7TH BIENNIAL CONFERENCE

Online and In-person

WHY STUDY MAMMOGRAPHIC DENSITY?

27th-28th September 2022

2022 PROGRAM

Hosted by MyBRISK Centre of Research Excellence
Melbourne School of Population and Global Health
The University of Melbourne

Venue: The Woodward Conference Centre
Level 10, 185 Pelham Street, Carlton, Victoria
www.mybrisk.org.au

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THE UNIVERSITY OF MELBOURNE

Contents

Program

Day 1 – Tuesday, September 27th, 2022

10:30am: Meeting Open (Registration available)

Session 1

Chair: Kara Britt

11:00am: Acknowledgement of Country

11:05am: Conference Welcome – John Hopper

11:15am: Sue Malta, Community Representative: *Why Study Mammographic Density?*

11:25am: Helen Frazer: *To the power of BRAIx: Transforming screening with Artificial Intelligence*

11:45am: Jennifer Brooks: *Risk stratified screening in the Ontario Breast Screening Program: Utility of mammographic density*

12:10pm: Rebecca Spouge: *The Added Value of Supplemental Breast Ultrasound Screening for Women with Dense Breasts: A Single Centre Canadian Experience*

12:30pm: Lunch

Session 2

Chair: John Hopper

1:30pm: Jennifer Stone: *The distribution of breast density in women aged 18-97 using optical breast spectroscopy*

1:50pm: Konstantin Momot: *Portable Nuclear Magnetic Resonance for quantification of breast density in vivo: Proof-of-concept measurements and comparison with quantitative MRI*

2:10pm: Rik Thompson: *Bright – The new white in mammographic density-associated breast cancer risk*

2:30pm: Rachel Lloyd: *Alternative methods to measure breast density in younger women*

2:50pm: Michelle Reintals: *The BreastScreen South Australia Breast Density Reporting Trial*

3:10pm: Avisak Bhattacharjee: *Assessing women's knowledge about breast density*

3:30pm: Afternoon tea

Session 3

Chair: Jennifer Stone

4:00pm: Mads Neilson: An Artificial Intelligence–based Mammography Screening Protocol for Breast Cancer: Outcome and Radiologist Workload

4:30pm: John Hopper: *Artificial Intelligence, detecting breast cancers, and short-term risk of breast cancer*

5:00pm: Mikael Eriksson: *Long-term performance of an image-based short-term risk model for breast cancer*

5:20pm: Celeste Damiani: *Evaluation of an automated system to assess future breast cancer risk using mammograms at screening*

5:40pm: Tuong L. Nguyen: *Application of the Deep-Risk digital mammogram risk scores to predict young and familial breast cancer using digitised mammograms*

6:00pm: Dinner

Session 4

Chair: Gretchen Gierach

7:00pm: Per Hall: *Individualised prevention and screening of breast cancer: The Karma experience*

7:30pm: Maeve Mullooly: *Associations of breast cancer risk factors with volumetric breast density measures defined at increasing thresholds among women undergoing image-guided breast biopsy: preliminary results*

7:50pm: Jessica O'Driscoll: *Reproductive factors and mammographic breast density: A cross-sectional study using data from the International Consortium of Mammographic Density*

8:10pm: Said Pertuz: *Comparing radiomic analysis and deep learning for breast cancer risk assessment based on the computerized analysis of mammographic images*

8:20pm: Siobhan Freeney: *The Patient Effect, Changing the narrative around Breast Cancer Screening and Imaging*

8:30pm: Day 1 close

Day 2 – Wednesday, September 28th, 2022

Session 5

Chair: Kara Britt

9:00am: Weiva Sieh: *Understanding the genetic basis of mammographic density phenotypes*

9:30am: Hela Koka: *Mammographic density in relation to breast cancer risk factors among Chinese women*

9:50am: Andre Kahlil: *Quantitative Visualization of Healthy vs. Risky Mammographic Breast Density*

10:10am: Rulla Tamimi: *Changes in mammographic density and texture associated with high-dose vitamin D supplementation*

10:30: Morning Tea

Session 6

Chair: Rik Thompson

11:00am: Jason Northey: *Mechanosensitive hormone signaling promotes mammary progenitor expansion and breast cancer progression*

11:30am: Kara Britt and Wendy Ingman: *Biological studies of mammographic density open the door for new approaches to prevent breast cancer*

11:40am: Satcha Foongkajornkiat: *Portable Nuclear Magnetic Resonance (pNMR) Quantitative Measurement of Mammographic Density in Breast Tissues*

11:50am: Dane Cheasley: *High mammographic density is associated with increased tumour-promoting immune cells in breast cancer*

12:10pm: Honor Hugo: *The effect of Rho-kinase inhibition on mammographic density*

12:30pm: Lunch

Session 7

Chair: Wendy Ingman

1:30pm: Gretchen Gierach: *Relation of pre- and post-breast cancer diagnosis measures of mammographic breast density with contralateral breast cancer risk within a general community healthcare setting*

2:00pm: Shivaani Mariapun: *Genome-wide association study identifies common variants associated with mammographic density in Asian women*

2:20pm: Ellie Darcey: *Should breast screening programs routinely collect height and weight information?*

2:40pm: Panel Discussion: Why Study Mammographic Density?

Invited Panel Members:

Gretchen Gierach, Chief of the Integrative Tumor Epidemiology Branch, National Cancer Institute, USA
Shivaani Mariapun, Cancer Research Malaysia; PhD Candidate, University of Nottingham Malaysia
Lisa Daniela Vacarro, Consumer Scholarship Awardee
Jennifer Brooks, Dalla Lana School of Public Health, University of Toronto, Canada
John Hopper, School of Population Health, University of Melbourne
Rita Butera, CEO of BreastScreen Victoria

3:30pm: Meeting Close

Keynote Speakers

Professor Per Hall

I worked as a medical oncologist at the Karolinska Hospital for many years before taking on a position as an epidemiologist at Karolinska Institutet. Currently I hold a part time position as an oncologist at Södersjukhuset, Stockholm.

My research focus is prevention and early detection of breast cancer. We are working on image based, AI derived breast cancer risk models and we are conducting trials aiming at identifying the optimal risk reducing medication for breast cancer. Much of what we do is based on the Karma Cohort https://karmastudy.org.

For more information, please see https://staff.ki.se/people/per-hall

Associate Professor Weiva Sieh

Weiva Sieh, MD, PhD, MS is an Associate Professor of Epidemiology and Genetics in the Department of Population Health Science and Policy, and Department of Genetics and Genomic Sciences at the Mount Sinai School of Medicine in New York, USA. Her research interests include understanding the genetic and lifestyle determinants of mammographic density, and the relationship of breast density and other imaging features with cancer risk.

Professor Mads Nielsen

Mads Nielsen has a BSc, in Physics and Computer Science, an MSc and a PhD in Computer Science, University of Copenhagen (UCPH) from respectively 1989, 1992, and 1995. He was guest researcher at INRIA Sophia-Antipolis 1993/94, post doc at Imaging Sciences Institute Utrecht, 3D-Lab, Faculty of Medicine, UCPH, associate professor and professor at IT-University of Copenhagen, and Head of Department and Professor at DIKU, Department of Computer Science, UCPH, where he is member of the Pioneer Centre of AI and PI on a number of grants related to computing in biomedicine.

In 2012 he published what we believe is the first work on using deep learning in medical image analysis together with Andrew Ng, Stanford; and have since contributed to fundamental and applied work in this direction. He has been invited to host workshops on this topic at SPIE, IEEE ISBI, and more. Towards medical application, he has contributed to among other applications in musculoskeletal diseases, cardiovascular diseases, lung diseases, breast cancer, infectious diseases including Covid-19, and dementias. He has published more than 300 peer reviewed papers. He has published more than 20 patents and founded a number of companies in this area including Biomediq, AIomic, Cerebriu

Abstracts

Assessing women's knowledge about breast density

Avisak Bhattacharjee[1,2], David Walsh[1], Leigh J Hodson[1,2], Pallave Dasari[1,2], Sarah J. White[3], Deborah Turnbull[4], Wendy V Ingman[1,2].

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2. Robinson Research Institute, The University of Adelaide, Adelaide, SA 5005, Australia
3. Centre for Social Impact, The University of New South Wales, Sydney, New South Wales, Australia
4. School of Psychology, The University of Adelaide, Adelaide, SA 5005, Australia

Background: There is an intense interest about breast density due to its association with increased breast cancer risk and its capacity to mask tumour on mammogram. However, it is unclear to what extent this interest has reached the Australian community, or what Australian women know about breast density. The purpose of this study is to assess women's existing knowledge about breast density and their interest in knowing their own breast density status.

Methods: This cross-sectional study is being conducted among women attending The Queen Elizabeth Hospital Breast/Endocrine Clinic outpatient department for a screening mammogram. Women attending for a diagnostic mammogram are excluded from the study. We aim to recruit 200 participants. While waiting for their mammogram, patients are given a questionnaire to assess their knowledge of breast density and whether they want to know their breast density. The questionnaire was adapted from the Breast Screen Western Australia breast density survey [1].

Results: Participant recruitment is ongoing. To date, a consecutive sample of 120 women have been invited to participate and 81 have responded (68% response rate). Among the responding cohort, 42% had not heard the term 'breast density' before. Of those who had heard of breast density, 67% knew it could mask breast cancer and 28% knew it could increase risk of breast cancer. Twenty six percent thought breast density could be determined by touch or feel. Interestingly, 61% reported that they wanted to know their own breast density.

Conclusion: This ongoing study suggests that many women are unaware of breast density. This participant cohort will be further studied to investigate how breast density notification affects anxiety status, and how best to communicate density information. This research will help shape future breast density communication strategies to improve women's breast health.

1. Dench EK, Darcey EC, Keogh L, McLean K, Pirikahu S, Saunders C, et al. Confusion and Anxiety Following Breast Density Notification: Fact or Fiction? Journal of Clinical Medicine [Internet]. 2020 Mar 30;9(4):955. Available from: http://dx.doi.org/10.3390/jcm9040955

Biological studies of mammographic density open the door for new approaches to prevent breast cancer

Kara L Britt[1,2], Honor J Hugo[3,4,5], Erik W Thompson[4,5], **Wendy V Ingman[6,7]**

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[2]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Victoria, Australia, 3010
[3]School of Health and Behavioural Sciences, University of the Sunshine Coast, Sippy Downs, QLD 4556, Australia
[4]School of Biomedical Sciences, Queensland University of Technology (QUT), Brisbane, QLD 4006, Australia
[5]Translational Research Institute, Woolloongabba, QLD 4102, Australia
[6]Discipline of Surgical Specialties, Adelaide Medical School, The Queen Elizabeth Hospital, University of Adelaide, Adelaide, SA 5011, Australia
[7]Robinson Research Institute, University of Adelaide, Adelaide, SA 5001, Australia

Background: Breast tissue with high mammographic density is characterised by increased abundance of epithelial and stromal cells, and reduced abundance of adipocytes compared to regions of low density. High mammographic density is associated with increased risk of all breast cancer subtypes and the cancers are most likely to originate within the dense tissue regions. An autopsy study of women without clinically detectable breast cancer demonstrated that precancerous microscopic columnar cell lesions are found in 1 of 4 women with dense breasts. This suggests high density is associated with a pro-tumorigenic biological environment present many years before a diagnosis. Through understanding the biological drivers of mammographic density, there is the potential to intervene early and reduce a woman's risk of developing breast cancer.

Methods: A major challenge in the field has been how to study mammographic density from a biological perspective. We have pioneered a methodological approach that employs comparison of high and low density regions of the same breast. The cellular and molecular components of these tissues are assessed under the microscope and analysed as paired samples. This is a powerful statistical approach that enables us to overcome heterogeneity within the breast and the high variability between individuals. Using this approach, we have demonstrated that the abundance of immune cells and immune signalling factors are strikingly different between high and low density breast samples. High density is associated with increased abundance of macrophages, dendritic cells, B cells and CD4 T cells as well as the inflammatory marker cyclooxygenase-2 (COX2), and macrophage chemoattractant CCL2.

Results: However, the finding of increased immune signalling in high mammographic density does not infer a causal relationship. This requires intervention studies, commonly done in mouse models, to investigate the role of specific biological components. We have shown a causal relationship between the pro-inflammatory protein CCL2 and density-associated breast cancer risk. A genetically modified mouse model was developed whereby a mammary gland-specific DNA promoter causes constitutive expression of CCL2. This led to increased abundance of mammary gland macrophages, increased stromal density, and increased susceptibility to carcinogen-induced cancer.

Conclusion: Our future studies will continue to unpack the immune signalling components that are drivers of mammographic density and identify the best biological targets for interventions to reduce breast cancer risk.

Risk stratified screening in the Ontario Breast Screening Program: Utility of mammographic density

Brooks JD[1], Blackmore KM[2], Walker MJ[1,2], Chang A[2], Stockley T[3], Eisen A[4], Fienberg S[2], Antoniou AC[5], Easton DF[5], Simard J[6], Chiarelli AM[1,2]

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[2]Ontario Health (Cancer Care Ontario), Toronto, Ontario, Canada
[3]Division of Clinical Laboratory Genetics, University Health Network, Toronto, Ontario Canada
[4]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario Canada
[5]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, School of Clinical Medicine, University of Cambridge, Cambridge United Kingdom
[6]CHU de Québec-Université Laval Research Center, Québec City, Quebec Canada

Background: The Ontario Breast Screening Program (OBSP) screens women aged 50-74 years with mammograms every two years. Within this, there is a provision for annual screening for women with a first-degree family history of breast or ovarian cancer, a personal history of ovarian cancer or those with dense breasts (defined as ≥75% dense area).

The PERSPECTIVE I&I (Personalized Risk Assessment for Prevention and Early Detection of Breast Cancer: Integration and Implementation) project seeks to improve personalized risk assessment to allow for a cost-effective, population-based approach to risk-based screening and determine best practices for implementation in Canada. The goal of this sub-analysis was to examine how effective the annual screening of women with dense breasts is at identifying women at high risk.

Methods: Women aged 50-69 years recruited as part of the PERSPECTIVE I&I study and undergoing screening in the OBSP were included in the current analysis (N=2,071). Ten-year breast cancer risk estimates were generated using BOADICEA and included the polygenic risk score (PRS). Women were classified as average, higher than average or high risk based on age-specific thresholds. The distribution of estimated risk in women screened annually due to a family history or dense breasts was examined.

Results: Among the 200 women that were screened annually because they have dense breasts, 52% were determined to be at average risk using BOADICEA, 36% at higher than average risk, and 12% at high risk. For the 221 women screened annually because of a first-degree family history of breast or ovarian cancer, 73% were average risk, 23% at higher than average risk, and 4% at high risk. For all groups (regardless of OBSP screening recommendation), those with high estimated risk had the highest mean PRS compared to those at average or higher than average risk.

Conclusions: Most women who are being screened annually because they have dense breasts and/or a family history of cancer are at average risk of breast cancer using BOADICEA. This supports the need for multi-factorial risk prediction (i.e., BOADICEA) including more than breast density and/or family history, and including the PRS, to inform risk-based screening recommendations.

High mammographic density is associated with increased tumour-promoting immune cells in breast cancer.

Dane Cheasley[1,2], Meagan Ruppert[1]. Carolyn Nickson[3], Lisa Devereux[1,4], Pietro Procopio[3], Grant Lee[3]. Ian G Campbell[1,2]. Kara L Britt[1,2]

[1]Peter MacCallum Cancer Centre, Melbourne, Australia; [2]The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne; [3]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia; [4]Lifepool Australia, Melbourne, Victoria, Australia.

Background: Epidemiological studies have shown that high mammographic density (HMD) is a strong risk factor for breast cancer. Our previous genomic analysis revealed that low mammographic density (LMD) breast carcinomas had a significantly increased frequency of *TP53* mutations, whilst HMD carcinomas showed enrichment of tumour-infiltrating lymphocytes in the stroma. This suggested the cancer growth promoting influence of the rich stromal microenvironment of dense breasts precluding the need for mutation of this strong somatic driver gene. In the present study, we aimed to further investigate the immune cell microenvironments in breast carcinomas originating in HMD and LMD breasts.

Method: We utilised Lifepool which is an Australian prospective population-based cohort of over 54,000 women currently in a mammographic screening program. Here we identified >160 cases of invasive breast carcinoma for analysis for which pathology reports, MD data, detection modality (screen-detected/interval) and tumour tissue were available. Tumour tissue microarrays were constructed with two independent 0.6 mm cores from each FFPE tumor tissue block. Sections were stained using the OPAL multiplexed immunohistochemistry for two immune panels a general panel (incl. CD4 T cells, CD8 T cells, B cells and Dendritic cells) and a myeloid panel (incl. CD68, CD163, CD206, IRF8). Tumours were classified into quintiles and percentiles, depending on the relative MD ranking of the most recent normal mammogram prior to tumour diagnosis. Pairwise comparison p-values were calculated using a negative binomial model. Additionally whole genome sequencing (WGS) analysis was performed on 2 LMD and 2 HMD luminal breast carcinomas.

Results: Breast cancers arising in women with HMD compared to LMD had an increased age at diagnosis, interval breast cancer rate, tumour size and were more likely to have a strong family history of breast cancer. WGS mutation analysis shows divergent mutation signatures between HMD and LMD breast carcinomas. Analysis of the breast tumour immune microenvironment showed a significant increase in adaptive immune cells (B cells and CD8 T cells) in the highest quintile (n=22) compared to the lowest quintile of MD (n=35). This difference was significantly stronger when comparing percentiles of MD. Additional tumour immune microenvironment changes were observed when the data was adjusted for tumour grade and detection modality.

Conclusion: Our data indicates that somatic genetic events and immune cell microenvironment differences are observed in breast carcinomas originating in HMD and LMD breasts.

Evaluation of an automated system to assess future breast cancer risk using mammograms at screening

Celeste Damiani[1], Alexey Antonov[2], Giovanni Montana[2,3], Adam Brentnall[1], Jack Cuzick[1]

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[3] Warwick Manufacturing Group, University of Warwick, UK

Background: Yala et al have developed a breast cancer risk assessment model (MIRAI) based on digital mammograms that appears to be stronger than mammographic density. Our primary objective was to assess the strength of MIRAI to assess breast cancer risk risk in women who attend the NHS Breast Screening Program in England and have a negative screening episode.

Methods: We designed a case-control study using the OPTIMAM Mammography Image Database (OMI-DB). This includes full-field digital mammograms from women attending the English National Health Service Breast Screening Program. Cases were women with breast cancer (invasive or DCIS) detected following a routine mammography screening appointment (n=2069), or women with cancer detected in between two triannual screening rounds (interval cancers, n=709). Cases were matched 1:1 to women who attended breast cancer screening but were not found to have cancer (controls). Further matching criteria were: mammography device, site, and age at mammogram (within 1y). MIRAI was evaluated using mammograms taken at the screening round up to 3y prior to cancer diagnosis (or pseudo diagnosis). Performance was evaluated by estimating the odds ratio per standard deviation (in controls) of the natural logarithm of MIRAI absolute 3y risk, adjusted for matching factors included in the study design (aOR); and the concordance index associated with MIRA 3y risk, after adjustment for matching factors (mC). Heterogeneity was assessed using a likelihood-ratio test for interaction.

Results: Overall MIRAI was a strong predictor of risk (aOR 1.72, 95%CI 1.63-1.83; mC 0.68, 95%CI 0.66-0.70). It was slightly stronger for interval cancers (P=0.085). Further results will be presented at the meeting.

Conclusion: MIRAI is likely to be a stronger predictor of breast cancer risk in the short term than mammographic density. There is an opportunity to learn more about breast cancer risk assessment using large datasets and modern computer vision methods.

Should breast screening programs routinely collect height and weight information?

Sarah Pirikahu[1], **Ellie Darcey[1]**, Helen Lund[2], Liz Wylie[2,3], Jennifer Stone[1]*

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[3] School of Medicine, The University of Western Australia, Perth, Western Australia

Background: Despite strong associations with breast cancer risk, breast density, and screening participation, body mass index (BMI) is not routinely collected by mammographic screening programs. BreastScreen Western Australia (WA) started routinely collecting height and weight information in 2016. This study investigates the impact of asking women their height and weight on rescreening rates and, the associations of BMI with key screening outcomes within a population-based screening program.

Methods: Core screening data from 647,056 screening events for 316,057 women aged 40+ who attended BreastScreen WA between 2016 and 2021 will be examined. Descriptive statistics will be used to compare rescreening rates for women who provided height and weight at the time of mammography versus those who did not, stratified screening round. Mixed effects logistic regression will be used to investigate associations of BMI with rescreening status, recalled status, screen- and interval-detection rates, and program sensitivity, adjusting for core screening characteristics (e.g., age, screening round, English spoken at home, Aboriginal and Torres Strait Islander status, family history, and socio-demographic variables).

Results: Preliminary analysis will be presented at the meeting.

Long-term performance of an image-based short-term risk model for breast cancer

Mikael Eriksson[1], Kamila Czene[1], Per Hall[1,2]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[2]Department of Oncology, Södersjukhuset University Hospital, Karolinska Institutet, Stockholm, Sweden

Background: Image-based risk models for breast cancer have shown promising discriminatory performance compared to traditional lifestyle familial-based risk models for assessing risk in the short-term. However, long-term performance has not been reported. We assessed short-term risk at study-entry in the prospective KARMA screening cohort and investigated the discriminatory performance after 10-years of follow-up.

Methods: The study-participants attended the Swedish mammography screening program between 2010-2020, in age 40-74 at study-entry. Using a nested case-control design, we included 1,548 incident breast cancers and a random sample of 8,944 healthy women matched on year at study-entry. We assessed risk using negative screens and followed the women for breast cancer status till January 2020. Absolute 2-year risks at study-entry were reported for the image-based model in relation to an established lifestyle familial-based risk model. Area Under the receiver operating characteristic Curves (AUC) were estimated across time 1-10-years after study-entry.

Results: The AUCs of the image-based risk model ranged from 0.67-0.77 for breast cancers developed 1-10 years after study-entry. The image-based risk model AUC was 0.67 after 10-years follow-up, similar to the lifestyle familial-based risk model performance (AUC=0.67) after 1 year follow-up, p=0.89. The image-based risk model AUCs for capturing interval cancers and estrogen negative cancers were ≥0.75 up till 2 years after baseline. For capturing estrogen-positive cancer, AUCs were 0.68-0.75 after 1-10 years follow-up. The model showed similar AUCs in women with high and low mammographic density. After 10-years follow-up, 21% and 6.1% of the cancers were captured in women who were identified as high-risk at study-entry by the image-based and lifestyle familial-based model, respectively, p<0.001.

Conclusion: An image-based risk model for breast cancer has the potential to assess short-term risk for capturing women with estrogen-negative breast cancers in need of supplemental screening and long-term risk for women who could benefit from primary prevention of estrogen-positive breast cancer.

Portable Nuclear Magnetic Resonance (pNMR) Quantitative Measurement of Mammographic Density in Breast Tissues

Satcha Foongkajornkiat[1]; Kamil Sokolowski[6]; James Stephenson[7]; Thomas Lloyd[7]; Erik W. Thompson[3,4]; Honor J. Hugo[2,5]; Konstantin I. Momot[1]

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[3]Translational Research Institute, Woolloongabba, Australia
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[5]School of Medicine and Dentistry, Griffith University Sunshine Coast
[6]Preclincal Imaging Facility, Translational Research Institute, Woolloongabba, Australia
[7]Department of Diagnostic Radiology, Princess Alexandra Hospital, Woolloongabba, Australia

Background: Alternative mammographic Density (MD) assessment method was developed to estimate the MD based on nuclear magnetic resonance (NMR). Single-sided portable NMR (pNMR) is proposed for quantitative measurement of MD of breast tissues compared to the gold standard measurement.

Methods: Breast tissues from nine participating patients were assessed by measuring relative water proportion using transverse relaxation (T2), Diffusion, inversion recovery (T1), µCT, and H&E histology. Correlation and Bland-Altman analysis were used for comparison to quantify the degree of agreement between the two different methods.

Results: Quantitative MD value of T2 exhibited strong correlation with H&E (R2 = 0.94) and µCT (R2 = 0.99,) and showed a strong agreement between H&E-T2 (bias = -0.44 pp, CI = 13.13) and between µCT-T2 (bias = -2.71 pp, CI = 7.65). Diffusion exhibited strong correlation with H&E (R2 = 0.96) and µCT (R2 = 0.98) and showed a good agreement between H&E-Diffusion (bias = 2.59 pp, CI = 11.32). and between µCT-Diffusion (bias = 2.51 pp, CI = 11.86). T1 exhibited a good correlation with H&E (R2 = 0.88) and µCT (R2 = 0.87) but showed a weak agreement between H&E-T1 (bias = -0.47 pp, CI = 27.66) and µCT-T1 (bias = 7.03 pp, CI = 33.36).

Conclusion: The result presents confidence in using single-sided pNMR to assess MD in breast tissues. In particular, the measurement of T2 and Diffusion exhibits the feasibility of using pNMR for measuring MD.

To the power of BRAIx: Transforming screening with Artificial Intelligence (AI)

Helen ML Frazer[1,2]

1. St Vincent's BreastScreen, St Vincent's Hospital Melbourne, Victoria, Australia
2. BreastScreen Victoria, Victoria, Australia

Background: In Australian women, breast cancer is the most common cancer (20,000 new cases annually) and the second most common cause of cancer related deaths (3,000 deaths annually) making it a priority public health issue. The current model of breast cancer screening has challenges of accuracy, experience, and costs. While every mammogram is read by at least 2 radiologists over 35,000 Australian women annually experience a false positive and over 1,000 Australian women annually experience an interval cancer before their next screening mammogram. The BRAIx Project aims to utilise AI to make better use of mammography in a way that is more accurate, more cost-effective and reduces harms.

Methods: The BRAIx project curated a large population breast health dataset with over 1 million screening episodes each with 4 annotated images, 200 non-image variables and strong ground truths of histopathological proof of cancer or two-year screening interval history without cancer. All screening episodes from a two-year period were held out as a population testing set and all remaining screening episode were used to train convolutional neural network models and develop a standalone AI reader system.

Results: The AI reader system was applied retrospectively to the two-year population testing dataset and achieved an area under the receiver operating curve (AUROC) of 0.911 (95% CI 0.907-0.917). When set at a 5% operating point, demonstrated superior performance to the average second reader in specificity and sensitivity ($p < 0.05$, McNemar test). Simulating the AI as second reader with the current system improved current screening outcomes with fewer human reads, fewer unnecessary recalls, fewer missed cancers and a reduction in reading and assessment costs.

Conclusion: Our retrospective cohort studies show that the use of an AI reader system can improve screening outcomes within the current screening process.

Relation of pre- and post-breast cancer diagnosis measures of mammographic breast density with contralateral breast cancer risk within a general community healthcare setting

Clara Bodelon[1], Maeve Mullooly[2], Erin J. Aiello Bowles[3], Ruth M. Pfeiffer[1], Rochelle Curtis[1], Lene H. S. Veiga[1], Cody Ramin[1], Jacqueline B. Vo[1], Diana S. M. Buist[3], Heather Spencer Feigelson[4], Amy Berrington de Gonzalez[1], **Gretchen L. Gierach[1]**

[1] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA
[2] School of Population Health, Royal College of Surgeons in Ireland, Dublin, Ireland
[3] Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA
[4] Kaiser Permanente Colorado Institute for Health Research, Denver, CO, USA

Background: Elevated mammographic breast density (MBD) is an established breast cancer risk factor; less is known about the relationship of MBD and contralateral breast cancer (CBC) risk.

Methods: We conducted a nested case-control study within a retrospective cohort of 10,734 patients aged 20-85 years and diagnosed with a first primary unilateral invasive breast cancer (1990-2016) within US integrated healthcare systems (median follow-up=6.4 years). We evaluated the role of MBD in relation to CBC risk among 304 CBC cases diagnosed ≥1 year after the first (index) breast cancer and 597 controls at risk of CBC over the same time matched 2:1 on age, year, ER status, and stage of the index breast cancer. Percent(%) MBD was assessed in the contralateral breast using Cumulus at baseline (median=0.7 months before index breast cancer) and follow-up (median=11.6 months post-diagnosis). Odds ratios (ORs; 95% confidence intervals[CIs]) for the association of MBD quartiles (based on control distribution) and CBC risk were estimated from logistic regression models adjusted for matching factors, body mass index, mammogram type (film/digital), and treatment (radiotherapy, chemotherapy, endocrine therapy).

Results: Median time between index breast cancer and CBC diagnoses was 7.1 years. Baseline %MBD was associated with increased CBC risk ($OR_{Q4vs.Q1}$=1.67, 95%CI=0.97-2.85; p-trend=0.045). Post-diagnosis %MBD was associated with over a 2-fold increased CBC risk ($OR_{Q4vs.Q1}$=2.42, 95%CI=1.46-4.01; p-trend<0.001); increased risk persisted for MBD ascertained closer in time (median=3.5 months) to CBC diagnosis and for patients whose index breast cancer was ER-positive. Elevated %MBD pre- and post-diagnosis was significantly associated with increased risk of CBC of a higher stage (II-IV) and grade (3/4). Analyses evaluating associations between serial MBD changes and CBC risk accounting for mammogram type and clinical/patient characteristics over follow-up are ongoing.

Conclusion: Our findings suggest the importance of both pre- and post-diagnosis MBD measures for CBC risk assessment among breast cancer survivors.

Individualised prevention and screening of breast cancer: The Karma experience

Per Hall[1], Mikael Eriksson[2]

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Background: In order for individualised prevention and screening of breast cancer to be efficient, the individual risk of breast cancer has to be correctly assessed. The use of artificial intelligence (AI) in breast cancer screening has recently received attention. Tools for detection and risk prediction of breast cancer have been developed. Broadly AI based models are used for pre-screen, decision support and post-screen. Over the years a number of breast cancer risk models have been developed. Most models are based on established risk factors and identifies a 5-, 10-year or lifetime risk. Image derived, AI based risk models have gained interest and sometimes also include established risk factors and genetic determinants of breast cancer.

Options for high-risk women ranges from supplemental examinations, more intensified screening and preventive measures. Tamoxifen is one of the risk reducing medications that has proven to lower the incidence of breast cancer. Uptake is however low due to side effects. Efforts have been taken to increase uptake. The advantage of tamoxifen is that it does not only lower the incident of breast cancer but also decreases mammographic density and thereby increases the sensitivity of a mammogram. Mammographic density has shown to be a good proxy for therapy response.

Conclusion: During my presentation I will discuss how image derived, AI based tools could be used in the breast cancer screening setting. I will discuss the advantage of short-term risk models and what risk factors that should to be included. Further, I will discuss the risk cut offs used today and suggest alternatives. Lastly, I will touch on what we are planning to do the coming years when it comes to targeted primary and secondary prevention.

Artificial Intelligence, detecting breast cancers, and short-term risk of breast cancer

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Background: Artificial intelligence (AI), such as agnostic learning using convolutional neural networks, is being applied to help radiologists detect breast cancers on mammographic images by comparing affected breasts with unaffected breasts. Studies to predict breast cancer risk from mammographic images use only the unaffected breasts of affected women. We sought to determine the ability of an AI cancer detection algorithm to predict breast cancer risk in the short-term (at or before their next regular screen) using the BRAIx study.

Methods: We studied 629,864 women attending BreastScreen Victoria from 2013-2019. A random 20% cohort of 94,786 women from 2016 and 2017 attendees (95,006 screening episodes) was used for testing. From the remaining, 159,740 images from 107,057 episodes and 101,786 women screened using Hologic, Siemens and Phillips machines were used for training. We also studied an age-matched set of 5,779 screen-detected cases and 46,505 controls screened using Hologic, Siemens and Fuji machines from which a random 10% sample of women was used for testing. We created two detection algorithms using DenseNet201, ResNet152V2, Xception, and InceptionV3.

Results: The areas under the receiver operating characteristic curve were about 0.65 for each AI detection algorithm when tested on its corresponding random testing set. We will present detailed analyses and address how these algorithms combine with other mammogram-based risk predicting algorithms including conventional mammographic density and other questionnaire-based risk factors.

Conclusion: AI algorithms to detect breast cancers provide information on future risk, though some published studies overestimate performance because they included the affected image in their testing sets. Use of these algorithms in practice will reveal a subset of women considered cancer free at screening but at substantial increased risk of breast cancer in the short term who will need to be informed of this risk and given appropriate advice. This will have substantial consequences for implementation.

Together Alone: Going Online during COVID-19 Is Changing Scientific Conferences

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Background: The COVID-19 pandemic caused many scientific conferences to move online, posing a great challenge for scientific communication. This change offers potential advantages and disadvantages for inclusion, diversity, and scientific advancement.

Methods: Here, we analyse participants' experiences of the Why Study Mammographic Density? Conference to explore some of these issues and identify key points of contention between different stakeholders.

Results: We found that while increasing participant diversity is facilitated by online conferencing, if the participants cannot interact informally with each other, there is value which is lost.

Conclusion: In returning to in-person conferences, it will be important not to "shut the door" on those whose participation was enabled by the online format.

The effect of Rho-kinase inhibition on mammographic density

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Background: High Mammographic Density is characterized by an increase in fibroglandular tissue. It therefore presents as an environment of increased stiffness, placing mammary epithelial cells under pressure. Rho-kinase is at the nexus of cellular mechanosensing, translating pressure into proliferation. We hypothesized that this signaling pathway, dependent upon rho-kinase activity, is important for the maintenance of mammographic density .

Methods: We studied the effect of the specific rho-kinase inhibitor Y27632 in modulating MD using a patient-derived explant (PDE) model of normal human mammary tissue. Baseline MD of explant tissue from women with high BiRADs (Breast Imaging and Database System) density (category C or D) was determined using single-sided NMR. These explants were then cultured for 7 days in which surrounding media was replenished with increasing concentrations of inhibitor. At endpoint, NMR readings for MD were again taken, so that MD change due to treatments could be calculated. Tissue pieces were then sectioned and half fixed for FFPE / IHC (ki67), Masson's Trichrome and other measures of tissue density, and the other half for gene expression analyses.

Results: MD was reduced by Y27632, a change which appeared to correlate with measures of cellular (glandular) density and proliferation.

Conclusion: Rho-kinase activity may be necessary for MD maintenance in vivo, thus providing a novel therapeutic target in the reduction of MD to improve cancer detection and treatment.

Quantitative Visualization of Healthy vs. Risky Mammographic Breast Density

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Background: Mammographic percent density (MPD) is a strong breast cancer risk factor [1]. However, not all women with dense breasts develop cancer. In an algorithmic implementation of a patented computational technology [2], we have found a subset of mammographic dense tissue that is associated with breast cancer [3, 4]. Therefore, we propose that mammographic dense tissue could be categorized as **healthy dense tissue vs. risky dense tissue**. Our results were thus far based on statistical analyses of quantitative metrics associated with mammogram image subregions. Now we propose to integrate a visual part to provide radiologists with a quantitative visualization of healthy vs. risky breast density.

Methods: Standard bilateral mammographic views are divided into thousands of small overlapping subimages. Each subimage is analyzed using a wavelet-based multifractal method to quantify the spatial structure of the subimage via the Hurst exponent [3], which is used to classify areas of fatty, healthy dense, or risky dense breast tissue. A color-coded overlay is constructed and merged with the original mammogram: Red (risky dense), Yellow (healthy dense) and Blue (fatty). By construction, these color pixel values are proportional to the number of overlapping subregions associated with each point in the mammogram.

Results: Our calculation of mammographic percent density correlates with ACR-BIRADS scores (n=745 screening mammography visits, Spearman's test: p<10-16). Moreover, the amount of risky density at a patient's first digital screening mammogram is significantly different for patients who eventually developed cancer within 7-10 years (n=47) vs. controls who remained cancer-free during the same period (n=27) (2-sample Wilcoxon test: p=0.006). These preliminary results suggest we can create the overlays that visually highlight healthy vs. risky density in mammographic breast tissue.

Conclusion: This technology can provide radiologists with a tool to visually track the temporal and spatial distribution of healthy vs. risky density.

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Mammographic density in relation to breast cancer risk factors among Chinese women

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Background: Higher mammographic density (MD) is a risk factor for breast cancer (BC), however, determinants of MD remain unclear in Asian populations, where MD is higher, but BC incidences are lower compared with Western populations. The goal of this work was to investigate associations of established BC risk factors with quantitatively measured MD in an unscreened Asian population.

Methods: The study population included 7,351 Chinese women, who had mammograms at a cancer hospital in-Beijing, China, who had non-malignant image findings (BI-RADS classifications of $1_{n=2,293}$, $2_{n=3,519}$, and $3_{n=1,539}$). VolparaDensity software was used to obtain quantitative MD measures, which were associated with risk factors in multivariable linear regression models with adjustments of age, body mass index (BMI), age at menarche, parity, and menopausal status.

Results: The mean age and BMI of this study population were 50.1(SD=8.3) years old and 24.0(SD=3.5) kg/m^2, respectively; the mean dense volume (DV) and percent density (PD) were 58.4 (32.1) cm^3 and 14.8(7.1) %, respectively. Density distributions and their associations with risk factors were similar across BI-RADS diagnostic classifications and we therefore combined these classes in the analysis. We found that DV and PD showed similar negative associations with increasing age and parity but positive associations with older age at menopause. On the other hand, longer breastfeeding duration showed negative association with only PD but not DV, and older age at menarche showed a strong negative association with non-dense volume (NDV) only. Interestingly, increasing BMI was positively associated with DV, but inversely associated with PD. However, when we further adjusted for total breast volume, the association with DV changed direction, suggesting that NDV may have confounded the DV-BMI association.

Conclusion: Generally, observed BC risk factor associations with quantitative MD in this Chinese population were overall similar to those previously reported in Western women.

Alternative methods to measure breast density in younger women

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Background: Breast density is a strong and potentially modifiable breast cancer risk factor. Almost everything we know about breast density has been derived from mammography, and therefore, very little is known about breast density in younger women aged <40, in whom screening mammography is not typically recommended. This study compares the acceptability and viability of two alternative breast density measures, Optical Breast Spectroscopy (OBS) and Dual X-ray Absorptiometry (DXA), in women aged 18-40 years.

Methods: Breast tissue composition (percent water, lipid, and collagen content) was measured in 539 women aged between 18-40 years using OBS and for a subset of 169 women, percent fibroglandular dense volume (%FGV), absolute dense volume (FGV), and non-dense volume (NFGV) was measured using DXA. The acceptability of OBS and DXA as tools to measure breast density was assessed using a validated questionnaire adapted for this study. Their viability as breast density measures was assessed by examining correlation and agreement between the measures, and their associations with known determinants of mammographic breast density.

Results: Over 93% of participants deemed OBS and DXA to be acceptable methods of measuring breast density. The correlation between OBS-%water and %FGV was 0.45 but varied significantly by breast cup size. Agreement between the measures was fair, but only after dichotomizing each measure into high/low density. Age and BMI were inversely associated with OBS-%water and %FGV and positively associated with OBS-%lipid and NFGV.

Conclusion: In the absence of a "gold standard" for comparing measures of breast density that are safe for younger women (aged<40) and predict breast cancer risk, this study provides evidence supporting OBS and DXA as acceptable and viable alternative methods. It informs future research investigating the utility of measuring breast density in younger women to identify and target those at increased risk of breast cancer later in life.

Genome-wide association study identifies common variants associated with mammographic density in Asian women

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Background: Mammographic density (MD), after accounting for age and BMI, is a strong heritable risk factor of breast cancer. Hitherto, 55 independent MD-associated loci have been identified from genome-wide association studies (GWASs), all of which have been conducted on women of European ancestry.

Methods: To identify novel loci, we conducted GWASs of MD phenotypes, adjusting for age, BMI and ancestry informative principal components, in a multi-ethnic cohort of Asian women, using STRATUS (N=2,450) and Volpara™ (N=2,257) for area and volumetric densities respectively. We determined whether top hits were associated with MD in 27,900 women of European ancestry, and with breast cancer risk in Asian women within the iCOGS (6,269 cases, 6,624 controls) and OncoArray (7,799 cases, 6,480 controls) GWASs in the Breast Cancer Association Consortium (BCAC) database.

Results: At $p<5x10^{-6}$ in either STRATUS or Volpara analyses, 176 novel loci were associated with at least one MD phenotype in Asian women. Of these, 84 were evaluable in European women (MAF>1%) and one novel variant was associated with MD at the Bonferroni corrected *p* value threshold (z=3.71, $p=2.1x10^{-4}$), and six variants with nominally significant associations ($p<0.05$). Of the 176 loci, we found 20 variants associated at nominal significance ($p<0.05$) with breast cancer risk in Asian women, one of which was the abovementioned novel variant that was also associated with MD in women of European ancestry.

Conclusion: More than 50% of the MD-associated SNPs in this study were monoallelic or had extremely low allelic frequencies in the European population and require replication in an independent Asian study. This study confirms the shared heritability between MD and breast cancer risk in women of Asian ancestry and reports the identification of a novel locus that may be associated with both mammographic density and breast cancer risk.

Portable Nuclear Magnetic Resonance for quantification of breast density *in vivo*: Proof-of-concept measurements and comparison with quantitative MRI

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Background: Mammographic Density (MD) is the degree of radio-opacity of the breast in an X-ray mammogram. It is determined by the Fibroglandular:Adipose tissue ratio. MD has major implications in breast cancer risk and breast cancer chemoprevention. This study aimed to investigate the feasibility of accurate, low-cost quantification of MD in vivo without ionising radiation.

Methods: We used single-sided portable nuclear magnetic resonance ("Portable NMR") due to its low cost and the absence of radiation-related safety concerns. Fifteen (N=15) healthy female volunteers were selected for the study and underwent an imaging routine consisting of 2D X-ray mammography, quantitative breast 3T MRI (Dixon and T_1-based 3D compositional breast imaging), and 1D compositional depth profiling of the right breast using Portable NMR. For each participant, all the measurements were made within 3-4 hours of each other. MRI-determined tissue water content was used as the MD-equivalent quantity. Portable NMR depth profiles of tissue water were compared with the reference standard – equivalent depth profiles reconstructed from Dixon and T_1-based MR images.

Results: The agreement between the depth profiles acquired using Portable NMR and the reconstructed reference-standard profiles was variable but overall encouraging. The agreement was somewhat inferior to that seen in breast tissue explant measurements conducted in vitro, where quantitative micro-CT was used as the reference standard. The lower agreement in vivo can be attributed to an uncertainty in the positioning of the Portable NMR sensor on the breast surface and breast compression in Portable NMR measurements.

Conclusion: The degree of agreement between Portable NMR and quantitative MRI is encouraging. While the results call for further development of quantitative Portable NMR, they demonstrate the in-principle feasibility of Portable NMR-based quantitative compositional imaging in vivo and show promise for the development of safe and low-cost protocols for quantification of MD suitable for clinical applications.

Associations of breast cancer risk factors with volumetric breast density measures defined at increasing thresholds among women undergoing image-guided breast biopsy: preliminary results

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Background: Recent evidence suggests breast density (BD) determined at higher thresholds may improve breast cancer risk prediction. We examined strengths of risk factor associations with standard volumetric BD (VBD) measures and thresholds based on varying pixel-level VBD percent or fibroglandular tissue (FGT) thicknesses.

Methods: VBD was estimated from raw full-field digital mammographic images of breasts contralateral to a clinically-indicated biopsy using TruDensity™ (Volpara Health Technologies;($VBD\%_{VOLPARA}$)) for 785 women aged 40-65 years at the University of Vermont Medical Center. $VBD\%_{VOLPARA}$ was recalculated from Volpara density maps after applying pixel-level thresholds of 5, 15 and 25% based on VBD% ($VBD\%_{VOLPARA\_5\%}$, $VBD\%_{VOLPARA\_15\%}$, $VBD\%_{VOLPARA\_25\%}$), or 5, 10 and 15mm based on FGT ($VBD\%_{VOLPARA\_5mm}$, $VBD\%_{VOLPARA\_10mm}$, $VBD\%_{VOLPARA\_15mm}$). Pixels below these thresholds were considered to have no FGT. Linear regression models examined associations between breast cancer risk factors and square-root transformed VBD% measures, adjusted for age and body mass index (BMI).

Results: Mean age was 50.9 (SD=6.9) years and BMI was 26.3 (SD=6.2) kg/m^2. Biopsy diagnoses included: benign/non-proliferative (33.6%), proliferative without (38.1%) and with atypia (6%), in situ (8.7%) and invasive breast cancer (13.6%). Mean $VBD\%_{VOLPARA}$ was 11.5% (SD=7.7). In general, similar patterns of association were observed for age, BMI, age at first birth, menopausal status and family history, with $VBD\%_{VOLPARA}$ and thresholded measures in expected directions. However, as thresholds increased, magnitudes of associations also tended to increase. For example, compared with non-proliferative diagnoses, those with proliferative disease with atypia had elevated $VBD\%_{VOLPARA}$ ($VBD\%_{VOLPARA}$: β=0.51, standard error [SE]=0.13), with somewhat stronger associations as VBD% thresholds increased ($VBD\%_{VOLPARA\_5\%}$: β=0.62, SE=0.16; $VBD\%_{VOLPARA\_15\%}$: β=0.83, SE=0.22; $VBD\%_{VOLPARA\_25\%}$: β=0.94, SE=0.25; all p<0.0001), and as FGT thresholds increased ($VBD\%_{VOLPARA\_5mm}$: β=0.69, SE=0.19; $VBD\%_{VOLPARA\_10mm}$: β=0.80, SE=0.23; $VBD\%_{VOLPARA\_15mm}$: β=0.82, SE=0.25).

Conclusion: Preliminary findings of risk factor associations with thresholded VBD% measures suggest their potential for better extracting information contained in mammograms for understanding breast cancer aetiology.

An Artificial Intelligence–based Mammography Screening Protocol for Breast Cancer: Outcome and Radiologist Workload

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Background: We investigate whether an AI system could detect normal, moderate-risk, and suspicious mammograms in a screening sample to safely reduce radiologist workload and evaluate across Breast Imaging Reporting and Data System (BI-RADS) densities.

Methods: We simulate in a retrospective cohort of 114421 screened women the effect on detection of cancer if the radiologists were replaced by an AI for those that the AI judge to have low risk of cancer.

Results: The outcome is non-inferior to the current screening program which a substantial reduction in radiologist workload.

Conclusion: This study has lead to a change in the Capitol Region Breast Cancer Screening Program. We comment on the introduction of new screening helped by AI.

Application of the *Deep-Risk* digital mammogram risk scores to predict young and familial breast cancer using digitised mammograms

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Background: Deep-Risk mammogram risk scores have been developed by applying Deep-Learning to digital images from the Measurement Challenge. We study their risk prediction of breast cancer diagnosed at younger ages and over sample of family history using digitised mammograms.

Methods: We conducted a family-based case-control study of 354 cases with on average age of diagnosis 48 years and 944 controls frequency matched for age at mammogram and family history. We measured the age and body mass index adjusted risk measures Altocumulus, Cirrocumulus, Cirrus, DeepRisk1, DeepRisk2 and conventional mammographic density (Cumulus).

Results: Cumulus was moderately correlated (r=0.4 to 0.7) with all measures except DeepRisk1. We estimated the odds ratio per standard deviation of a measure for controls after adjusting for age and body mass index (OR) using logistic regression. The univariable OR (95% confidence interval) estimates were: 1.50 (1.25 to 1.81), 1.73 (1.27 to 2.37), 1.71 (1.50 to 1.95), 1.90 (1.38 to 2.61), 1.42 (1.20 to 1.69), 1.98 (1.63 to 2.40), for Cumulus, Altocumulus, Cirrocumulus, Cirrus, DeepRisk1 and DeepRisk2, respectively. When fitted together, the corresponding estimates were: 0.79 (0.61 to 1.03), 1.23 (0.87 to 1.72), 1.40 (1.15 to 1.69), 1.52 (1.12 to 2.06), 1.20 (1.05 to 1.38) and 1.46 (1.31 to 1.62). For the best-fitting combination of all mammogram-based measures, the OPERA was 2.35 (2.33 to 2.38) which, on the log scale, is twice the risk gradient of the latest polygenic risk score. All the new measures were positively associated with risk before and after adjusting for the other measures. Cumulus, however, was positively associated when fitted alone but negatively associated after adjusting for the new measures.

Conclusion: We conclude that the positive crude risk association of conventional mammographic density is due in part to it being correlated with multiple different and causal aspects of mammograms.

Mechanosensitive hormone signaling promotes mammary progenitor expansion and breast cancer progression

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Background: Tissue stem-progenitor cell frequency has been implicated in tumor risk and progression. Tissue-specific factors linking stem-progenitor cell frequency to cancer risk and progression remain ill defined.

Methods: Using a genetically engineered mouse model that promotes integrin mechanosignaling with syngeneic manipulations, spheroid models, and patient-derived xenografts we determined that a stiff extracellular matrix and high integrin mechanosignaling increase stem-progenitor cell frequency to enhance breast tumor risk and progression.

Results: Studies revealed that high integrin-mechanosignaling expands breast epithelial stem-progenitor cell number by potentiating progesterone receptor-dependent RANK signaling. Consistently, we observed that the stiff breast tissue from women with high mammographic density, who exhibit an increased lifetime risk for breast cancer, also have elevated RANK signaling and a high frequency of stem-progenitor epithelial cells.

Conclusion: The findings link tissue fibrosis and integrin mechanosignaling to stem-progenitor cell frequency and causally implicate hormone signaling in this phenotype. Accordingly, inhibiting RANK signaling could temper the tumor promoting impact of fibrosis on breast cancer and reduce the elevated breast cancer risk exhibited by women with high mammographic density.

Reproductive factors and mammographic breast density: A cross-sectional study using data from the International Consortium of Mammographic Density

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Background: Elevated mammographic density (MD) is an established breast cancer risk factor. Reproductive factors, including higher parity and younger age at first birth are associated with reduced risk of breast cancer but their relationship with MD across diverse populations are less clear. We examined the associations of these factors with MD measures within the International Consortium of Mammographic Density (ICMD).

Methods: ICMD is an international consortium of MD studies with pooled individual-level epidemiological and MD data from 11,755 women without breast cancer aged 35-85 years from 22 countries. MD was centrally measured using the semi-automated area based tool Cumulus. Population-specific meta-analyses and linear regression models were used to examine associations of square-root transformed percent mammographic density (PMD) with parity status and age at first birth across population groups. Models were adjusted for body mass index, age, menopausal status, ever use of hormone replacement therapy, mammogram view, image type, and MD reader.

Results: For the ICMD sample, 90.1% women were parous, with 12% of these women having 5 or more births. Mean age at first birth was 24.3 years (standard deviation 5.1 years) across the studies. An inverse association was observed between √PMD and increasing parity (√PMD per birth: -0.06 (95% CI: -0.08, -0.05; I^2 = 0%). Among parous women, there was an increase in √PMD per 5-year increase in age at first birth (√PD: 0.06 (95% CI: 0.03, 0.09; I^2 = 19.1%).

Conclusion: Preliminary findings from the population-specific meta-analyses demonstrate small but consistent associations, which support the established inverse relationship between increasing parity and PMD and the positive association between increasing age at first birth with PMD. Ongoing analyses will also examine associations with absolute measures, including dense area and non-dense area. Further pooled analyses will explore associations between other reproductive factors such as breastfeeding and all three mammographic measures.

Comparing radiomic analysis and deep learning for breast cancer risk assessment based on the computerized analysis of mammographic images

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Background: Radiomic analysis aims at the extraction of high throughput computerized texture descriptors from radiological images. Radiomic features extracted from mammography images have shown a possitive association with breast cancer risk which is independent to known risk factors. However, more recently, the computerized analysis of mammographic images using Deep Learning (DL) methods has shown promising results for breast cancer risk assessment. In this talk, we are interested in comparing the differences of these two approaches for breast cancer risk assessment.

Results: For this purpose, we conduct a pilot study following a retrospective case-control design and collect 1144 mammograms corresponding to 143 women diagnosed with breast cancer and 143 healthy controls matched by age and mammographic system. We compare and discuss the performance of radiomic-based and DL-based mammographic analysis in terms of their OPERA for the task of breast cancer risk assessment.

Understanding the genetic basis of mammographic density phenotypes

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Background: Mammographic density (MD) phenotypes are highly heritable and strongly associated with breast cancer risk. Genetic variants identified by genome-wide association studies (GWAS) explain only a small fraction of the heritability, and the responsible genes remain largely unknown. Transcriptome-wide association studies (TWAS) can improve the power of GWAS and identify genes associated with MD through their genetically regulated expression levels.

Methods: The study population included 24,158 women of European ancestry who underwent screening with Hologic (n=20,282) or GE (n=3,876) digital mammography and participated in the Research Program on Genes Environment and Health (RPGEH) at Kaiser Permanente. Dense area (DA), nondense area (NDA), and percent density (PD) were measured centrally using Cumulus6. Gene expression was estimated using PrediXcan models for mammary tissue, fibroblast cells, subcutaneous and visceral adipose tissues, and assessed for their associations with MD in linear regression models adjusted for age, BMI and other covariates. Tissue-specific results were combined, and genes that were significant at a false-discovery rate of 0.05 were carried forward for replication ($p<0.05$) in an independent GWAS of MD in up to 27,900 European ancestry women.

Results: In the discovery sample, 58 genes in 36 distinct regions were associated with MD. In the replication sample, a subset of 32 genes in 21 regions was associated with MD, including 8 novel genes in 7 regions. *LRRC17*, *PPP2R3A*, and *TNFSF12* were novel genes for DA. *KCNN4*, *NKX6-1*, *MYEOV* and *RP11-211G23.2* (both at 11q13.3) were novel genes for NDA. *SNX16* was a novel gene for PD. Among the replicated MD genes, 17 genes in 12 regions also were associated with breast cancer risk.

Conclusion: This TWAS identified novel genes for MD and breast cancer risk, and prioritized genes at known GWAS loci that are likely to be causally associated with MD phenotypes through their expression levels.

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The Added Value of Supplemental Breast Ultrasound Screening for Women with Dense Breasts: A Single Centre Canadian Experience

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Background: Individuals with dense breast tissue are at an increased risk of breast cancer which may not be detected on mammographic screening. Ultrasound examination in this population has been shown to improve cancer detection rates with publicly insured supplemental ultrasound screening introduced in 2019 in British Columbia, Canada. The purpose of this study was to evaluate the contribution to cancer detection of supplemental breast ultrasound screening in women with dense breasts based on a single centre experience by comparing our results with similar programs elsewhere.

Methods: We performed a retrospective review of handheld sonographer-performed screening ultrasound exams at our academic breast imaging center, from January 1st to December 31st, 2019. Breast density, breast cancer risk factors, BI-RADS assessment, and lesion pathology were reviewed and tallied, followed by derivation of the biopsy rate, breast cancer detection rate, PPV3 and average tumor size. These values were compared to published results of breast screening programs elsewhere.

Results: 695 screening breast ultrasounds for women with dense breasts and negative mammograms were performed in 2019. The biopsy rate was 1.3%, breast cancer detection rate was 7 in 1000, PPV3 was 42%, and the average tumor size was 9.0 ± 1.4 mm.

Conclusion: The first-year data of the breast screening ultrasound program at our practice are promising, demonstrating comparable cancer detection rate, higher PPV3, and similar biopsy rate in those with dense breasts compared with similar programs elsewhere. Longitudinal analysis and larger sample size are required for validation. Comparison of incidence and prevalence screening data is also warranted to elucidate the true value of this program.

The distribution of breast density in women aged 18-97 using optical breast spectroscopy

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Background: Age and body mass index (BMI) are critical considerations when assessing individual breast cancer risk for women notified of their breast density. However, age- and BMI-standardized estimates of breast density are not currently available for screen-aged women and very little is known about the distribution of breast density in women aged <40, who are not recommended mammographic screening. This study employs three different modalities: Optical Breast Spectroscopy (OBS), Dual Energy X-Ray Absorptiometry (DXA) and mammography, to describe and compare the distribution of breast density for adult women across categories of age and BMI.

Methods: Breast density measures estimated using OBS (percent (%) water) and DXA (percent and absolute fibroglandular dense volume (%FGV and FGV, respectively)) from 1961 women were combined with mammographic measures (percent and absolute dense area (%DA and DA, respectively) from 354 women, to describe their distributions by 10-year age-categories and by clinically-defined categories of BMI.

Results: Women were aged between 18 and 97 years with a mean of 38.35 (SD=15). Median breast density measures decrease with age and BMI for all three modalities, except perhaps for DXA-FGV which increased with BMI and only decreased with age after age 30. Similarly, the variation in the breast density measures were largest for younger women and decreased with increasing age and BMI.

Conclusion: This unique study describes, for the first time, the distribution of breast density measures for adult women aged 18-97 using both alternative and conventional breast density measuring methods. The age- and BMI-categorised distributions enable individual comparison of breast density to other women of similar age or BMI. In future, the goal is to provide clinically useful, age-standardized measures of breast density that can be obtained safely and easily to inform breast cancer risk assessment at any age or BMI.

Changes in mammographic density and texture associated with high-dose vitamin D supplementation

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Background: Experimental studies have shown anti-carcinogenic properties of vitamin D. However, population-based studies, limited to lower doses of vitamin D, have not demonstrated strong inverse associations. We tested the hypothesis that women taking high dose vitamin D_3 supplementation will have greater decreases in (i) percent mammographic density (PMD) and (ii) V (i.e., gray-scale pixel variation) compared with women randomized to placebo.

Methods: As part of an ancillary study to the VITamin D and OmegA-3 TriaL (*VITAL*) trial, we collected digital mammograms from women randomized to high dose vitamin D_3 (2,000 IU/day) supplementation (n = 1317) or placebo (n = 1280) arms. Mammograms were collected prior to randomization, and at 1, 3, and 4 year(s) post randomization. Automated PMD and V were determined using validated algorithms. Measurements are standardized to the distribution of baseline Hologic images. An intention-to-treat analysis of linear mixed-effects models was used to estimate the percent (%) changes in PMD and V from baseline to year 4 post-randomization adjusted for baseline age, BMI, and omega-3 randomization status.

Results: The mean age in both study arms was 64 years of age; 27% self-reported their race as Black and 71% White. Both arms experienced significant declines in PMD and V from baseline to year 4. For PMD, the vitamin D arm had a 19.4% decline and placebo arm had a 19.5% decline (p=0.99). For V, the vitamin D arm had a 6.1% decline compared with placebo arm's 4.2% decline (p=0.19). There was a marginally significant p-trend in net effect of vitamin D_3 over time for V (p=0.09).

Conclusion: Overall, the randomization of high dose vitamin D_3 did not have a significant effect on PMD compared with placebo. There was suggestive evidence that high dose vitamin D_3 may have a stronger impact on V compared with placebo.

Bright – The new white in mammographic density-associated breast cancer risk

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Background: Mammographic density (MD), the area of whiteness on a mammogram, is a well established risk factor for breast cancer, and we and others have confirmed that this is largely due to the amount of fibroglandular tissue present in the breast. Since breasts of low mammographic density contain a ductal tree, the fibrous stromal tissue is likely the main contributor to the MD differential. MD also impedes the efficiency of mammographic screening for breast cancer, resulting in higher rates of interval cancers – cancers arising after a clear mammogram – in women with higher MD. Recently, Nguyen, Hopper and colleagues found that whole overall MD levels (total MD) associated more closely with interval cancers / masking, the regions of higher 'brightness' on the mammogram associated best with breast cancer risk (1). We undertook this study to identify the tissue structures associated with these regions of highest density.

Methods: With ethics approval, material from prophylactic risk-reduction mastectomy that was surplus to pathology needs was subjected to slice mammography after overlaying with chicken wire to allow easy localisation of regions of low, medium and high MD (n=9). These were excised and subjected to MD analysis (%water content) using the single-sided NMR Mouse (portable MRI; Magritek, Wellington, New Zealand (2)) at 0.8 and 1.8 mm depth, and corresponding histological assessment. Two of the cases were also subjected to micro-CT analysis (10 uM resolution) and serially sectioned at 100 uM intervals, including 0.8 and 1.8 mm.

Results: Strong concordance was seen between the proportion of fibroglandular tissue determined histologically and the % water as determined by NMR Mouse. Regions of enhanced brightness after segmentation of the micro-CT data were consistent with fibroglandular tissue in corresponding histological sections.

Conclusion: The MR Mouse and CT could provide non-invasive higher resolution images of tissue structures associated with the higher brightness seen on mammograms, and may help resolve the relationship between highest levels of MD and breast cancer risk.

Notes: