessed at the first screening after cohort entry. MD was defined as mixed/dense or fatty. Traffic-related air pollution at residence was assessed by modeled levels of nitrogen oxides (NOx) and nitrogen dioxide (NO2). The association between mean NOx and NO2 levels since 1971 until cohort baseline (1993-97) and MD was analyzed using logistic regression, adjusting for confounders, and separately by menopause, smoking status, and obesity.

Results:
We found inverse, statistically borderline significant associations between long-term exposure to air pollution and having mixed/dense MD in our fully adjusted model (OR; 95% CI: 0.96; 0.93-1.01 per 20 µg/m3 of NOx and 0.89; 0.80- 0.98 per 10 µg/m3 of NO2). There was no interaction with menopause, smoking, or obesity.

Conclusion:
Traffic-related air pollution exposure does not increase MD, indicating that if air pollution increases breast cancer risk, it is not via MD.

Abstract Proffered Talks

Friday, June 12, 2015

1:45 pm - 2:15 pm

Title of Abstract:
Assessing Breast Cancer Masking Risk in Full Field Digital Mammography with Automated Texture Analysis

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Purpose:
The goal of this work is to develop a method to assess the risk of breast cancer masking, based on image characteristics beyond breast density.

Method:
From the Dutch breast cancer screening program we collected 285 screen detected cancers, and 109 cancers that were screen negative and subsequently appeared as interval cancers. To obtain mammograms without cancerous tissue, we took the contralateral mammograms. We developed a novel machine learning based method called convolutional sparse autoencoder to characterize mammographic texture. The method was trained and tested on raw mammograms to determine cancer detection status in a five-fold cross validation. To assess the interaction of the texture scores with breast density, Volpara Density Grade was determined for each image.

Results:
We grouped women into low (VDG 1/2) versus high (VDG 3/4) dense, and low (Quartile 1/2) versus high (Q 3/4) texture risk score. We computed odds ratios for breast cancer masking risk (i.e. interval versus screen detected cancer) for each of the subgroups. The odds ratio was 1.63 (1.04-2.53 95%CI) in the high dense group (as compared to the low dense group), whereas for the high texture score group (as compared to the low texture score group) this odds ratio was 2.19 (1.37-3.49). Women who were classified as low dense but had a high texture score had a higher masking risk (OR 1.66 (0.53-5.20)) than women with dense breasts but a low texture score.

Conclusion:
Mammographic texture is associated with breast cancer masking risk. As such, automatic texture analysis offers opportunities to enhance personalized breast cancer screening. We were able to identify a subgroup of women who are at an increased risk of having a cancer that is not detected due to textural masking, even though their breasts are non-dense.

Title of Abstract:
Density, Dose, and Digital Breast Tomosynthesis

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Purpose:
The addition of digital breast tomosynthesis (DBT) to conventional mammography (CM) improves screening performance to varying degrees depending on breast density. We sought to evaluate the extent to which mean glandular dose (MGD), on DBT versus CM, is affected by volumetric breast density (VBD), and how MGD differences might offset potential gains in screening performance using DBT.

Method:
This study consisted of 100 women imaged on a DBT system in “combo mode” (DBT and CM under the same compression). Using Volpara algorithm v1.5.0, VBD thresholds of <4.5, 4.5-7.5, 7.5-15.5 and >15.5% were used to assign women into Volpara Density Grades (VDG) 1 – 4, respectively (equivalent to BIRADS 4th Edition density categories). The mid-points of each VDG threshold (i.e. 3.75, 6, 11 and 25.5%) were used to further dichotomize each VDG category. Stratifying by “low” and “high” VDG, the manufacturer-reported MGD for each CM and DBT study was considered in light of CM sensitivity results previously determined at this center.

Results:
Median MGD was significantly higher on DBT versus CM (1.90 and 1.73 mGy, respectively, p<0.001). comparing mgd on dbt versus cm, women in the low vdg1 to low vdg3 categories received higher mgd, whereas women in the high vdg3 to high vdg4 categories experienced similar or reduced mgd. cm sensitivity at this center ranged from 100% (low vdg1) to 58% (high vdg4). considering cm sensitivity was previously shown to be 95% in vdg1 women at our center, an average mgd increase of ~36% on dbt alone versus cm for these women should be weighed against the potential gain in sensitivity from dbt.

Conclusion:
Mammographic performance is excellent for women in the lower density categories. Any sensitivity improvement by performing DBT in these women may be limited and should be taken into consideration given the increased MGD for DBT, alone or in combo mode.