9th International Breast Density & Cancer Risk Assessment Workshop

June 5-7, 2019 • Prince Waikīkī | Oʻahu, HI

www.ibdw2019.com

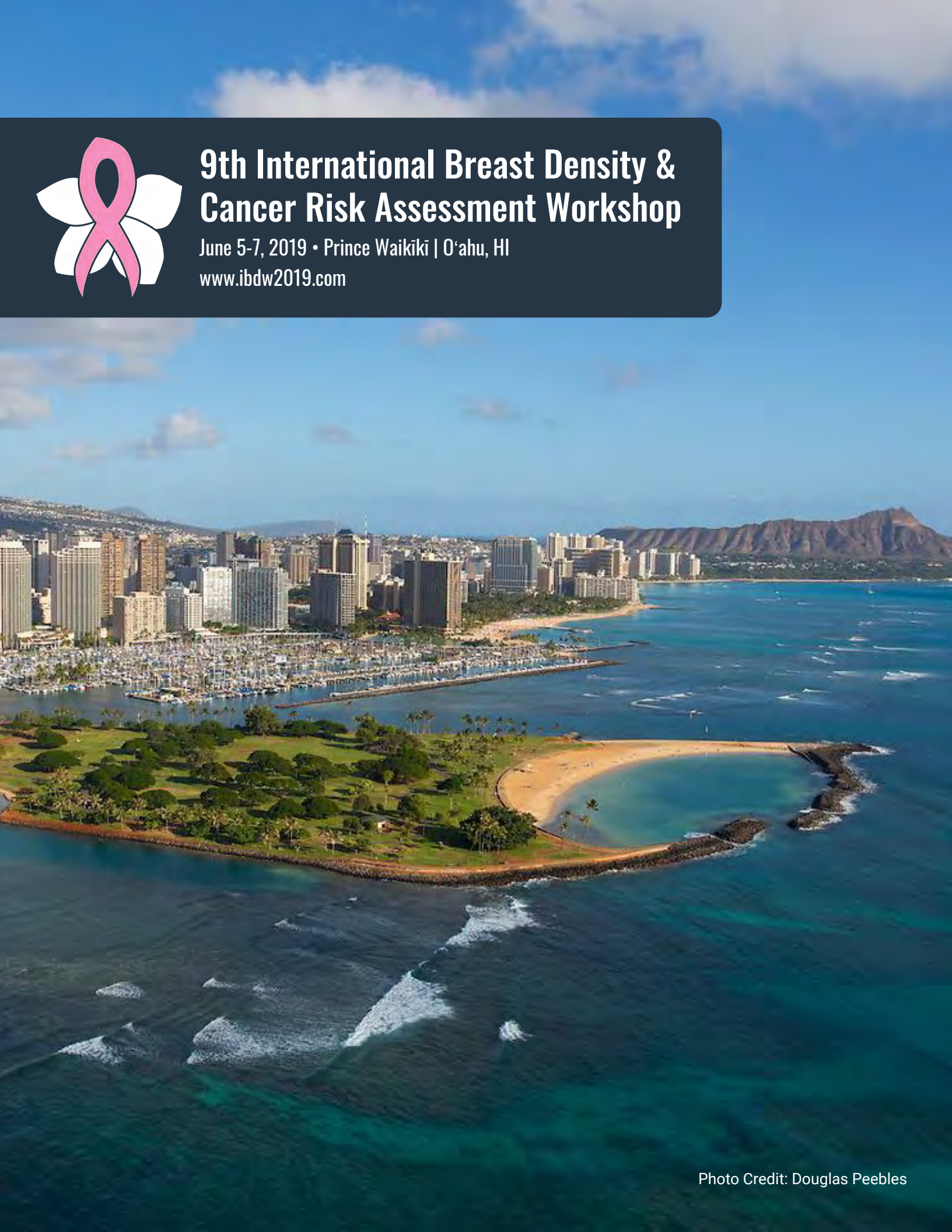

Photo Credit: Douglas Peebles

ABOUT OUR HOSTS

University of Hawai‘i Cancer Center

The University of Hawai‘i Cancer Center (UHCC) is the only National Cancer Institute-designated cancer center in Hawai‘i and the Pacific. The Center's mission is to reduce the burden of cancer through research, education, patient care and community outreach with an emphasis on the unique ethnic, cultural and environmental characteristics of Hawai‘i and the Pacific.

It is a state of the art facility that has the ability to attract the best scientists to research cancer, conducting both population-based and laboratory-based research. Their work is unique because they research how cancer affects people with different ethnic, cultural and environmental characteristics. Since Hawai‘i has one of the most diverse populations in the world, it's an ideal place to study why some ethnic populations are more susceptible to certain cancers and how genetic susceptibility interacts with environmental factors in producing cancer risk.

CPMC Research Institute - Sutter Health

From physician offices to hospitals, to outpatient care centers and home services, Sutter Health proudly supports the more than 3 million people in our care—nearly 1 percent of the U.S. population, in one of the most diverse and innovative regions in the world. Sutter Health is more than 60,000 people strong thanks to its integrated network of physicians, employees and volunteers. Rooted in Sutter Health’s not-for-profit mission, these team members partner to deliver exceptional care that feels personal. Sutter team members adopt new technologies, make novel discoveries and embrace creative thinking to help patients and communities achieve their best health. From its street nurse program that provides check-ups for homeless people, to telemedicine-aided specialist consultations, to walk-in care clinics, to smart glass technology, the Sutter Health team goes beyond traditional models to make care more convenient and to nurture and empower people throughout their medical journey.

Workshop Overview


2002 Breast Density Workshop

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 over 37 states, including Hawai‘i, requires reporting of breast density to women with dense breasts undergoing mammography. Recently, the Food and Drug Administration proposed updating the Mammography Quality Standards Act requiring mammography reports to healthcare providers and women include information informing women whether their breast density is high or low.

The International Breast Density & Cancer Risk Assessment Workshop has been held biennially since 2002 in San Francisco, CA. This is the first year in Hawai‘i hosted by the University of Hawai‘i Cancer Center. I relocated here in 2018 to join the efforts of many others at the Cancer Center to reduce the burden of cancer in the Pacific. I and my co-chairs, Karla Kerlikowske (UC San Francisco) and Steve Cummunigs (Sutter Health) welcome you to the 9th Workshop.

In this workshop, we will explore all aspects of the evolving story of breast cancer risk factors derived from mammography and how these radiomic biomarkers add to clinical risk factors to determine overall risk of breast cancer. On day one, we will survey what is known and is clinically useful to those on the front line of patient care. On day two, we will go deep into the biology of breast density and novel methods of deriving risk information from imaging. On the last day, we will bring it all together by combining what is known about integrating imaging risk factors with clinical risk factors.

Lastly, I hope you take the opportunity to get to know Hawai‘i on your visit. Visit the Cancer Center, meet our advocates, and most importantly discover why Hawai‘i is an ideal location for this meeting. Our need is great, our people are diverse and representative of virtually all continents. Hawai‘i wants to get to know you and I hope you reach out and get to know us.

Mahalo, John Shepherd - for the Chairs of the Workshop


2017 Breast Density Workshop

Our Sponsors

This workshop would not have been possible without financial support from our industry and academic partners. Please thank them for their continued support of our workshop.

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EXHIBITORS

Disclosures

The following faculty speakers have disclosed a financial interest/arrangement or affiliation with a commercial company who has provided products or services relating to their presentation(s) or commercial support for this educational activity.

Please also take note of disclosures mentioned during the presentations and talks.

Sue Astley
My research is supported by the *NIHR Manchester Biomedical Research Centre*. Software licences for *Volpara*, *Densitas* and *Hologic* breast density algorithms were provided to the PROCAS study free of charge under research agreements. PROCAS was funded by the *NIHR* and *Prevent Breast Cancer*.

Carla van Gils
The DENSE trial is financially supported by several governmental and charity funds and by *Bayer AG Pharmaceuticals*. *Volpara Health Technologies Limited* has provided non-financial support by providing us with Volpara Imaging Software for the trial.

Per Hall
iCAD, where we use their algorithms for analyses of mammograms. In a joint project we try to develop a risk prediction model. *Atossa*, where we collaborate in identifying compounds to be used for breast cancer prevention.

Diana L. Miglioretti
Served on the Scientific Advisory Board for *Hologic* in 2017.

Soo-Hwang Teo
Served on speaker's bureau for *AstraZeneca*.

Organizing Committee

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Jennifer Harvey, MD
University of Virginia Health Systems

Per Hall, MD, PhD
Karolinska Institutet

Celine Vachon, PhD
Mayo Clinic

Faculty

Vignesh Arasu, MD, PhD
Kaiser Permanente Vallejo Medical Center

Vignesh Arasu, MD, is a breast radiologist at Kaiser Permanente Vallejo Medical Center and a Ph.D. student in Epidemiology and Translational Science at University of California, San Francisco. His research focuses on background parenchymal enhancement (BPE), an emerging imaging biomarker assessed on breast MRI and applied to primary risk and treatment response prediction. He is a BCSC collaborator evaluating primary risk prediction of BPE and comparative effects with mammographic breast density. He is also a co-investigator in the NIH/NCI funded ISPY2 and ISPY2+ trials in the research lab of Dr. Nola Hylton, where he is helping develop quantitative imaging prediction models of neoadjuvant chemotherapy response and evaluating the adjunctive role of quantitative BPE in this setting.

Sue Astley, PhD
University of Manchester

Sue Astley leads work at the University of Manchester on the development and evaluation of imaging biomarkers for breast cancer risk, and the science underpinning stratified screening. Her research encompasses a range of technologies including Computer Aided Detection, Digital Breast Tomosynthesis, electrical impedance measurement of breast density, and quantification of Breast Parenchymal Enhancement in MRI. Her group is currently using AI to predict density and risk from standard and low dose mammograms, with the aim of early risk stratification. A mathematician and physicist by training, she worked as an astronomer and cosmic ray physicist before developing an interest in medical imaging.

Regina Barzilay, PhD
Massachusetts Institute of Technology

Regina Barzilay is a professor in the Department of Electrical Engineering and Computer Science and a member of the Computer Science and Artificial Intelligence Laboratory at the Massachusetts Institute of Technology. Her research interests are in natural language processing. Currently, Prof. Barzilay is focused on bringing the power of machine learning to oncology. In collaboration with physicians and her students, she is devising deep learning models that utilize imaging, free text, and structured data to identify trends that affect early diagnosis, treatment, and disease prevention. Prof. Barzilay is poised to play a leading role in creating new models that advance the capacity of computers to harness the power of human language data. Regina Barzilay is a recipient of various awards including the MacArthur Fellowship, NSF Career Award, the MIT Technology Review TR-35 Award, Microsoft Faculty Fellowship and several Best Paper Awards in top NLP conferences. In 2017, she received a MacArthur fellowship, an ACL fellowship and an AAAI fellowship. Prof. Barzilay received her MS and BS from Ben-Gurion University of the Negev. Regina Barzilay received her PhD in Computer Science from Columbia University, and spent a year as a postdoc at Cornell University.

Wolfgang Buchberger, MD, MSc
UMIT

Education and professional experience:
1981: Doctor of Medicine (M.D.), University of Vienna, Austria
2003: Master of Science (M.SC.) in Health Sciences, UMIT – Private University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria
1982-91: Training in general medicine and diagnostic radiology
1991-95: Staff Radiologist, Dept of Diagnostic Radiology, University of Innsbruck, Austria (UIA)
1995-2003: Assoc Professor of Radiology, Dept of Diagnostic Radiology, UIA
2004-2009: Medical Director, University Hospital Innsbruck, Austria
2009-2018: Chief Medical Officer (CMO), Tirol Kliniken (Tyrolean Hospitals) Ltd.
2018-: Head of Institute of Quality and Efficiency in Medicine, UMIT, Hall in Tirol, Austria

Lynn Chollet-Hinton, PhD
University of North Carolina at Chapel Hill

Dr. Lynn Chollet-Hinton is a research associate in the Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill. She holds a BA in Biology from Grinnell College and obtained an MSPH (2013) and PhD (2017) in Epidemiology at UNC-Chapel Hill before joining the LCCC for postdoctoral research in 2017. Her research interests center on examining normal breast histology as well as the molecular epidemiology of breast cancer etiology and progression. She is particularly interested in understanding young women's breast cancer and identifying biologic factors associated with the development of aggressive breast tumors. In her work, she has focused on examining interactions between aging, epidemiologic risk factors, breast tissue composition, and molecular and gene expression biomarkers of poor-prognostic breast tumors. Recently, she has utilized digital histologic methods to identify patterns in normal breast tissue morphology related to aging and exposure to breast cancer risk factors, providing insight into the role of breast stroma as a mediator of breast cancer risk.

Christine Gunn, PhD
Boston University

Dr. Gunn is a health services researcher at the Boston University Schools of Medicine and Public Health. Her research is focused on risk communication, decision-making, and the utilization of evidence-based care. She has conducted an array of research on how patients and providers negotiate the experience of being at risk for cancer and its impact on the utilization of health services. She is the recipient of a K07 career development award from the National Cancer Institute that focuses on health literacy-related disparities in mammogram decision-making and behaviors. Her work has helped to characterize the experiences of patients and primary care providers in response to the implementation of dense breast legislation, especially in Massachusetts. Dr. Gunn has extensive experience in qualitative research methods, surveys, and mixed methods approaches to studying risk and prevention behaviors.

Per Hall, MD, PhD
Karolinska Institutet

I am a medical oncologist by training and have spent the last 20 years as a full time researcher at the Karolinska Institutet. Over the last 4 years I also have a part time position at the South General Hospital, Stockholm. Breast cancer is a potentially fatal disease that has increased dramatically throughout the world over the last decades. We believe that individualize screening and prevention is what is needed to lower the burden breast cancer. The first step is therefore to identify women at high risk and offer them better breast cancer screening. Preventive measures should be suggested to those at very high risk. Using the Karma Cohort (karmastudy.org) we are developing a risk model that takes mammographic features, lifestyle factors and genetics in to consideration. In the Karisma trial we are testing if lower doses of the anti-estrogen compound, tamoxifen, has the same protective effect as the established 20 mg dose. In 2020 we launch a study where we will compare risk based screening to ordinary age based screening. We will invite the 20% women with the highest risk of breast cancer for additional examinations. The aim is to contrast sensitivity, specificity and stage distribution between the two arms.

Susan Hankinson, ScD
University of Massachusetts

Susan Hankinson, ScD, is Professor of Epidemiology at the University of Massachusetts, Amherst, and past Chair of the Department of Biostatistics and Epidemiology at UMASS. She received her doctoral degree in epidemiology from the Harvard Chan School of Public Health, and prior to joining UMASS, served as Professor of Medicine at Harvard Medical School. Dr. Hankinson has been a long-term investigator with both the Nurses' Health Study (NHS) and NHSII cohorts and past Principal Investigator of the NHS (2006-11). Her research focuses on the etiology and prevention of breast cancer. Her primary scientific interest has been in determining the role of lifestyle factors (e.g., adiposity and dietary intake), as well as endogenous hormones to risk of breast cancer, and improving current breast cancer risk prediction models. Further, she has broad expertise in the use of biomarkers (including blood, urine and tissue markers) in epidemiologic research. Recently, Dr. Hankinson and colleagues published on the joint contributions of plasma hormones, mammographic density and a genetic risk score to several breast cancer risk prediction models in the NHS cohort. Efforts to expand and validate this work are ongoing.

Solveig Hofvind, PhD
Oslo Metropolitan University

Hofvind is radiographer by training and did her master at the Norwegian school of sport sciences (Physical activity and risk of breast cancer). After 13 years work at Akershus University hospital, where she was the pioneer in establishing a breast clinic and BreastScreen Norway, she started to work at the Cancer Registry of Norway. The Cancer Registry is responsible for the administration and quality assurance of the screening program. She finished her PhD in 2005 (The Norwegian Breast Cancer Screening Program: Selected process indicators and their utilization in epidemiological research). Hofvind was guest professor at the University of Vermont, 2006-07, and 2010-11 and has a substantial network internationally. She has about 150 peer-review publications, mainly related to epidemiological aspects of breast cancer and mammographic screening. The has been actively involved in the European and International Cancer Screening Network, the Guideline Developing Group of European Commission Initiative on Breast Cancer and presented as an observer at several IARC workshops.

Gertraud Maskarinec, MD, PhD
University of Hawai'i Cancer Center

During the last 25 years, Dr. Maskarinec, a Professor at the University of Hawai'i Cancer Center,has conducted epidemiologic research related to the development of breast cancer, type 2 diabetes, and other chronic conditions. To understand the disparate rates of disease across the multiethnic population of Hawai'i, her work has focused on obesity and nutritional factors, in particular soy foods, carotenoids, and diet quality. In collaboration with colleagues and trainees, she has successfully designed and executed investigations and analyses within the Multiethnic Cohort, a large prospective study conducted in Hawai'i and California. Her contributions have examined mammographic densities, obesity, hormonal factors, and inflammatory biomarkers as predictors of breast cancer incidence and survival. Several comparative mammographic density investigations included participants from Hawai'i, Guam, the US, Japan, and Europe. In addition to observational studies, she has directed a number of randomized nutritional trials that examined intermediate endpoints of cancer risk as outcomes. Dr. Maskarinec's education includes a medical degree from the Albert-Ludwigs Universität in Freiburg, Germany, and a doctoral degree in epidemiology from the University of Hawai'i. As Assistant Director of Cancer Research Career Enhancement and Education, training of the next generation of cancer researchers constitutes a major part of her efforts.

Diana L. Miglioretti, PhD
University of California, Davis

Diana L. Miglioretti, PhD, is the Dean's Professor of Biostatistics at University of California Davis and a Senior Investigator at Kaiser Permanente Washington Health Research Institute. Her research focuses on breast cancer screening, diagnosis, and risk prediction and radiation exposure from medical imaging. She is a fellow of the American Statistical Association. Dr. Miglioretti co-leads the U.S. Breast Cancer Surveillance Consortium (BCSC), a network of six breast imaging registries with information collected on over 10 million mammography examinations since 1994. She is the contact PI of an NCI-funded program project and the PI of a PCORI-funded large pragmatic study using BCSC data to evaluate methods for improving breast cancer screening and surveillance by identifying women who might benefit from more frequent or intense imaging. She is also developing statistical methods for evaluating screening outcomes using the BCSC's clustered, longitudinal observational data. Her research has provided evidence to inform breast cancer screening guidelines by the American Cancer Society and the U.S. Preventive Services Task Force. Dr. Miglioretti has collaborated on over 200 publications and enjoys mentoring graduate students and early-stage faculty.

Jennifer Stone, PhD
University of Western Australia

A/Prof Jennifer Stone is an epidemiologist/biostatistician with expertise in breast cancer, specifically mammographic density research. Most of her research aims to support accumulating evidence for the clinical use of mammographic breast density to improve breast cancer screening. She is currently a National Breast Cancer Foundation-funded Principal Research Fellow and is leading several nationally funded grants investigating novel measures of breast density in young women, knowledge and awareness of breast density in the general population, the impact of breast density notification in Western Australia and mammographic breast density in Western Australian Aboriginal women. She is also involved with several international projects investigating the genetic determinants of breast density as a strong and highly heritable intermediate phenotype for breast cancer risk.

Parisa Tehranifar, DrPH
Columbia University

Dr. Tehranifar's broad research interests are in breast cancer prevention and health disparities. One area of her work focuses on understanding the contribution of emerging medical interventions as a source of health disparities, and includes leading an ongoing study that investigates a broad range of psychological outcomes and breast cancer screening and prevention behaviors in relation to state mandated disclosure of mammographic breast density in a racially/ethnically diverse populations. She collaborates on several life course studies of breast cancer, in which she examines the role of social factors in shaping adult cancer risk and risk factors, including mammographic breast density as a biomarker of breast cancer risk. Her current research focuses on midlife as a critical life-course stage for breast cancer risk, and includes several studies of determinants and distribution of mammographic density in women of racially/ethnically diverse and predominantly immigrant backgrounds. Dr. Tehranifar is also working on integration of mammographic density in clinical risk assessment, through a nested case-control study within the Sister Study.

Soo-Hwang Teo, MD
University of Malaysia

Professor Dr. Soo-Hwang Teo OBE established, and is now Chief Executive of Cancer Research Malaysia, Malaysia's first independent cancer research non-profit organization, which is specifically focused on research of cancers prevalent in Malaysia. Professor Teo is the Principal Investigator of the Malaysian Breast Cancer Genetic Study (MyBrCa), The Cancer Genome Atlas Malaysia (TCGA-Malaysia), the Malaysian Ovarian Cancer Genetic Study (MyOvCa) and the Malaysian Mammographic Density Study (MyMammo). Professor Teo's team builds models for risk assessment in the Asian population integrating lifestyle, genetic and mammographic images. MyBrCa has been part of the Breast Cancer Association Consortium and this has led to the identification of more than 100 genetic loci associated with an increased risk to breast cancer. MyBrCa makes an important contribution as these studies are only possible through collaboration involving large numbers of patients and the Malaysian studies are one of the few large Asian studies globally. Professor Teo's team has completed a genomic and transcriptomic map of Asian Breast Cancers and shown that population specific influences may have an impact in treatment options and outcomes. Finally, Professor Teo's team works on improving the survival of underserved Malaysian breast cancer patients, through nurse led programs.

Jeffrey A. Tice, MD
University of California, San Francisco

Dr. Tice is a Professor of Medicine in the Division of General Internal Medicine at the University of California, San Francisco. He received Building Interdisciplinary Research Careers in Women's Health (BIRCWH) career development award after his Clinical Research Fellowship. His research focus is on breast cancer risk assessment, mammographic density, and breast cancer screening. Dr. Tice is currently a co-investigator on a P01 using data from the Breast Cancer Surveillance Consortium (BCSC), where he led the development of the BCSC model of breast cancer risk, which has been extended to include SNPs. He is also a co-investigator on a PCORI-funded pragmatic randomized trial, which uses the BCSC model with SNPs to guide screening recommendations based on breast cancer risk in 100,000 women.

Carla van Gils, PhD
University Medical Center Utrecht

Carla van Gils, PhD is clinical epidemiologist and head of the Cancer Research Program of the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands. She has been doing research on mammographic density and breast cancer screening since 1994 and is now the principal investigator of several projects on mammographic density funded by national and international organizations. This also includes a personal research award from the Dutch Cancer Society for her research line on breast density. Her interests are in ways of measuring mammographic density, determinants of mammographic density and the nature of the relationship between breast density and breast cancer risk. She uses breast density in risk prediction modelling in the population-based screening program and also among BRCA1/2 mutation carriers. Besides that she is evaluating ways of improving early breast cancer detection in women with dense breasts. She is the principal investigator of the DENSE trial (Dense tissue and Early breast Neoplasm ScrEening) trial, a large multicenter randomized controlled trial (>30,000 women) investigating the additional value of MRI for women with extremely dense breasts in the population based breast cancer screening program in the Netherlands. She is also a member of international consortia on mammographic density and a member of the Breast Cancer Working Group of the European Prospective Investigation into Cancer and Nutrition (EPIC), where she collaborates with researchers from 10 European countries to study mammographic density, genes, hormones, nutrition and lifestyle in relation to breast cancer risk. She has co-authored over 200 papers in peer-reviewed international journals.

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OLI ALOHA - HAWAIIAN WELCOME

Kalani Brady, MD, MPH

Before written language, Hawaiians devised the *oli*, elaborate chants, composed to record important information, e.g. births, deaths, triumphs, losses, good times and bad. Within the overall category of *oli* there are 1) genealogies, 2) tales of powerful chiefs, 3) stories of the beauty of various lands, and 4) expressions of love to woo a potential lover. A chanter oftentimes weaves *kaona* or double-meaning creating three, four, or five different levels of possible translation. So while some may hear the *mele* and think it means one thing, others more familiar with the context would understand a very different interpretation. It is often said that it is nearly impossible to fully understand the meaning of a chant because of this use of *kaona*. Only the intended recipient of the composition would be able to grasp its true meaning.

Hawaiian	English
Onaona i ka hala me ka lehua *He hale lehua nō ia na ka noe*	Fragrant with the breath of hala and lehua This is the sight I long to see
ʻO kaʻu nō ia e ʻanoʻi nei *E li`a nei hoʻi o ka hiki mai*	Of this, my present desire Your coming fills me with eagerness
A hiki mai nō ʻoe *A hiki pū nō me ke aloha*	Now that you have come Loves comes with you
Aloha ē, aloha ē	Greetings, greetings

Kalani Brady traces his roots to the Keliʻikanakaʻoleaipolani family (Kauaʻi), was raised in Hawaiʻi, and educated at Harvard, UH Mānoa, and PENN. While at Harvard, he performed with the Opera Company of Boston and Boston Symphony Orchestra. Currently, he is a faculty of the Department of Native Hawaiian Health of the UH John A. Burns School of Medicine. His honors include Master of the ACP, Laureate - Hawaiʻi Chapter of the ACP, Physician of the Year - Hawaiʻi Medical Association (2007). In the performing arts, he has served as soloist in the NBC National Christmas Service, the Honolulu Symphony and the Royal Hawaiian Band. Television credits include One West Waikīkī, Mr. Leninsky in the CBS Hawaiʻi 5-0 pilot, and Fantasy Island.

HULA PERFORMANCE

Wahine Hula Akala

Wahine Hula Akala, or the Pink Ladies of Hula, began as a research study at the University of Hawai'i Cancer Center. Researchers at the Cancer Center and the Hula teacher, TeMoana Makolo, set out to better understand whether Hula could be a feasible, adherent, and effective type of physical activity for female specific cancer survivors. Two biobehavioral pilot studies have taken place.

The first pilot study included eleven breast cancer survivors, with the second pilot study including 43 breast and gynecologic cancer survivors. The intervention included six months of Hula two times per week, with additional practice of one hour per week encouraged. Assessments of blood in the first pilot; blood, fecal samples, and saliva, in the second. In addition, self-report measures of mood, fatigue, pain, and social functioning were taken in both studies. Data was collected at three timepoints: baseline, six months, and again at twelve months. Feasibility and early indicators of effectiveness have been demonstrated in blood markers and self-report data.

We are most excited, though, about the maintenance of the physical activity. After the six-month intervention, many of the ladies dancing on Wednesday, came to the investigators and asked if they could continue with the practice. With the support of the Cancer Center many participants have continued dancing three years after the completion of the study. The benefits of physical activity have been well established, although the maintenance of many health behaviors, including physical activity are challenging. We are encouraged by Hula as a type of physical activity and would like to promote culturally relevant forms of physical activity interventions for cancer survivors.

History of Hula in Hawai'i

Before western contact, written language did not exist. Hula and its chants played an important role in keeping history, genealogy, mythology and culture alive. With each movement – a hand gesture, step of foot, swaying of hips – a story would unfold. Through the hula, the Native Hawaiians were connected with their land and their gods. The songs and chants of the hula preserved Hawaii's history and culture. Many believe hula was born on the island of Moloka'i, but other legends tell of hula originating on Kaua'i. For many years following the arrival of missionaries, the hula as well as the Hawaiian language and music were suppressed. The hula, specifically, was even outlawed. It wasn't until King David Kalakaua came to the throne in 1874 that Hawaiian cultural traditions were restored. Today, this unique art form, deeply rooted in culture, has become a worldwide symbol of Hawaiian culture.

General Information

CONFERENCE COMMITTEE

If you have any questions during the conference please do not hesitate to see one of us. We are here for you!

Stephanie Rania
IBDW Program Manager
Clinical Research Coordinator
University of Hawai'i Cancer Center

Nicki Neimy
Manager, Conference & Event Services
University of Hawai'i at Mānoa

WiFi Access
Please use the login credentials below for accessing the WiFi during the workshop.

Username: IBDW2019
Password: breastdensity

Feedback Survey
At the start of the workshop, you will receive a link for the feedback survey. Please be sure to complete your speaker evaluation online at the conclusion of the workshop as we appreciate your feedback and use it to plan future workshops.

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 anywhere.

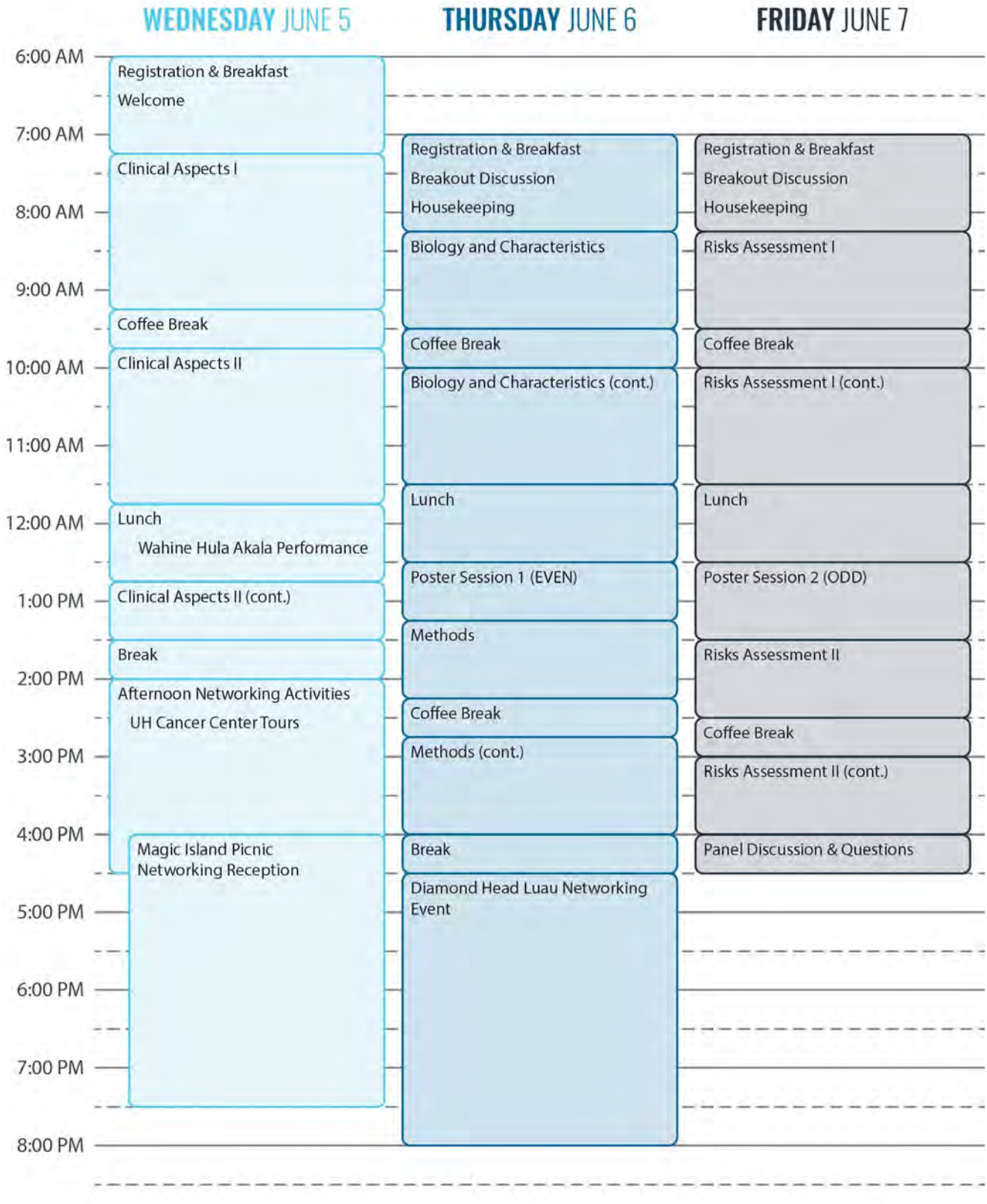
Exhibits
Industry exhibits will be available in the lobby right outside the meeting room during breakfasts, breaks, and lunches.

Poster Sessions and Presenter Information
The poster sessions will take place in Pi'inaio Ballroom 2. Session 1 will be held on Thursday, June 6 for the EVEN numbered posters, and Session 2 will be held on Friday, June 7 for the ODD numbered posters. Please look for your poster number on the bottom of page where your abstract is found.

Oral Presentation Sessions and Presenter Information
Please provide your final presentation to our AV staff the morning of your talk at the latest.

Final Presentations
A private link to PDF versions of the final presentations will be sent via email 3-4 weeks after the course.

Schedule Overview



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HEALTH™

Breast Cancer Research Highlights

The American Cancer Society's Investment

The American Cancer Society helps people with breast cancer in every community. Our research program has played a role in many of the prevention, screening, and treatment advances that help save lives from breast cancer today. And, we continue to fund research to help save even more lives in the future.

ACS Staff Research

The American Cancer Society employs a staff of full-time researchers who pursue the answers that help us understand how to prevent, find, and treat cancer, including breast cancer.

Research Grants

The American Cancer Society funds scientists and medical professionals who research cancer or train at medical schools, universities, research institutes, and hospitals throughout the United States. We provide millions of dollars to multiple grants each year.

Thanks to the generous support of our donors, as of August 1, 2018, the American Cancer Society is funding:

155
GRANTS

Total Breast Cancer Grants in Effect

$61
MILLION

Total Breast Cancer Grant Funding in Effect

WEDNESDAY | JUNE 5, 2019
Clinical Aspects of Breast Density

REGISTRATION & BREAKFAST

6:00 AM - 7:00 AM — Pi‘inaio Foyer & Ballroom 2

WELCOME

7:00 AM - 7:15 AM — Pi‘inaio Ballroom 1

Opening Oli Chant
Kalani Brady

Introduction
Co-Director John Shepherd

CLINICAL ASPECTS I

7:15 AM - 9:15 AM — Pi‘inaio Ballroom 1
Moderator: Steve Cummings

Diana Miglioretti, PhD | Department of Public Health Sciences, University of California, Davis
Risk-Based Screening: When to Start and When to Use Supplemental Imaging Based on Breast Density and Risk

Carla van Gils, PhD | Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht
MRI screening and interval cancers (DENSE)

Susan Hankinson, ScD | School of Public Health and Health Sciences, University of Massachusetts
Breast cancer risk models that combine a polygenic risk score, mammographic density and endogenous hormones

COFFEE BREAK

9:15 AM - 9:45 AM — Pi‘inaio Ballroom 2

CLINICAL ASPECTS II

9:45 AM - 11:45 AM

Pi'inaio Ballroom 1
Moderator: Gertraud Maskarinec

Jennifer Stone, PhD | Centre for Genetic Origins of Health and Disease, University of Western Australia
The Measurement Challenge – International case-control study of mammographic measures that predict breast cancer risk

Per Hall, MD, PhD | Karolinska Institutet
Factors that change breast density and impact breast cancer risk

Christine Gunn, PhD | Women's Health Unit, General Internal Medicine, Boston University School of Medicine
Dense Breast Legislation: What does it mean for patients and providers?

LUNCH

11:45 AM - 12:45 PM

Pi'inaio Ballroom 2

Hula Performance
Wahine Hula Akala

CLINICAL ASPECTS II (CONT.)

12:45 PM - 1:25 PM

Pi'inaio Ballroom 1
Moderator: Gertraud Maskarinec

Vignesh Arasu, MD, PhD | Kaiser Permanente Vallejo Medical Center
Breast MRI Background Parenchymal Enhancement: Emerging Risk and Response Imaging Biomarker

BREAK

1:25 PM - 2:00 PM

AFTERNOON NETWORKING ACTIVITIES

2:00 PM - 7:30 PM

Various Locations

UH Cancer Center Tours
2:30 PM, 3:30 PM / walk or van

Magic Island Picnic Networking Reception
4:00 PM - 7:30 PM / walk or van

Risk-Based Screening: When to Start and When to Use Supplemental Imaging Based on Breast Density and Risk

[1]Miglioretti, Diana
[1]Department of Public Health Sciences, University of California, Davis

Risk-stratified screening offers the potential to improve the balance of screening benefits to harms by tailoring screening intensity and modality to individual risk factors. We introduce a new approach to risk-stratified screening that bases screening decisions on the probability of favorable and unfavorable screening outcomes relative to risk of harms. We propose that women should consider starting screening when their chance of benefiting is high enough to warrant the test given the risk of potential harms and women should consider supplemental screening if they have a high risk of an advanced or interval breast cancer within 1 year of a screen. In this presentation, I will discuss results of risk models developed using data from the Breast Cancer Surveillance Consortium that support using breast density and other risk factors to inform decisions around when to start screening and when to consider supplemental screening.

Title of Abstract: MRI screening and interval cancers (DENSE)

Presenting Authors Full Name: Carla H. van Gils, PhD

Institution: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht

MRI is the most sensitive breast cancer imaging technique currently available and recommended for screening women with high breast cancer risk. Women with dense breasts have a moderately increased breast cancer risk. In addition, their dense tissue limits the detection of a tumor with mammography and therefore additional screening with MRI could provide a solution for these women as well. However, MRI is not included in screening recommendations for women with dense breasts. The effects of MRI, and also those of other supplemental imaging methods, on breast cancer outcomes remain as yet unclear due to a lack of comparative studies with interval breast cancer rates, stage at diagnosis or breast cancer mortality as the outcome.

In this presentation I will give an overview of the results of the first round of the DENSE (Detection of Early Neoplasms in ScrEening) trial. In the DENSE trial we investigated the effect of supplemental MRI for women with extremely dense breasts within a population-based screening program. Between 2011 and 2015, we randomized 40,373 screening participants (aged 50-75) with a negative screening mammography and extremely dense breasts (ACR category 4 by Volpara software) to (an invitation for) supplemental 3.0-T MRI at 8 sites (intervention arm; n=8,061) or mammography screening only (control arm; n=32,312). The primary outcome will be presented, which is the difference in interval cancers, during the two-year screening interval. This is considered to be the best proxy for a difference in breast cancer mortality. This difference was investigated by intention-to-treat (ITT) analysis, and by
complier-average causal effect (CACE) analysis to account for noncompliance. Other outcomes that I will present are: participation rate, supplemental cancer detection rate by MRI, recall rate, biopsy rate, positive predictive value, and distribution of tumor characteristics of the cancer patients diagnosed in both trial arms.

Funding for this study

Funding sources: UMC Utrecht, ZonMw, Dutch Cancer Society, Pink Ribbon/A Sister's Hope, Bayer AG Pharmaceuticals.

Breast cancer risk models that combine a polygenic risk score, mammographic density and endogenous hormones

Hankinson, SE for the Nurses' Health Study Research Group
Department of Biostatistics and Epidemiology, University of Massachusetts, Amherst MA 01003 and Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston MA USA.

INTRODUCTION:

Risk prediction models are used clinically to help guide decisions related to screening and prevention, though the discriminatory ability of these models remain relatively modest. Among such models, the Gail and Rosner-Colditz models have been well validated; these two models generally include only traditional breast cancer risk factors (e.g., parity, family history of breast cancer). A number of biomarkers, specifically plasma estrogens, androgens, prolactin and sex hormone binding globulin (SHBG), mammographic density (MD), and a polygenic risk score (PRS) have been consistently associated with breast cancer risk in postmenopausal women in multiple large studies. Whether and how much the inclusion of this set of biomarkers into the Gail and Rosner-Colditz models has not been previously addressed.

OBJECTIVES:

To evaluate the independent and joint contribution of multiple biomarkers to several validated breast cancer risk prediction models among postmenopausal women.

METHODS:

We conducted a nested case-control study within the prospective Nurses' Health Study cohort among postmenopausal not using exogenous hormones at blood collection. Among 437 invasive breast cancer cases and 775 age-matched controls, we first selected the best subset of plasma hormones (from among estradiol, estrone, estrone sulfate, testosterone, dehydroepiandrosterone sulfate, prolactin and SHBG) using stepwise linear regression, and then assessed their contribution to both risk models. Next, we assessed the joint influence of the best set of plasma hormones, as well as a PRS (using 67 single nucleotide polymorphisms) and MD to the same two models. We evaluated improvement in the area under the curve (AUC) for 5-year risk of invasive breast cancer by adding the biomarkers to modified-Gail and Rosner-Colditz risk scores.

RESULTS:

Estrone sulfate, testosterone, and prolactin were the subset of hormones selected by stepwise regression and together increased the AUC by 5.9 units ($p=0.003$) for the Gail model and 3.4 ($p=0.04$) for the Rosner-Colditz model. For estrogen receptor positive (ER+) tumors, estrone sulfate, testosterone, prolactin and SHBG were selected and the AUC improvements were somewhat larger. For all biomarkers combined (hormones, MD, PRS), for the Gail model, the AUC improved (p-values < 0.001) from 55.5 to 66.0 (10.5 units). For the Rosner–Colditz model, the corresponding AUCs improved by 6.2 units (p-value < 0.001). For ER+ tumors, the AUCs improved (p-values < 0.001) by 14.3 units for the Gail model and 7.3 units for the Rosner–Colditz model.

CONCLUSION:

These results suggest substantial improvements in several validated breast cancer risk prediction models with the addition of multiple biomarkers among postmenopausal women. Validation in independent samples as well as assessments of clinical utility and cost benefit are needed and ongoing.

REFERENCES:

1. Tworoger SS et al. Inclusion of endogenous hormone levels in risk prediction models of postmenopausal breast cancer. J Clin Oncol 2014;32(28):3111-7.
2. Zhang X et al. Addition of a polygenic risk score, mammographic density, and endogenous hormones to existing breast cancer risk prediction models: A nested case-control study. PLoS Med. 2018 Sep 4;15(9):e1002644.

The Measurement Challenge – International case-control study of mammographic measures that predict breast cancer risk

Evenda Dench[1], Daniela Bond-Smith[2], Ellie Darcey[1], Grant Lee[3], Ye K. Aung[3], Ariane Chan[4], Jack Cuzick[5], Ze Yang Ding[6], Christopher F. Evans[3], Jennifer Harvey[7], Ralph Highnam[4], Meng-Kang Hsieh[8], Despina Kontos[8], Shuai Li[3], Shivaani Mariapun[9,10], Carolyn Nickson[3], Tuong L. Nguyen[3], Said Pertuz[11], Pietro Procopio[3], Nadia Rajaram[9,10], Kathy Repich[7], Maxine Tan[6,12], Soo-Hwang Teo[9], Nhut Ho Trinh[3], Giske Ursin[13], Chao Wang[14], Isabel dos-Santos-Silva[15], Valerie McCormack[16], Mads Nielsen[17], John Shepherd[18], John L. Hopper[3], **Jennifer Stone[1]***

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Introduction: For women of the same age and body mass index, increased mammographic density is one of the strongest predictors of breast cancer risk. There are multiple methods of measuring mammographic density and other features in a mammogram that could potentially be used in a screening setting to identify and target women at high risk of developing breast cancer. However, it is unclear which measurement method provides the strongest predictor of breast cancer risk.

Methods and analysis: The Measurement Challenge has been established as an international resource to offer a common set of anonymized mammogram images for measurement and analysis. To date, full field digital mammogram images and core data from 1650 cases and 1929 controls from five countries have been collated. The Measurement Challenge is an ongoing collaboration and we are continuing to expand the resource to include additional image sets across different populations (from Contributors) and to apply additional measurement methods (by Challengers). The intended use of the Measurement Challenge resource is for refinement and validation of new and existing mammographic measurement methods. The Measurement Challenge resource provides a standardized dataset of mammographic images and core data that enables investigators to directly compare methods of measuring mammographic density or other mammographic features in case/control sets of both raw and processed images, for the purposes of the comparing their predictions of breast cancer risk.

Factors that change breast density and impact breast cancer risk

[1]Hall, Per
[1]Karolinska Institutet, Stockholm, Sweden

Several factors influence breast density and breast cancer risk. Most, but not all, factors that increases density also increase risk of breast cancer. It could be that breast density change is a stronger risk factor for breast cancer than a single measure of density. Few studies have reported on factors that influences density change. A handful studies have described tamoxifen induced density change as a proxy for therapy response. In my presentation I will describe and discuss the determinants of breast density, density change and the possible clinical use of therapy induced density change.

Dense Breast Legislation: What does it mean for patients and providers?

[1]Gunn, Christine
[1]Women's Health Unit, Section of General Internal Medicine, Department of Medicine, Boston University School of Medicine, Boston, MA, USA

INTRODUCTION:

With 36 states have passed legislation notifying women of their breast density, and Congress recently approved a national notification law to be implemented by the FDA. There is a need to define the scope of impact of state-level legislation on both patients and providers to inform future implementation.

OBJECTIVES:

The goal of this session is to review the current state of the literature on dense breast notification as it relates to both patient and provider experience, and to chart a path forward to improve the impact of such laws on various clinical and psychosocial outcomes. There will be a particular focus on the scope of outcomes used to measure the impact of dense breast notifications.

METHODS:

We reviewed the literature to identify studies that related to a) patient-reported outcomes related to the implementation of breast density legislation; b) provider-reported outcomes of breast density legislation; and c) any other descriptive or interventional studies related to the implementation of density notification laws. We summarized outcomes represented in these studies and explored how these fit into broader health and care delivery frameworks for achieving evidence-based care.

RESULTS:

Patient outcomes associated with dense breast legislation have centered on the concepts of awareness, knowledge and discussion of breast density with physicians. Both qualitatively and quantitatively, awareness and perceptions have differed across, racial and ethnic, income, education, and language groups; favoring White, educated, English-speaking populations. While supplemental screening procedures have increased following legislation, data on the value of such procedures to patients has yet to be determined. Most studies to date have emphasized cancer detection rates. Studies on provider experience have produced some evidence that radiology facilities have shifted their services to respond to notification implementation. However, a significant minority of primary care practitioners who are tasked with downstream effects of these laws do not feel prepared or comfortable counseling women on breast density. Further, there is little systems support for practices to conduct comprehensive breast cancer risk assessment to support decision-making for supplemental screening.

CONCLUSION:

Given the pending implementation of national legislation, it is a critical moment to reflect on how we meaningfully measure the outcomes of notification laws and provide appropriate support around medical communications to support positive outcomes at the level of the patient, provider, and health system. Building on a foundation of inclusive communication standards, patient education, provider education, and health system supports can help define and build an evidence base for processes that produce impactful clinical outcomes.

Breast MRI Background Parenchymal Enhancement: Emerging Risk and Response Imaging Biomarker

Vignesh Arasu, MD[1,2]
[1]Kaiser Vallejo Medical Center; [2]University of California, San Francisco

Accumulating evidence suggests elevated background parenchymal enhancement (BPE), assessed on breast magnetic resonance imaging (MRI), may predict primary breast cancer risk and response to therapy. BPE describes the phenomenon observed on breast MRI in which normal breast tissue demonstrates signal enhancement related to uptake of gadolinium-based intravenous contrast, which is used in routine MRI examinations. Biologically, BPE may represent increased tissue microvascularity and/or permeability regulated by endogenous hormones (primarily estrogen) and may represent tissue at risk for neoplasia. BPE is dynamic in appearance and distribution within a woman's breast tissue and sensitive to the phase of menstrual cycle and lactation, as well as in response to antihormonal therapy, chemotherapy, and radiotherapy. Similar to mammographic breast density, BPE is qualitatively codified in the BI-RADS Atlas as four ordinal levels of increasing enhancement—minimal, mild, moderate, and marked. In contrast to breast density, BPE indicates overall breast tissue contrast enhancement assessed on MRI.

This talk will provide an overview of the imaging appearance of BPE, its clinical application, current research in the primary risk and treatment response setting, current limitations of its use, and gaps in knowledge.

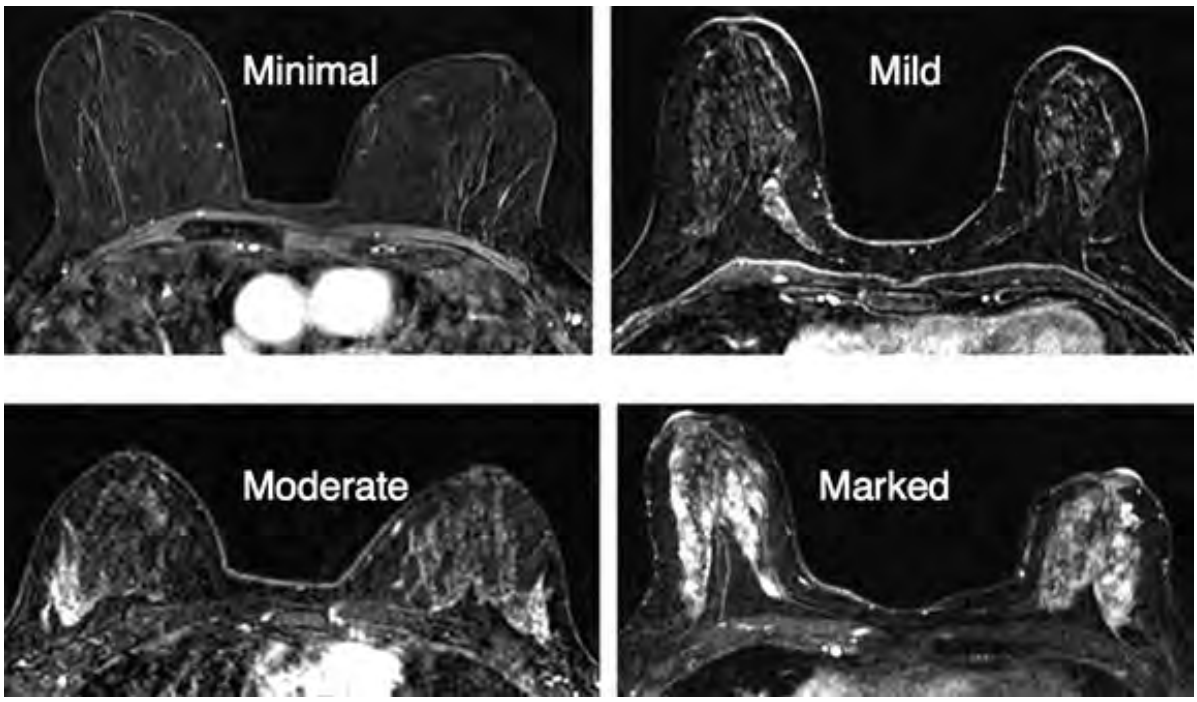

Figure 1: BI-RADS categories of background parenchymal enhancement (BPE) assessed on breast MRI (by increasing order): minimal, mild, moderate, and marked

WEDNESDAY | JUNE 5, 2019

Afternoon Networking Activities

After the last talk on Wednesday, starting at 2 pm, networking activities will begin!

- **UH Cancer Center Tours**
  2:30 PM, 3:30 PM / walk or van
  If you are interested in touring the Cancer Center, Gertraud Maskarinec will be giving casual tours of this special building. More info the day of event.
- **Magic Island Picnic Networking Reception**
  4:00 PM - 7:30 PM / walk or van
  Bring your workshop sunscreen and beach towel and meet us on the beach. We will have a tent setup, games, and food. The food will be catered by a popular Hawaiian lunch truck that will be serving a variety of Hawaiian favorites. Plan on staying until 7:11 pm to watch what Hawai'i is famous for - beautiful sunsets. You may get lucky and see a rainbow!

INSTRUCTIONS

What to wear: Hawaiian shirts, of course, swimwear, walking shoes to get to Magic Island, slippahs for the beach (local slang for flip flops).

We will have some chairs but it will be casual around the beach area.

Safety: Waikīkī is very safe but plan on walking back just after sunset.

Van service: For those who don't want to walk, we will have a van to shuttle people back and forth to the beach, Cancer Center, and Hotel.

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THURSDAY | JUNE 6, 2019
Breast Density Workshop

REGISTRATION & BREAKFAST / BREAKOUT DISCUSSION

7:00 AM - 8:00 AM — Pi‘inaio Foyer & Ballroom 2

HOUSEKEEPING

8:00 AM - 8:15 AM — Pi‘inaio Ballroom 1

BIOLOGY AND CHARACTERISTICS

8:15 AM - 9:35 AM — Pi‘inaio Ballroom 1
Moderator: Per Hall

PLENARY TALK 1
Lynn Chollet-Hinton, PhD | Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill
Morphometric features of benign breast tissue: Implications for breast cancer risk

POSTER TALK 1
Clara Bodelon, PhD | National Cancer Institute
Mammary collagen architecture and its association with mammographic density and lesion severity among women undergoing diagnostic image-guided breast biopsy

POSTER TALK 2
Maeve Mullooly, PhD | Royal College of Surgeons in Ireland
Opportunities and Challenges for the Identification of Histological Correlates of Mammographic Density in Patients with Benign Breast Disease

COFFEE BREAK

9:35 AM - 10:05 AM — Pi‘inaio Ballroom 2

BIOLOGY AND CHARACTERISTICS (CONT.)

10:05 AM - 11:25 AM

Piʻinaio Ballroom 1
Moderator: Per Hall

PLENARY TALK 2

Parisa Tehranifar, DrPH | Mailman School of Public Health, Columbia University Medical Center
Breast density research in diverse populations and health disparities

PLENARY TALK 3

Soo-Hwang Teo, MD | Breast Cancer Research Programme, Cancer Research Malaysia
Mammographic breast density and cancer risk in Asian women

LUNCH

11:25 AM - 12:25 PM

Piʻinaio Ballroom 2

POSTER SESSION 1 (EVEN-NUMBERED)

12:25 PM - 1:10 PM

Piʻinaio Ballroom 2

P2. Erica Warner, ScD, MPH | Department of Medicine, Massachusetts General Hospital
Variation in Volumetric Breast Density and A Novel Texture Feature According to Race/Ethnicity

P4. Andrew Maidment, PhD, FAAPM | University of Pennsylvania
Quantifying the Realism of an Anthropomorphic Phantom for 3D Mammography Using Radiomic Texture Features

~~**P6**. Inger Gram, MD, PhD | Department of Community Medicine, University of Tromsø~~
~~*Exposure to passive smoking from parents during childhood and risk of Breast Cancer*~~

P8. Marije Bakker, PhD | Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht
Reproductive determinants of high pre- and postmenopausal mammographic breast density in Dutch breast cancer screening participants

P10. Jami Fukui, MD | University of Hawaiʻi Cancer Center
Exercise Program to Increase and Sustain Physical Activity after Breast Cancer Diagnosis

P12. Ioannis Sechopoulos, PhD | Department of Radiology and Nuclear Medicine, Radboud University Medical Center
Breast Density Analysis with Dedicated Breast CT

P14. Rulla Tamimi, ScD | Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School
Changes in mammographic density and texture associated with high-dose vitamin D supplementation

P16. Kerrie Nelson, PhD | Department of Biostatistics, Boston University
Measuring the effects of rater training on ordinal ratings in large-scale breast imaging screening studies

POSTER SESSION 1 (EVEN-NUMBERED)

12:25 PM - 1:10 PM — Pi‘inaio Ballroom 2

P18. Dilukshi Perera | Centre for Genetic Origins of Health and Disease, Curtin University and University of Western Australia, Perth
Novel methods for measuring breast density in younger women: TiBS and DXA

P20. Mary Marsh, PhD | Department of Radiology, University of North Carolina, Chapel Hill
Supplemental Screening Availability vs. Utilization: Examining N.C. Mammography Facility Services for Women with Dense Breast Tissue

P22. Teofilia Acheampong, MPH, PhD | Department of Epidemiology, Columbia University
Aspirin Use and Mammographic Breast Density

P24. Daniella Dougherty | School of Medicine, University of Adelaide, North Terrace
Anastrozole and Enobosarm (GTx-024): the effect of an aromatase inhibitor and selective androgen receptor modulator on mammographic breast density and breast pain in premenopausal women

P26. Roni Falk, MD | National Cancer Institute
Circulating Anti-Müllerian Hormone in Relation to Mammographic Density and Measures of Lobular Involution among Premenopausal Participants in the BREAST Stamp and Komen Tissue Bank Studies

P28. Brenda Hernandez, PhD, MPH | University of Hawai‘i Cancer Center
Breast tumor size and population disparities: elucidation of the role of screening mammography

P30. Chloe Asato | Epidemiology Program, University of Hawai‘i Cancer Center
Validation of Breast Cancer Polygenic Risk Scores in the Multiethnic Cohort

P32. Christine Gunn, PhD | School of Medicine, Boston University
Partnering with Advocates to Assess Breast Density Patient Educational Materials

P34. Jennifer Stone, PhD | Centre for Genetic Origins of Health and Disease, University of Western Australia
What do women know and do about breast density?

METHODS

1:10 PM - 2:10 PM — Pi‘inaio Ballroom 1
Moderator: John Shepherd

PLENARY TALK 4

Sue Astley, PhD | Division of Informatics, Imaging and Data Science, Faculty of Medicine, Biology and Health, University of Manchester
Machine Learning and Texture Features

POSTER TALK 3

Ana Pereira, PhD | Institute of Nutrition and Food Technology, University of Chile
Portable spectroscopic device an alternative method to measure Breast Density at young ages and large population studies. Pilot Study.

COFFEE BREAK

2:10 PM - 2:40 PM — Piʻinaio Ballroom 2

METHODS (CONT.)

2:40 PM - 4:00 PM — Piʻinaio Ballroom 1
Moderator: John Shepherd

PLENARY TALK 5

Regina Barzilay, PhD | Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology
A Deep Learning Mammography-based Model for Improved Breast Cancer Risk Prediction

POSTER TALK 4

John Hopper, PhD, NHMRC Senior Principal Research Fellow | School of Population and Global Health, University of Melbourne
New mammography-based measures of breast cancer risk

POSTER TALK 5

Bilal Malik, PhD | QT Ultrasound Labs
AI-based quantitative breast density assessment using transmission ultrasound

BREAK

4:00 PM - 4:30 PM — Piʻinaio Ballroom 2

NETWORKING EVENT

4:30 PM - 8:00 PM — Diamond Head Luau
https://www.diamondheadbeachluau.com/

Morphometric features of benign breast tissue: Implications for breast cancer risk

[1]Chollet-Hinton, Lynn
[1]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, NC

INTRODUCTION:

Histologic studies of benign breast tissue provide a window into the breast microenvironment and may inform assessment of breast cancer risk[1]. More complete age-related epithelial involution reduces breast cancer risk, and stroma modifies epithelial characteristics of breast tissue with consequences for cancer etiology and progression. Research evaluating breast histology as a marker of risk has been constrained by biospecimen availability and variability in tissue sampling. Quantifying measures of stroma and epithelium may reveal risk stratification strategies for women undergoing breast biopsy.

OBJECTIVES:

1) To evaluate measures of stromal content and epithelial involution developed using a novel digital histologic analysis algorithm.
2) To assess intraindividual variability in benign breast histology and discuss strategies to address heterogeneity in tissue sampling.
3) To consider the dual roles of histologic breast density in breast cancer risk and progression.

METHODS:

This presentation discusses recent studies of breast tissue composition with a focus on the Normal Breast Study (NBS), a cross-sectional study of normal breast tissue and breast cancer microenvironment conducted at the University of North Carolina Hospitals[1]. Breast tissue was obtained for 416 participants undergoing breast surgery between October 2009 and April 2013. Digital image analysis of approximately 1,800 hematoxylin and eosin (H&E) stained sections of benign breast tissue was conducted using Aperio Imagescope. Measures of age-related involution (density of epithelial nuclei in epithelial areas) and stromal characteristics (percentage of section area comprised of stroma) were defined using a pathologist-trained, validated Aperio Genie algorithm. Intraindividual variability was explored by comparing 2-16 H&E slides per woman from different regions of the breast. Other studies examining associations between microenvironment, benign breast histology, and breast cancer risk and progression are presented.

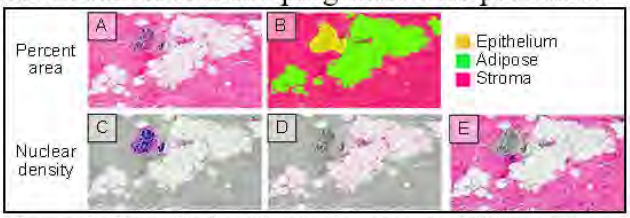

Figure 1. Quantitative histologic measures of breast tissue by novel morphometric methods. A) H&E image with no annotations; B-E) Annotation overlay of percent epithelial, adipose, and stromal area (B, see key) and epithelial nuclei (C), adipose nuclei (D), and stromal nuclei (E) in blue.

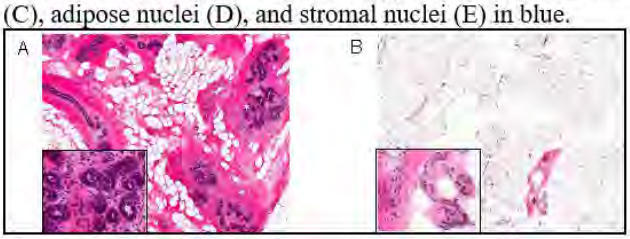

Figure 2. Variability in breast tissue composition across repeated tissue sampling. H&E images (2X) from a 39-year old woman with both high stroma (A) and mostly fat (B) samples. Inlays (10X, see *) represent regions of higher epithelial nuclear density.

RESULTS:

In the NBS, stromal area modified the dynamic range of epithelial nuclear density, and patterns of age-dependent involution were evident only in samples with at least 10% stroma. Breast tissue composition varied substantially across repeated tissue sampling, highlighting the need for systematic breast tissue sampling strategies.

CONCLUSION:

Stromal composition has important implications for epithelial involution and breast cancer risk. Histologic studies of breast tissue reveal stroma as a key marker of the complex relationship between breast density and breast cancer risk.

REFERENCE:

1. Chollet-Hinton L, et al. 2018. Stroma modifies relationships between risk factor exposure and age-related epithelial involution in benign breast. *Mod Pathol* 31:1085-1096. PMCID: PMC6076344.

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Mammary collagen architecture and its association with mammographic density and lesion severity among women undergoing diagnostic image-guided breast biopsy

Clara Bodelon[1], Maeve Mullooly[1,2], Ruth M. Pfeiffer[1], Shaoqi Fan[1], Mustapha Abubakar[1], Pamela M. Vacek[3], Donald L. Weaver[3], Sally D. Herschorn[3], Jason Johnson[4], Brian L. Sprague[3], Stephen Hewitt[1], John Shepherd[5], Amir Pasha Mahmoudzadeh[6], Jeff Wang[7], Bo Fan[5], Serghei Malkov[8], Kevin W. Eliceiri[9], Patricia J. Keely[9,†], Mark E. Sherman[1,10*], Matthew W. Conklin[9*], Gretchen L. Gierach[1*]
[1]National Cancer Institute, Bethesda, MD, USA; [2]Royal College of Surgeons in Ireland, Dublin, Ireland; [3]University of Vermont College of Medicine and Vermont Cancer Center, Burlington, VT, USA; [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]University of Hawaii Cancer Center, Honolulu, HI, USA; [6]Accenture, San Francisco, CA, USA; [7]Hokkaido University, Graduate School of Medicine, Sapporo, Japan; [8]Applied Materials, Santa Clara, CA, USA; [9]University of Wisconsin-Madison, Madison, WI, USA; [10]Mayo Clinic, Jacksonville, FL, USA; [†]Deceased. *These authors contributed equally to this work.

INTRODUCTION:

Elevated mammographic density (MD) is a strong breast cancer risk factor, but the mechanisms underlying the association are poorly understood. Increased deposition of collagen, one of the main fibrous proteins present in breast stroma, has been associated with increased MD[1,2], and stromal collagen architecture has been linked to breast carcinogenesis[3]. However, relationships of collagen features, such as alignment, length or width, with MD and breast biopsy diagnoses have not been well established.

OBJECTIVES:

Using high-resolution second-harmonic generation (SHG) microscopy for imaging collagen fibers in diagnostic breast biopsies (**Figure**), we investigated the relation between features of collagen with global and local measures of MD and lesion severity.

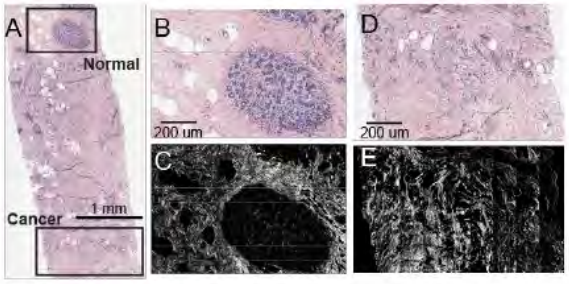
METHODS:

Using Hematoxylin & Eosin (H&E) stained sections from diagnostic breast biopsies from 65 breast cancer cases and 73 controls with a benign biopsy result, ages 40-65 years, collagen fibers were measured in up to three regions of interest (ROIs) selected by a pathologist (MES): a region of normal tissue, a region with benign breast disease and a region with cancer among the cases. Individual collagen fiber measurements from SHG imaging were extracted for analysis and included length, curvature, width, alignment, orientation and density (total # fibers/μm^2). Global MD volume was quantified in craniocaudal views of the ipsilateral breast in pre-biopsy full-field digital mammograms using Single X-ray Absorptiometry. Local density measures were computed in volumes surrounding (peri-lesional) and including (lesional) the biopsy targets. Associations between collagen fiber and MD measurements were evaluated using generalized estimating equation models with an independent correlation structure to account for the multiple ROIs within each biopsy tissue section.

RESULTS:

The proportion of stroma on the H&E biopsy slide was positively associated with collagen fiber density (P=0.002). Fiber density was also positively associated with local percent MD volume at the biopsy target (P=0.035) and in a 2mm perilesional ring (P=0.02), but not global MD measures. No other fiber features were associated with MD. When comparing collagen fiber architecture across the ROIs, fiber density was significantly lower in benign compared with normal ROIs (P<0.001), cancer compared with benign ROIs (P=0.007) and cancer compared with normal ROIs (P=0.008). Also, as lesion severity increased at the ROI level, collagen fibers tended to be shorter, curvier, thinner and more aligned with one another (P<0.05).

Figure. Collagen fibers were measured using second harmonic generation (SHG) microscopy in each of the selected ROIs (A) of H&E-stained biopsy sections. Shown are the magnifications of the normal (B) and cancer (D) ROIs, with corresponding SHG images of collagen fibers (C, E).



CONCLUSION:

Collagen fiber density was associated with local, but not global, volumetric percent MD, suggesting that stromal collagen microarchitecture may not translate into macroscopic mammographic features. Collagen architecture may be a marker of cancer risk among women referred for biopsy based on breast imaging.

REFERENCES:

[1]Li T, *et al. CEBP* 2005;14:343-9.
[2]McConnell JC, *et al. Breast Cancer Res* 2016;18:5
[3]Provenzano PP, *et al. BMC Med* 2008;6:11.

Opportunities and Challenges for the Identification of Histological Correlates of Mammographic Density in Patients with Benign Breast Disease

*Maeve Mullooly[1], *Samantha Puvanesarajah[2], Shaoqi Fan[3], Ruth M. Pfeiffer[3], Linnea Olsson[4], Manila Hada[3], Erin L. Kirk[4], Pamela M. Vacek[5], Donald L. Weaver[5], John A. Shepherd[6], Amir Pasha Mahmoudzadeh[7], Jeff Wang[8], Serghei Malkov[7], Jason M. Johnson[9], Stephen M. Hewitt[3], Sally D. Herschorn[5], #Mark E. Sherman[10], #Melissa A. Troester[4], #Gretchen L. Gierach[3].

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INTRODUCTION:

The histological correlates of breast density remain ill-defined. Understanding its histological underpinnings may provide insights into molecular mechanisms driving the established associations between elevated breast density and increased risk of breast cancer, particularly among women diagnosed with high-risk benign precursor lesions (benign breast disease, BBD). Microscopic measures of breast epithelial lobules, which involute with aging, have been identified as independent risk markers and correlates of breast density among women with BBD.[1]

OBJECTIVES:

This study aimed to examine epithelial features of breast tissue histology and their associations with global and localized measures of breast density among women diagnosed with BBD.

METHODS:

In digitized whole slide images of 262 image-guided clinical breast biopsies with BBD diagnoses, epithelial breast tissue composition was assessed using two methods: 1) visual quantification of terminal duct lobular units (TDLU counts/100mm^2, median acini count/TDLU); and 2) application of a digital pathology algorithm[2] that estimated nuclei count per unit epithelial area, or epithelial nuclear density (END, **Figure**). Single X-ray absorptiometry of pre-biopsy ipsilateral FFDM was used to measure global % and localized % fibroglandular volume (FGV) in a specified volume surrounding (peri-lesional) and including (lesional) the biopsy target. Analysis of covariance examined mean differences in % FGV across tertiles of END, adjusting for age and body mass index (BMI).

Figure. Application of the END algorithm to the whole slide breast biopsy image to estimate epithelial nuclei count per unit epithelial area.

RESULTS:

TDLU measures were positively associated with increasing tertiles of END (TDLU count/100mm^2, OR_{T3vsT1}: 3.42, 95%CI: 1.87, 6.28; acini count/$TDLU_{T3vsT1}$, OR: 2.40, 95%CI: 1.39, 4.15). TDLU measures were also positively associated with global and localized % FGV. However, END was significantly associated with local, but not global, measures of % FGV (**Table**).

Table. Relation of END with Global and Local % FGV

	% Global FGV	% Peri-lesional FGV	% Lesional FGV
END tertiles	Mean (95% CI)[a]	Mean (95% CI)[a]	Mean (95% CI)[a]
T1 (≤9592.3)	38.2 (35.4, 41.0)	41.4 (38.2, 44.6)	44.7 (41.3, 48.0)
T2 (≥9598.3)	39.2 (36.9, 41.5)	44.2 (41.2, 47.2)	48.3 (45.3, 51.2)
T3 (≥10674.4)	40.9 (38.0, 43.8)	48.9 (45.4, 52.3)	51.7 (48.2, 55.2)
P-trend	*0.30*	***0.016***	***0.028***

[a] Models adjusted for age and BMI. P-trend<0.05 is in bold font.

CONCLUSIONS:

As improvements in automated digital pathology continue, the information that can be gained and lost through such approaches must be recognized. These findings suggest that END reflects independent, but complementary information to the histological information captured by visual TDLU assessment and radiological FGV measures. END and TDLU metrics reflect different histologic features, quantitative scales and tissue architecture. Future applications of digital pathology to breast biopsies may provide opportunities to extend our understanding of breast cancer risk among women with BBD and the underpinnings of specific risk factors, such as breast density.

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Breast density research in diverse populations and health disparities

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Background: Research on breast density in diverse populations provides important insight for understanding breast density etiology and mechanism, and is necessary for effective integration of breast density in breast cancer prevention and detection and averting health disparities.

Objective: This presentation will provide an overview of current understanding of international and racial/ethnic differences in the distribution and determinants of mammographic breast density. Additionally, key considerations and factors related to implementation of breast density into clinical practice serving diverse and medically underserved patient populations will be discussed.

Methods: Findings will include review of larger empirical published literature as well as ongoing research conducted in New York City with predominantly Hispanic and immigrant women.

Results: Variations in the distribution of mammographic density appear to map to variations in breast cancer incidence across countries and across racial/ethnic groups within the same country, but these patterns depend on the measurement of mammographic density. Limited studies in immigrant populations also show that mammographic density reflects the transition in breast cancer risk accompanied with migration, showing lower mammographic density in women who were born in lower-incidence countries, and with shorter length of residence in the higher-incidence host country. In addition to the need to study breast density within diverse populations for etiology, there is a growing urgency for studying the impact of the integration of breast density in personalized screening and breast density notification in populations with diverse backgrounds. Growing evidence supports significant racial/ethnic and socioeconomic disparities in women's understanding, and screening-related cognitions and emotions in response to breast density notification, with the potential to exasperate breast cancer health disparities. Important gaps in translating breast density evidence into breast cancer prevention and screening in racial/ethnic minority and low socioeconomic populations will be presented.

Conclusions: Studies of breast density within diverse populations give further evidence on the importance of breast density for reducing the burden of breast cancer and are essential for ensuring that all women are equally poised to receive benefits arising from the unfolding policy and clinical actions.

Mammographic breast density and cancer risk in Asian women

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Although breast cancer incidence in Asians historically has been less than half of that in Europeans, it is rising by >3% per annum because of decreasing parity and increasing Westernisation and urbanization. Today, more women die of breast cancer in Asia than in North America and Europe. In the majority of Asian countries, breast cancer is the most common cancer accounting for up to one third of cancers in women, and it is the most common cause of cancer-related deaths. In part because of lack of funding within the national health services and lack of justification for population-based screening, only opportunistic screening is practiced in the majority of Asian countries, but this is suboptimal and inequitable. A viable alternative may be to identify high-risk women who should be targeted for screening, particularly given the financial constraints that prohibit population-based screening. In my talk, I will describe the differences in mammographic density in Asian compared to European women, and provide an update on our efforts in describing the lifestyle and genetic determinants of mammographic density in Malay, Indian and Chinese women living in Malaysia, in the context of building risk stratified approaches to screening for breast cancer in Asian women.

Machine Learning and Texture Features

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INTRODUCTION:

Mammographic density, measured both visually and using computer-based methods, has been shown to relate to both risk of developing cancer and risk of cancers being missed by mammography. Software that calculates the volume of dense fibroglandular tissue is widely used for this purpose, but when compared with visual assessment it was less predictive [1]. This implies that in addition to quantity, pattern and distribution of dense fibroglandular tissue contributes to risk prediction.

OBJECTIVES:

This talk will review the use of texture to improve density assessment, show how we can estimate mammographic density using machine learning, how this can encapsulate texture information, and discuss some of the challenges in developing and evaluating such approaches.

METHODS:

In building and evaluating markers for mammographic density and texture we have used data from the PROCAS study in which visual assessment of density using VAS (Visual Analogue Scales) was made by two expert readers on over 55,000 digital mammograms. We have experimented with a variety of network architectures, using average VAS score as a gold standard [2]. Independent training, test and validation cohorts were used, and results obtained for 'for processing' and 'for presentation mammograms', along with images synthesised to replicated mammograms acquired at a reduced radiation dose. The approach has also been applied to evaluate change in density in women undergoing risk-reducing therapy.

RESULTS:

Results will be presented in the context of alternative density and texture approaches, including those which seek to model texture explicitly [3]. Results on reduced resolution and reduced dose mammograms indicate that fine scale features such as microcalcifications are not crucial to matching expert performance.

CONCLUSION:

Whilst we have demonstrated that we can match the performance of expert assessors, there is still the capacity to improve further using machine learning and increased resolution solutions.

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Portable spectroscopic device an alternative method to measure Breast Density at young ages and large population studies. Pilot Study.

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INTRODUCTION:

Dual X-Ray Absorptiometry (DXA)[1], Magnetic Resonance Imaging[2] and Optical Spectroscopy[3] are methods that can be used to measure breast density (BD) in young ages; however, their complexities and costs make them difficult to use them at a large scale or primary health care.

SCIO is a portable (68 mm x 41 mm x 19 mm) optical spectrometer that operates in the near-infrared wavelength range. It does not have X-ray exposure neither compress the breast. Working models for total body composition and nutritional models for food have been developed.

OBJECTIVES:

To assess if SCIO is a feasible method to measure BD in women.

METHODS:

We set up a pilot study in the GOCs cohort, which represents 1190 children born in 2002-2003 from low-medium socioeconomic level, South East Area of Santiago. We included 40 daughters and their mothers. We measured as biological data: weight, height, breast skin & nipple color (Fitzpatrick scale).

SCIO protocol: We scanned each breast 5 times (including the nipple) in a clockwise direction as shown in **Figure 1**. Measures were carried out 2 cms from the middle point of the nipple.

All participants' right and left breast were scanned using DXA and we estimated the % of fibroglandular volume (%FGV).

We extracted the raw spectra from SCIO and used Principal Component Analysis to reduce the dimensionality of SCIO spectrum dataset.

We fitted linear regression models with biological data and the first 13 principal components (PC) that explained better the variability of the data (eigenvalue >1). We compared the coefficient of determination (R^2) between the different models. Testing and validation of the model will be carry out in a new sample during 1st semester 2019.

RESULTS:

Girl's mean age was 14.6y (SD=0.6), BMI of 24.3 kg/m^2 (SD=5.2) and %FGV of 43.1% (SD=13.8), while mothers were 46.5y (SD=6.6, 11 postmenopausal)), 30.3 kg/m^2 (SD=5.9) and 30.2% (SD=8.2), respectively.

R^2 of models including biological data and 13 PC were over 0.8 in the girls and left breast of mothers (**Table 1**). Models in the mothers were better if restricted only to premenopausal women (data not shown).

Figure 1: SCIO scanning protocol

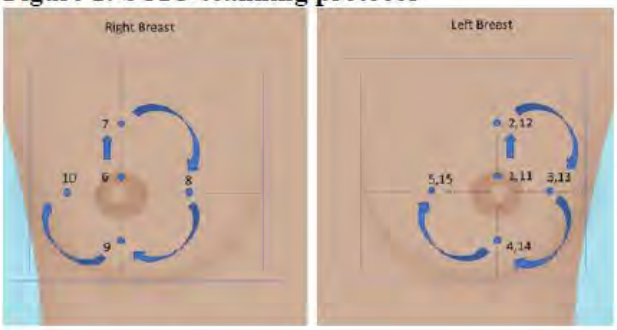

Table 1: %FGV Coefficient of Determination in 3 different models, stratified by daughters and mothers.

Breast side	Daughters Left R^2	Daughters Right R^2	Mothers Left R^2	Mothers Right R^2
Biological data*	0.62	0.69	0.36^	0.44^
PC 1-13**	0.38	0.54	0.46	0.26
Biological + PC 1-13	0.83	0.85	0.82^	0.74^

* Includes age, height, BMI, skin and nipple color
** PC: Pricipal components
^further adjusted by menopausal status

CONCLUSION:

Preliminary results are encouraging to support SCIO as a feasible measure to quantify breast density at a population level and at young ages. Results will be validated in a new dataset during 1st semester of 2019.

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A Deep Learning Mammography-based Model for Improved Breast Cancer Risk Prediction

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INTRODUCTION:

Mammographic density improves the accuracy of breast cancer risk models. However, the use of breast density is limited by subjective assessment, variation across radiologists, and restricted data. A mammography-based deep learning (DL) model may provide more accurate risk prediction.

OBJECTIVES:

To develop a mammography-based DL breast cancer risk model that is more accurate than established clinical breast cancer risk models.

METHODS:

This retrospective study included 88,994 consecutive screening mammograms in 39,571 women between January 1, 2009, and December 31, 2012. For each patient, all examinations were assigned to either training, validation, or test sets, resulting in 71,689, 8,554, and 8,751 examinations, respectively. Cancer outcomes were obtained through linkage to a regional tumor registry. By using risk factor information from patient questionnaires and electronic medical records review, three models were developed to assess breast cancer risk within 5 years: a risk-factor-based logistic regression model (RF-LR) that used traditional risk factors, a DL model (image-only DL) that used mammograms alone, and a hybrid DL model that used both traditional risk factors and mammograms. Comparisons were made to an established breast cancer risk model that included breast density (Tyrer-Cuzick[1] model, version 8 [TC]). Model performance was compared by using areas under the receiver operating characteristic curve (AUCs) with DeLong test ($P < .05$).

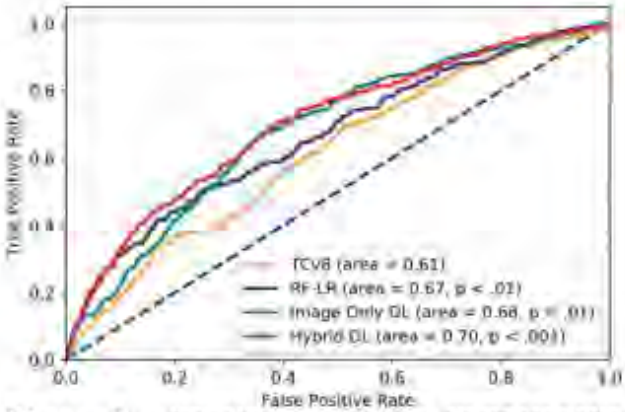

Figure 1: Receiver operating characteristic curve of all models on the test set. All *P* values are comparisons with Tyrer-Cuzick version 8 (TCv8).

RESULTS:

The test set included 3,937 women, aged 56.20 years ± 10.04. Hybrid DL and image-only DL showed AUCs of 0.70 (95% confidence interval [CI]: 0.66, 0.75) and 0.68 (95% CI: 0.64, 0.73), respectively. RF-LR and TC showed AUCs of 0.67 (95% CI: 0.62, 0.72) and 0.62 (95% CI: 0.57, 0.66), respectively. Hybrid DL showed a significantly higher AUC (0.70) than TC (0.62; $P < .001$) and RF-LR (0.67; $P = .01$).

CONCLUSION:

Deep learning models that use full-field mammograms yield substantially improved risk discrimination compared with the Tyrer-Cuzick (version 8) model.

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New mammography-based measures of breast cancer risk

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INTRODUCTION:

Conventional mammographic density, the white or bright areas on a mammogram (Cumulus), is associated with risk of breast cancer, including interval and screen-detected cancers. We challenged the paradigm and found two new risk factors by: (i) redefining mammographic density as the bright, or brightest regions on the mammogram (we call the latter Cirrocumulus[1]); and (ii) applying machine learning to textural patterns (we call this measure Cirrus[2]).

OBJECTIVES:

To estimate the risk gradients for multiple mammography-based measures of breast cancer risk when fitted together and combined.

METHODS:

We measured Cumulus, Cirrocumulus and Cirrus for: (i) 669 cases and 2629 matched controls from the Melbourne Collaborative Cohort Study (MCCS); (ii) 384 cases and 1314 controls from Australian breast cancer family studies (ABCFS). We estimated odds ratio per standard deviation adjusted for age and BMI (OPERA)[3] and area under ROC curve (AUC) ~ Φ(log (OPERA)/1.414); Φ is a Normal (0,1) df.

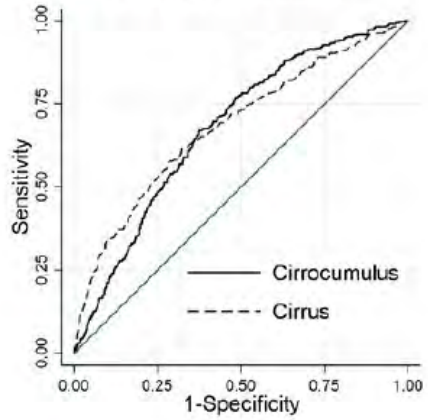
RESULTS:

Table 1: OPERAs (95% CIs) from fitting Cumulus (%), Cirrocumulus and Cirrus together.

Outcome	Cumulus (%)	Cirro	Cirrus
Interval (MCCS)	**1.73** (1.21-2.47)	*1.09* (0.80-1.48)	**1.73** (1.39-2.16)
Screen-detected (MCCS)	*0.78* (0.64-0.96)	**1.36** (1.14-1.64)	**1.59** (1.39-1.82)
All cases (ABCFS)	*0.89* (0.72-1.10)	**1.54** (1.27-1.86)	**1.61** (1.35-1.92)

For ABCFS, the AUCs were: Cirrocumulus: 0.68; Cirrus: 0.68; Combined: 0.71 cf. 314 SNP polygenic risk score[3]: 0.63. The equivalent OPERAs are 1.86, 1.86, 2.16 cf. 1.61.

Figure 1: Receiver Operating Characteristic (ROC) curve for Cirrocumulus and Cirrus for Australian case-control study



CONCLUSION:

Conventional mammographic density predicts risk of interval cancer, better as a percentage, most likely due to its role in masking tumours. Mammographic density defined by higher pixel brightness thresholds is more likely to be causally-related to intrinsic risk and does better at identifying women at higher than average breast cancer risk. Textural features are also more likely to be causally-related to intrinsic risk and do better at identifying women at lower than average breast cancer risk. Conventional mammographic density adds little or no information on intrinsic risk to these two measures. In differentiating women who will or will not get breast cancer on a population basis, the combination of these new mammography-based risk measures does >50% better than does all the known genetic risk factors.

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AI-based quantitative breast density assessment using transmission ultrasound

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INTRODUCTION:

A growing body of evidence indicates that breast density is one of the most important independent risk factors of breast cancer. Currently, mammography is the only FDA-cleared means to evaluate breast density in a general screening population. However, mammography (1) uses ionizing radiation with concerns of cumulative dose, and (2) represents a series of 2D projection images, making it difficult to estimate the true 3D volume of fibroglandular tissue. We present 3D transmission ultrasound (TU) as a method to visualize and differentiate fibroglandular tissue within the breast and use a fully automated segmentation method based on unsupervised machine learning to quantitatively assess the breast density

OBJECTIVES:

The aim of this study was to investigate the accuracy of quantitative breast density (QBD) evaluated using TU, which can differentiate and segment fibroglandular tissue volume within the whole breast tissue and compare it to the quantitative volumetric breast density as assessed by mammography with tomosynthesis [1].

METHODS:

The TU scanner (QT Ultrasound Breast Scanner 2000) collects projection data of the whole breast in a water bath, and reconstructs speed-of-sound, acoustic attenuation, and reflection image volumes of the whole breast. The first step in QBD assessment was segmenting the whole breast in the image volume from the surrounding water. This was followed by application of Fuzzy C-means (FCM) clustering to segment the whole breast into two compartments: (1) fibroglandular tissue; and (2) fatty tissue [2]. The QBD was calculated as a ratio of 3D fibroglandular tissue volume and the total breast volume. The algorithm was first tested in realistic tissue phantoms to demonstrate its quantitative accuracy. This was followed by application of the algorithm to clinical images of 100 breasts for which quantitative volumetric breast density (VolparaDensity™, v3.1) using mammography with tomosynthesis was also available and performed within 90 days of the TU scan. The breast density scores calculated by QBD and VolparaDensity were compared and correlated and the corresponding Spearman coefficient was computed.

RESULTS:

The application of QBD algorithm to tissue phantoms resulted in high quantitative accuracy with percentage error of less than 5%. The segmentation of fibroglandular tissue in clinical images showed high visual correlation, as shown in Figure 1. The comparison of QBD and VolparaDensity™ evaluations demonstrated a very strong correlation with Spearman r of 0.94 (CI: 0.91-0.96; $p<0.0001$).

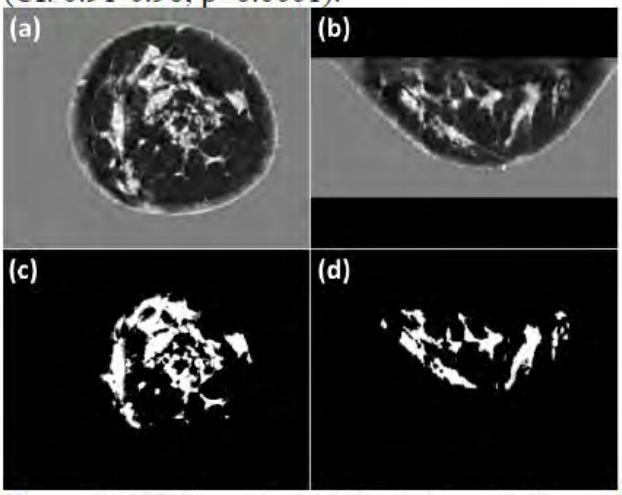

Figure 1: (a) Coronal and (b) axial speed-of-sound images generated by transmission ultrasound; (c) and (d) show the segmented fibroglandular tissue (with the skin), respectively.

CONCLUSION:

The results indicate that breast density as assessed in fully automated means by 3D TU can be of significant clinical value and play an important role in breast cancer risk assessment.

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Variation in Volumetric Breast Density and A Novel Texture Feature According to Race/Ethnicity

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INTRODUCTION:

There is significant racial/ethnic variation in breast cancer incidence and mortality. Racial/ethnic variation in breast density, a breast cancer risk factor, could contribute to observed disparities. Other mammographic features, collectively known as texture, have been identified and independently contribute to breast cancer risk. Racial/ethnic differences in V, a summary texture measure of variation in gray scale intensity on a mammogram,[1] have not been assessed.

OBJECTIVE: Evaluate if there are racial/ethnic differences in percent volumetric density (PVD), dense volume, non-dense volume, and V, a summary texture measure.

METHODS:

Our study population includes 2,351 female participants of the Boston Mammography Cohort Study (premenopausal N=1148, mean age 45.4 years; postmenopausal N=1203, mean age 59.3 years) with no personal history of cancer and data on density, BMI, and race/ethnicity. Volumetric density measures were estimated using Volpara software on baseline digital mammograms. V measures were not available for 519 participants. V was quantified using an automated computer-assisted analysis that assessed grayscale variation. Linear regression models with robust standard errors were used to estimate beta coefficients (ß) and 95% confidence intervals (CIs) for the relationships between race/ethnicity and square-root transformed density measures and V, adjusting for age and potential confounders including a linear and quadratic term for BMI. All analyses were stratified by menopausal status at time of mammogram.

RESULTS:

Compared to NH-White women, NH-Black and Hispanic women had higher mean BMI, consumed less alcohol, had lower physical activity, were more likely to be parous, and more likely to have never used postmenopausal hormones. Among postmenopausal women, we observed no differences in V across groups. NH-Blacks had higher non-dense volume and PVD in fully-adjusted models. Among premenopausal women, NH-other or unknown race women had lower absolute non-dense and dense volume as compared to NH-Whites. In the subset of 1832 women with data on density measures and V, observed associations were attenuated with mutual adjustment. We did not observe evidence of interaction with BMI.

Table 1: Racial/Ethnic Differences in Volumetric Percent Density and V among 1203 Postmenopausal Women

	NH-White	NH-Black	Hispanic	NH-Other Race
	ß (95% CI)			
	Percent Volumetric Density (PVD)			
N	897	137	100	69
Age adjusted	(Ref)	**-0.37**	**-0.22**	**-0.25**
		(-0.53, -0.21)	**(-0.38, -0.06)**	**(-0.45, -0.05)**
+BMI	(Ref)	0.07	0.06	-0.08
		(-0.06, 0.21)	(-0.08, 0.20)	(-0.22, 0.06)
+MV	(Ref)	**0.16**	0.12	-0.01
		(0.02, 0.29)	(-0.03, 0.26)	(-0.16, 0.15)
	V			
N	700	108	84	58
Age adjusted	(Ref)	**-1.3**	-0.11	-0.68
		(-1.9, -0.66)	(-0.09, -0.64)	(-1.4, 0.07)
+BMI	(Ref)	-0.10	0.52	-0.21
		(-0.67, 0.48)	(-0.19, 1.2)	(-0.82, 0.36)
+MV	(Ref)	0.19	0.70	0.005
		(-0.44, 0.81)	(-0.03, 1.4)	(-0.66, 0.67)

CONCLUSION: We observed limited evidence of differences in volumetric density measures and V across racial ethnic groups after adjusting for BMI.

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Quantifying the Realism of an Anthropomorphic Phantom for 3D Mammography Using Radiomic Texture Features

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INTRODUCTION: We have developed a pipeline for conducting virtual clinical trials (VCTs) in breast imaging, and have demonstrated that VCTs can reproduce the results of a clinical trial.[1] Creating populations of breast phantoms is an important step in a VCT. Our previous work showed that a population of simulated phantoms can be created with similar characteristics as a clinical population, specifically in terms of breast density and thickness.[2] To ensure that the parenchymal texture distribution is also comparable to women's parenchyma, radiomic texture features also need to be analyzed. These features may be indicators of the risk for breast cancer.[3]

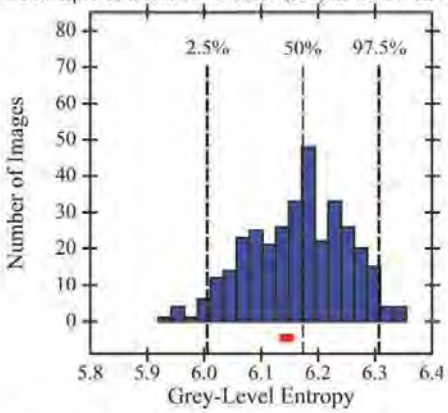
OBJECTIVES: We quantify the textural realism of a physical phantom for digital breast tomosynthesis. The phantom was manufactured by CIRS, Inc. (Norfolk, VA) under license from the University of Pennsylvania (Fig. 1). This work expands upon our previous analysis of this phantom[4] in that we extend the calculation of realism from 26 features to 344 parenchymal texture features.

Figure 1. Central slice of breast tomosynthesis reconstruction (left) and synthetic 2D image (right).

METHODS: A population of 1,000 women with negative screening exams obtained with the Hologic Selenia Dimensions system was analyzed. Radiomic texture features were calculated in the central slice of the reconstruction and the synthetic 2D image (C-View™) using a lattice-based software pipeline.[3] To validate the textural realism of the phantom, we focused specifically on the subset of women with 45-55 mm thickness in mediolateral oblique (MLO) views, since these patients were comparable to the physical phantom (50 mm thick). The phantom images were acquired with auto-timed technique settings with kV ranging between 30 and 32. These kV settings were chosen based on the patients with 45-55 mm thickness. Each acquisition was repeated twice.

For each feature, the six data points derived from the phantom were compared against the distribution of the clinical values. A feature was considered realistic in the phantom if all six data points were found to lie within the middle 95% of the clinical distribution. An example of a realistic feature is shown in Fig. 2; the six phantom data points are plotted in red below the clinical distribution. A feature was unrealistic if at least one of the six data points was outside the middle 95% of the clinical distribution.

Figure 2. Example of a realistic feature (red) in the reconstruction.



RESULTS: For each feature family, the percentage of features that exhibit clinical realism is shown in Table 1. Out of 344 features, 70.3% were found to be realistic in the reconstruction (63.4% in synthetic 2D imaging).

Table 1. Percentage of features (per family) demonstrating realism.

Feature Family (Number of Features)	Reconstruction	Synthetic 2D
Co-occurrence (8)	50%	25%
Co-occurrence Laws (120)	52.5%	50%
Edge Enhancement (1)	0%	0%
Fractal Dimension (2)	50%	50%
Gabor Wavelet (32)	100%	100%
Grey Level (12)	100%	50%
Laws (125)	80.8%	72%
LBP (36)	69.4%	63.9%
Power Spectrum (1)	100%	0%
Run Length (7)	42.9%	57.1%

CONCLUSION: Texture features were overall realistic in the reconstruction. There was less realism in synthetic 2D imaging. The phantom lacked realism mostly in fine structural detail (*e.g.*, co-occurrence features). There are inherent limitations to the fine detail that can be created in a physical phantom with 3D printing. Future work should extend these calculations to virtual phantoms which can be simulated with even finer detail.

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Exposure to passive smoking from parents during childhood and risk of Breast Cancer.

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WITHDRAWN

Reproductive determinants of high pre- and postmenopausal mammographic breast density in Dutch breast cancer screening participants

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INTRODUCTION:

Mammographic density (MD) is a breast cancer risk factor and reduces sensitivity of mammography. In most women MD decreases around menopause, but around 10% have extremely dense breasts even after the age of 50. Whether determinants of high postmenopausal MD differ from those of high premenopausal MD remains unclear.

OBJECTIVES:

To examine differences in reproductive determinants of pre- and postmenopausal MD in Dutch screening participants.

METHODS:

We studied screening participants aged ≤60 years and selected women on the extremes of MD: 3,560 with extremely dense breasts and 1,206 with almost entirely fatty breasts. MD was determined fully automatically by Volpara™ (Volpara Density Grade (VDG) 4 and VDG 1). We used logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs), for associations between age at menarche, parity, breast feeding, age at first birth and MD, adjusted for age at mammogram, socio-economic status and body mass index, and stratified for menopausal status.

RESULTS:

In postmenopausal women, using women with menarche <12 years as the reference group, the OR for extremely dense breasts was 1.40 [95%CI:0.89-2.18] for those with menarche at age 12-13 years, OR 1.72 [95%CI:1.07-2.75] for menarche at age 14-15 years, and OR 1.32 [95%CI:0.71-2.48] for menarche at age ≥16 years. The number of children was inversely associated with MD in postmenopausal women (OR 0.57 [95%CI:0.33-0.97] for 1 child, decreasing to OR 0.34 [95%CI:0.17-0.68] for ≥4 children).

Age at menarche and parity were not statistically significantly associated with MD in premenopausal women.

Breast feeding duration and age at first birth were not associated with MD in postmenopausal as well as premenopausal parous women.

CONCLUSION:

The risk of having high MD increases with higher age at menarche and nulliparity. These relationships in age at menarche and parity were mainly seen in postmenopausal women.

REFERENCES:

DENSE-on and DENSE (ClinicalTrials.gov ID-number: NCT01315015)

Exercise Program to Increase and Sustain Physical Activity after Breast Cancer Diagnosis

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INTRODUCTION:

Obesity and weight gain are significant concerns for breast cancer survivors. Obesity at diagnosis of breast cancer is an established negative prognostic factor and several studies report an inverse relationship between weight gain and disease free survival[1]. Weight gain is more common in women receiving adjuvant therapy. Results from the Women's Intervention Nutrition Study suggest that decreased dietary fat intake and weight loss after breast cancer diagnosis may decrease breast cancer recurrence. Although physical activity can lead to weight loss, body composition changes may be an important metric to evaluate and may occur independently of weight loss[2]. Anthropometry and regional composition measures are better predictors of obesity-related diseases and mortality risk than body mass index[3].

OBJECTIVES:

Primary Outcomes:

-Changes in Body Composition

-Sustainability of Exercise Activity after Randomized Intervention

Secondary Outcomes:

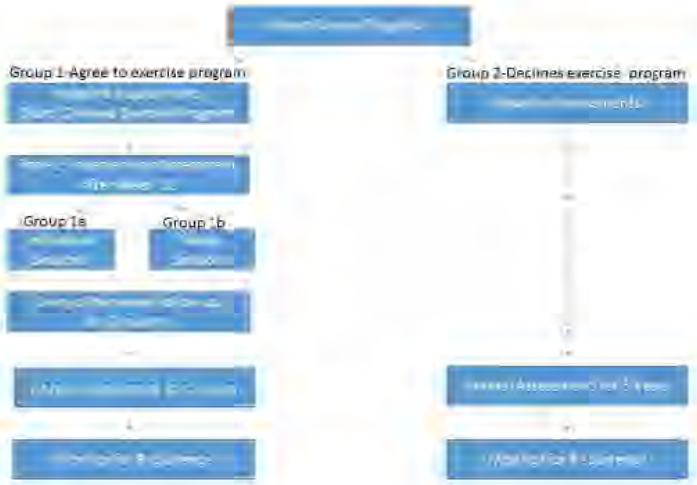
-Recurrence Free Survival/Invasive Disease Free Survival

-Quality of Life measures

-Biomarkers

METHODS:

We will enroll women who have been diagnosed with breast cancer into one of two groups. The participants will initially be offered either to participate in the exercise program or only receive body composition measurements. Women in the exercise program will attend 90min sessions at the Rehab Hospital of the Pacific, 3x/week, for a total of 12 weeks. After which, participants will then be randomized to continued individual vs group sessions for an additional 12 weeks, 2x/week. Body composition metrics, biomarkers and questionnaires will be collected prior to initiation of the exercise program and at the end of the exercise sessions. Follow up during the first year will be done to determine sustained physical activity levels. Biometric and medical follow up will be collected yearly for 5 years total to monitor for recurrence.



CONCLUSION:

Given the adverse consequences of weight gain after diagnosis, continued efforts to identify appropriate weight management interventions aimed at promoting overall health and long term survivorship are needed. It is particularly important to identify methods that maintain these physical activity behaviors.

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Breast Density Analysis with Dedicated Breast CT

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INTRODUCTION:

Dedicated breast computed tomography (BCT) is a novel x-ray imaging modality capable of acquiring breast images with high spatial and contrast resolutions. Due to its fully tomographic nature, BCT, along with the use of an automated tissue classification algorithm we have developed, makes it ideal for automatic quantification of breast density, providing an important benefit in determining breast density per patient and gaining insight into the distribution of breast density in the population.

OBJECTIVES:

To automatically determine the breast density in patient breasts from BCT images and characterize the distribution of breast densities among women of screening age (50 – 75 y) in the Netherlands.

METHODS:

Patient population

Women recalled from screening due to suspicious findings were recruited to undergo a single non-contrast BCT acquisition of the recalled breast for an unrelated study. Written informed consent was obtained for that ethics board-approved study, during which the patients released their anonymized images for additional research.

Image acquisition

Standard non-contrast enhanced BCT imaging was performed of the recalled breast only, using the automatic exposure control of the system (1). The 300 projections acquired in 10 s over 360° were used to reconstruct the 3D volume with 273μm isotropic voxels.

Breast tissue classification

A previously described and validated automatic classification method for BCT images was applied (2). The algorithm classifies the images into adipose, glandular, and skin tissues. The number of each voxels was counted and the percent glandular tissue by mass was calculated.

RESULTS:

To date, 92 patient BCT images were analyzed, resulting in the density distributions described in Table 1 and Figure 1. As can be seen, a *typical* breast has a density between 10% and 20%, with breasts above 50% density being very rare.

Table 1: Summary of the breast density distribution of the 92 BCT patient images.

Mean	20.4%
Median	17.9%
Minimum	1.1%
Maximum	57.0%

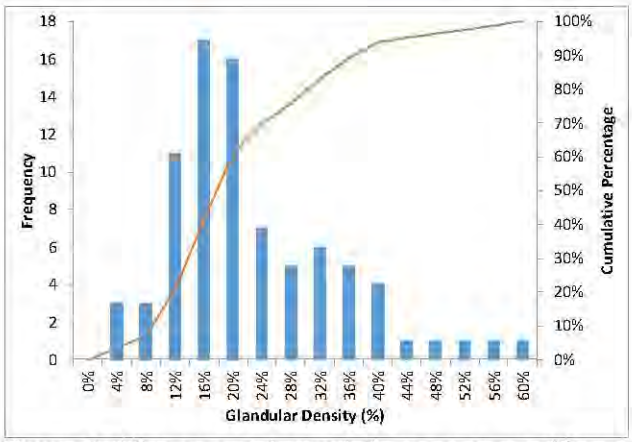

Figure 1: Histogram and cumulative percentage of breast densities for the 92 patient BCTs.

CONCLUSION:

Accurate quantitative evaluation of breast density, such as that obtained here with BCT, is important to characterize the real relationship of this biomarker to risk of cancer development. More advanced tissue texture analysis, which could potentially be better correlated to breast cancer risk, on the BCT images will be performed next.

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

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INTRODUCTION:

Vitamin D is a multifunctional pro-hormone. Despite its well-recognized role in bone mineralization and calcium homoeostasis, compelling experimental studies show that vitamin D exhibits anti-carcinogenetic properties. However, population-based cohort studies and randomized clinical trials have not demonstrated strong inverse associations between vitamin D with breast cancer risk. Previous studies, may have been limited in their abilities to answer questions related to higher doses / higher circulating levels of vitamin D. The VITamin D and OmegA-3 TriaL (*VITAL*) represents a unique opportunity to examine effects of high dose vitamin D supplementation on breast tissue architecture in the context of a randomized trial.

OBJECTIVES:

We propose to test the hypothesis that high dose vitamin D_3 (2,000 IU/day) supplementation will lead to (i) greater decreases in percent mammographic density (PMD) and (ii) greater decreases in "V" measure (i.e., single measure of gray-scale pixel variation) compared with women randomized to placebo.

METHODS:

As part of an ancillary study to the VITAL trial, we collected digital mammograms from women randomized to high dose vitamin D_3 (2,000 IU/day) supplementation or placebo. Mammograms were collected prior to randomization, and at 1 year and 3 years post randomization. Automated PMD and V were determined using an automated computer algorithm at the Moffitt Cancer Center. PMD was square root transformed to improve normality. Our primary analysis was an intention-to-treat analysis. We used linear mixed-effects models to estimate the changes in mammographic density and V from baseline to year 1, and year 3 post-randomization. Models were adjusted for age, BMI, and omega-3 randomization status.

RESULTS:

In this preliminary examination, we had data for 159 women randomized to vitamin D and 165 women to placebo. Overall we did not see a difference in change in PMD or V for women randomized to vitamin D compared to placebo (Table 1).

Table 1. Effect of vitamin D randomization on changes in PMD (square root transformed) and changes "V" measure from pre-randomization baseline in the VITAL trial. Adjusted for omega-3 randomization, baseline age and baseline BMI.

	Estimate (95% CI)	p-value
Changes in PMD		
Baseline to year 1	0.06 (-0.04; 0.16)	0.253
Baseline to year 3	0.06 (-0.05; 0.18)	0.283
Changes in "V" measure		
Baseline to year 1	-0.58(-19.50; 18.34)	0.952
Baseline to year 3	4.35 (-17.51; 26.20)	0.696

CONCLUSION:

In this preliminary analysis, we did not observe significant changes in mammographic density in women randomized to high dose vitamin D. This preliminary study represents only a fraction (~10%) of the observations that will be included in the final study. In the future, we will also examine >500 mammographic texture features and will examine differences by race.

Measuring the effects of rater training on ordinal ratings in large-scale breast imaging screening studies

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INTRODUCTION:

Women at high-risk for breast cancer may undergo supplemental screening via magnetic resonance imaging (MRI). In a similar manner to breast density on a mammogram, due to the visual nature of a radiologist's interpretation, the classification of background parenchymal enhancement (BPE) on an MRI is vulnerable to variability of rater scoring. A recent large-scale study examined whether a training intervention for radiologists improved the consistency of BPE interpretation. However, challenges arise due to many raters contributing ratings at more than one time point, the ordinal scale, and correlation between ratings. Here we describe the impact of training on radiologists' classifications due to training using a novel statistical approach that incorporates all the radiologists' classifications.

OBJECTIVES:

A novel statistical approach to measure the consistency between radiologists' ordinal ratings in large-scale breast imaging studies with the aim of assessing the impact of a training intervention is described. These methods are used to examine agreement between BPE ratings in a recent large-scale study of patients' breast MRIs.

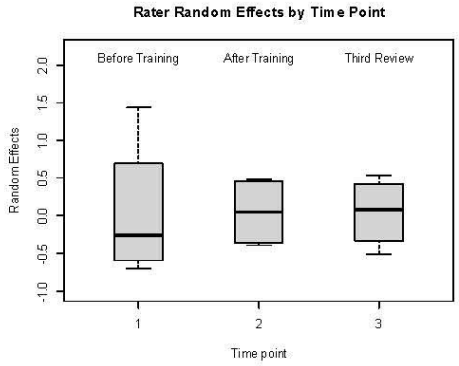
METHODS:

Four radiologists at one institution each independently rated 119 patients' breast MRIs according to the BI-RADS four-category BPE ordinal scale of increasing BPE at three different time points - before and after training (a two-hour interactive presentation) in a randomized order and again three weeks later[1]. A new statistical approach[2] based upon the class of generalized linear mixed models is used to measure the consistency (agreement) of ratings before versus after training.

Table 1: Results for the Melsaether study

Kappa measures of Agreement and Association	Before versus After Training	Between 2nd and 3rd viewings
Agreement κ_{agree}	0.49 (0.03)	0.52 (0.02)
Association κ_{assoc}	0.76 (0.02)	0.78 (0.02)

Figure 1: Variability of Radiologists in Melsaether et al study.



RESULTS:

Results indicate training improved the variability between radiologists' BPE ratings. Radiologists tended to assign more consistent ratings in their second and third viewings of the MRIs.

CONCLUSION:

The novel statistical approach provides an efficient approach to assess agreement between the ordinal ratings many radiologists in a large-scale breast imaging study.

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Novel methods for measuring breast density in younger women: TiBS and DXA

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INTRODUCTION:

Breast density is one of the most prevalent risk factors for breast cancer. Almost everything we know about breast density has been gleaned from mammographic breast density; it is highly variable at all screening ages, decreases as a woman gets older and is highly correlated over time within women[1]. Breast density is also modifiable and reduction in breast density has been shown to be associated with decreased breast cancer risk[2]. Very little is known about breast density in younger women as mammography is not typically recommended to women aged under 40. Extrapolating our understanding of breast density variation in younger women is key to improving early detection and informing primary prevention strategies; hence, novel methods of measuring breast density in younger women are needed.

OBJECTIVES:

This study investigates the feasibility, acceptability and validity of two methods of measuring breast density in younger women aged 18-40: Transillumination Breast Spectroscopy (TiBS) and an adapted Dual Energy X-ray Absorptiometry (DXA). TiBS is quick, simple, low cost, safe, and painless method of measuring breast density and ideal for younger women. It uses visible and near infrared light to measure spectral differences in breast tissue composition. Both measures have been shown to correlate closely with mammographic breast density in older women (40+).

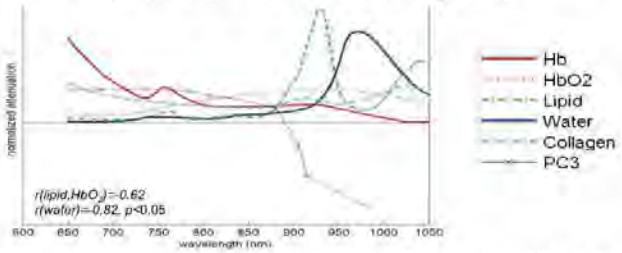
METHODS:

We measured TiBS-breast density in 547 female volunteers aged between 18-40 years without history of breast cancer or breast surgery, sourced via the University of Western Australia's crowd research program. Of these, 175 also had a DXA-breast density scan. Breast tissue composition was analysed by Principal Component Analysis (PCA) of the TiBS data. Component scores were evaluated for their correlation with DXA-breast density measures.

RESULTS:

PCA score analysis confirmed that Principal Component 3 (PC3) (Figure 1) and 4 (PC4) correlated most with DXA breast tissue density measures.

Figure 1: PC3 compared to normalized attenuation of breast tissue chromophores



Mean age of our subjects was 31.46 years (*SD*±5.8) and mean BMI was 31.46 kg/m^2 (*SD*±5.8). PC3, PC4 scores and DXA breast density were negatively correlated with age and BMI. PC3 and PC4 scores were both positively correlated with DXA breast density.

CONCLUSION:

Both TiBS and DXA breast density measures are significantly correlated with each other and with known determinants of mammographic breast density suggesting they are suitable methods for measuring breast density in women not recommended for mammography. A quick, simple, safe, and painless method like TiBS could help us understand the life-course of breast density and how it relates to breast cancer later in life.

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Supplemental Screening Availability vs. Utilization: Examining N.C. Mammography Facility Services for Women with Dense Breast Tissue

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INTRODUCTION:

Breast density is one of the most important factors contributing to false negative screening mammography results and is an independent predictor of breast cancer risk.[1] Data from a representative sample of mammography practices in the U.S. estimate that approximately 50% of women undergoing breast cancer screening have dense breasts, defined as heterogeneously dense or extremely dense tissue.[2] As of 2014, N.C. legislation encourages women with dense breasts to explore supplemental breast cancer screening modalities such as digital breast tomosynthesis (DBT), breast ultrasound (US), and breast magnetic resonance imaging (MRI).

OBJECTIVES:

We sought to explore the available supplemental screening modalities in N.C. and to determine if and when these modalities are being used for supplemental screening in women with dense breast tissue.

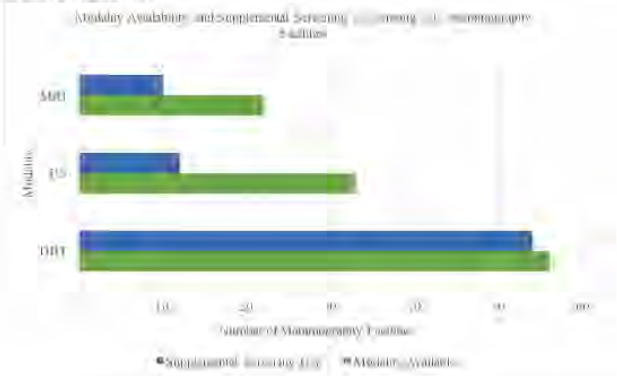
METHODS:

In 2017, we mailed a 50-item survey to 156 N.C. mammography facilities using the Tailored Design Method. The survey included questions pertaining to facility demographics, breast cancer screening services, supplemental screening services, and patient referral recommendations. We evaluated facility responses for available modalities, use of supplemental screening, and reasons for supplemental screening. Using logistic regression, we explored differences by facility location (urban versus rural) for modality availability, supplemental screening availability, and reason for supplemental screening use.

RESULTS:

Overall, 94 of the 156 facilities responded (60.3% survey response rate). Of the responding facilities, all offer digital mammography, 59.6% (n=56) offer DBT, 35.1% (n=33) offer breast US, and 23.4% (n=22) offer MRI. More urban facilities offer MRI, compared to rural facilities (p=0.021). Approximately 63% (n=59) of facilities reported using DBT, US or MRI for supplemental screening. Among facilities that offer DBT, nearly all (96.4%) use DBT as a supplemental screening modality. Of those that offer breast US, 35.7% use it as a supplemental screening modality, and of those that offer MRI, 46.7% use it as a supplemental screening modality (**Figure 1**). For sites that offer any supplemental screening modality and use that modality for supplemental screening, 47.5% base that use on breast density. Interestingly, 55.0% of responding facilitates who have breast US available and use it for supplemental screening base that use on patient breast density, compared to 46.3% for DBT, and 42.9% for MRI. Facilities also reported basing supplemental screening use on provider recommendations, patient risk assessments, and patient request. Comparing use of supplemental screening by facility location revealed that urban facilities are marginally more likely to report using MRI for supplemental screening compared to rural facilities (p-value=0.05). There were no significant location differences in use of supplemental screening for other imaging modalities and no significant differences in the proportion that used supplemental screening based on breast density.

FIGURE 1:



CONCLUSION:

It is promising that supplemental screening modalities are widely available throughout N.C.; however, future work should examine why these modalities are not being universally utilized for supplemental screening.

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Aspirin Use and Mammographic Breast Density

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INTRODUCTION:

Dense breast tissue, an area with more fibrous and glandular tissue than fat, is one of the strongest risk factors for breast cancer. Yet, currently there are limited methods to reduce breast density. Aspirin has been an agent of interest for the reduction of breast density and subsequent breast cancer risk, however previous observational studies report conflicting results and utilize a mostly postmenopausal study population. Over 40% of women have dense breast in the US, thus it may be of interest to investigate more options that are safe for prevention.[1]

OBJECTIVES: We examined the association of mammographic breast density with aspirin use and demographic covariates in women of diverse ethnic and predominantly immigrant backgrounds

METHODS: We used interview data from 770 women, aged 40-60 years, recruited during mammography appointments in NYC. Self-reported aspirin use was ascertained from the study questionnaire asking, "Have you ever taken or are you currently taking aspirin on a regular basis to prevent or treat any medical conditions?" Breast density outcome measures were collected from screening mammograms and reports. Linear regression models were used to estimate the association between mammographic breast density (measured by percent density, dense and non-dense area) with aspirin use, while adjusting for age, BMI, education, race ethnicity and reproductive factors.

RESULTS: The average age of the study population was 52 (5.6), average BMI was 30.9 (6.7), and women were predominantly of Hispanic background (78.9 %). About 16.9% reported current use of aspirin and this group was significantly older (average age 54.8 (4.7) vs 51.4 (5.6), p-value <0.0001) and had a higher BMI (32.4 (6.2) vs 30.6 (6.6), p-value= 0.001). In linear regression models, current aspirin use was associated with decreased percent density compared to women who reported prior or never aspirin use (β= -3.5, 95% CI: -6.4, -0.6). Such association is more evident in women who were overweight and obese (β= -3.9, 95% CI: -6.7, -1.0). When modeling dense area, we found that parous women displayed a decrease (β= -6.8, 95% CI: -13.5, -0.1) in dense area amongst current aspirin users. In the separate model of non-dense area, current aspirin use was associated with a strong increase in non-dense area (β= 21.2, 95% CI: 10.0, 32.5). This association was also stronger in overweight and obese women (β= 23.1, 95% CI: 10.8, 35.3).

CONCLUSION: Current aspirin use was associated with lower mammographic breast density within this ethnically diverse study population measured by continuous relative and absolute measures of mammographically dense breast tissue. Associations were stronger in overweight and obese women. Investigation of safe and affordable prevention agents for breast cancer warrant further testing in large diverse study populations.

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Anastrozole and Enobosarm (GTx-024): the effect of an aromatase inhibitor and selective androgen receptor modulator on mammographic breast density and breast pain in premenopausal women

[1]Dougherty, Daniella; [2]Good, Suzanne B; [1]Rolan, Paul; [3]Birrell, Stephen N
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INTRODUCTION:

The breast responds to alterations in its estrogen/androgen ratio[1]; when it shifts towards an androgenic environment there is a substantial change in mammographic breast density (MBD)[2]. The only widely accepted intervention shown to achieve this effect in premenopausal women is tamoxifen, a selective estrogen receptor modulator (SERM), this can result in significant adverse events. Aromatase inhibitors (AIs) are also able to promote an androgenic tissue environment but are contraindicated in premenopausal women due to the effect on ovarian function. By administering a selective androgen receptor modulator (SARM) with the AI, the impact of an AI on the hypothalamic-pituitary axis may be circumvented; not resulting in ovarian hyper-stimulation.

OBJECTIVES:

To evaluate the effect of Enobosarm (GTx-024) and anastrozole on MBD and breast pain in premenopausal women with high breast density and to evaluate its safety and tolerability.

METHODS:

This was an open-label, single center, 12-month pilot trial. Eight premenopausal women with high MBD and breast pain were administered 9mg of Enobosarm and 1mg of anastrozole daily. Percentage volumetric breast density (%VBD), total fibroglandular volume (TFV) and total breast volume (TBV) were analyzed at baseline and at 12 months using VolparaDensity™ analysis software. Breast pain was measured using a 100mm VAS at baseline and months 1, 3 and 12. Blood tests were conducted at baseline and months 1, 3, 6, 9 and 12 for hematology, biochemistry and a hormonal profile. All adverse events were documented.

RESULTS:

Table 1: Absolute change from baseline to 12 months

Variable	Change from baseline	p-value
%VBD	3.2%	0.065
TFV	94.73cm^3	<0.005
TBV	320.63cm^3	<0.005
Breast Pain	67.50mm	<0.005

There were dramatic decreases in TFV and TBV and breast pain although reductions in %VBD did not reach significance, this was due to significant reductions in breast size across the 12 months. The drug was well tolerated and there were no serious adverse events, deaths or withdrawals from the study due to AEs.

CONCLUSION:

This study has demonstrated a remarkable efficacy of Enobosarm and anastrozole in combination in reducing MBD and breast pain and warrants further evaluations.

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Circulating Anti-Müllerian Hormone in Relation to Mammographic Density and Measures of Lobular Involution among Premenopausal Participants in the BREAST Stamp and Komen Tissue Bank Studies

[1]Falk RT, [1]Pfeiffer R, [1]Fan S, [2]Oh H, [3]Sluss P, [4]Vacek PM, [4]Weaver DL, [4]Herschorn SD, [1]Hewitt S, [5]Shepherd J, [6]Mahmoudzadeh AP, [7]Wang J, [8]Fan B, [9]Storniolo AMV, [10]Sherman ME, [11]Figueroa J, [1]Gierach GL

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INTRODUCTION:

Recent epidemiologic evidence links elevated pre-menopausal Anti-Müllerian Hormone (AMH) with excess pre- and post-menopausal breast cancer risk[1]. Relationships between AMH and intermediate measures of breast cancer risk, including the degree of mammographic density (MD)[2] and of lobular involution, have not been well characterized.

OBJECTIVES:

We investigated whether serum AMH is associated with mammographic breast density (MD) and terminal duct lobular unit (TDLU) involution to understand potential mechanisms underlying AMH-associated breast cancer risk and perhaps inform screening guidance for younger women.

METHODS:

Serum AMH was measured by picoAMH enzyme-linked immunoabsorbent assay (Ansh Labs) in premenopausal women from two studies: the Susan G. Komen Tissue Bank (KTB, healthy breast tissue donors aged 18-54 years: 500 Caucasian, 184 African American), and the BREAST Stamp Project (Stamp, 160 Caucasian women aged 40-54 years referred for diagnostic breast biopsy). Metrics of TDLU involution in breast biopsies included whether TDLUs were observed (yes/no), the number of TDLUs per 100mm^2 of breast tissue area, and the number of acini/TDLU. MD was only available in Stamp, assessed using thresholding software, in pre-biopsy FFDM mammograms of the contralateral breast. Generalized linear models were used to estimate geometric means and 95% CIs of AMH adjusted for age and BMI, according to breast cancer risk factors and categories of involution and breast density metrics.

REFERENCES:

1. Ge W, et al. (2018). *Int. J. Cancer*, 142: 2215-2226.
2. Bertrand KA, et al (2015). *Cancer Epidemiol Biomarkers Prev*.24(5):798-809.

RESULTS:

AMH declined with age (**Table**) and was higher in obese women. In Caucasians, AMH was lower in women without observed TDLUs (**Figure 1**), but overall, AMH did not correlate with other TDLU metrics. In Stamp, AMH declined with increasing % MD ($p=0.07$) and absolute dense area ($p=0.16$) but increased with non-dense area (**Figure 2**).

Table: AMH (pg/ml) by Study, Race, Age and BMI

	Komen						STAMP		
	Caucasian			African American			Caucasian		
	N	% not detected	mean (95% CI)	N	% not detected	mean (95% CI)	N	% not detected	mean (95% CI)
Age group (years)									
<30	162	0%	1503.6 (1015.7, 2225.6)	46	0%	1290.9 (780.4, 2135.4)			
30-39	169	1%	1815.8 (1497.0, 2202.5)	78	0%	2045.7 (1499.4, 2791.1)			
40-49	146	8%	716.8 (552.7, 929.6)	54	16%	1108.5 (737.0, 1667.3)	131	10%	806.5 (585.5, 1114.7)
50-54	23	48%	261.2 (153.0, 445.9)*	6	80%	362.3 (115.0, 1140.7)	33	42%	245.5 (132.8, 453.7)*
Body mass index (kg/m^2)									
<25	183	6%	1033.8 (774.9, 1379.3)	33	11%	931.5 (510.5, 1699.7)	91	11%	981.8 (657.7, 1465.7)
25-29.9	117	11%	840.7 (656.0, 1077.4)	47	6%	922.1 (554.6, 1533.2)	38	22%	1142.8 (646.6, 2020.0)
≥30	199	7%	700.5 (576.4, 851.3)*	104	10%	899.7 (632.4, 1280.1)	35	31%	711.7 (394.6, 1383.8)

*p<0.05

Figure 1: Boxplots of AMH (pg/ml) by study, race and TDLUs

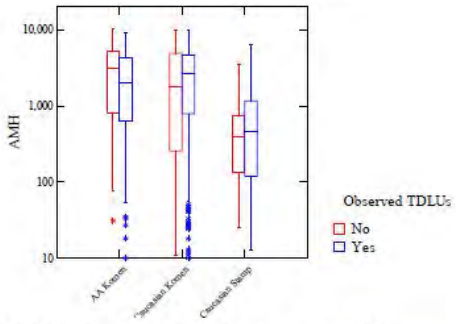
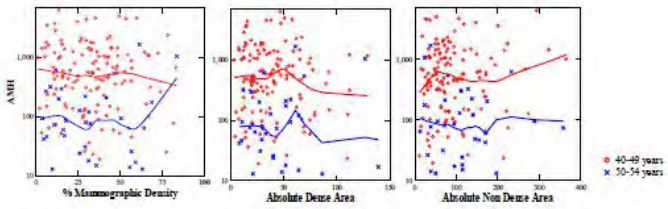


Figure 2: AMH Measures with Mean Curves for Different Age Groups by Percent MD, Absolute Dense Area and Absolute Non-Dense Area



CONCLUSION:

In these populations, AMH did not correlate consistently with metrics of TDLU involution or breast density which have been previously linked to breast cancer risk.

Breast tumor size and population disparities: elucidation of the role of screening mammography

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INTRODUCTION:

Hawaii's breast cancer incidence exceeds that of the U.S. overall, ranking 6th among all states. The rate of newly diagnosed cases continues to rise with an average increase of over 2% per year. Racial and ethnic disparities are prominent with the highest rates among Native Hawaiians and recent increases most pronounced among Japanese. Use of mammographic screening in Hawaii began in the mid-1980s with widespread use established over the following decade. The initial introduction of mammography was estimated to contribute to a 23% increase in statewide breast cancer incidence through the early 1990s.[1] However, later trends have not been examined.

OBJECTIVES:

Breast tumor size was evaluated to elucidate the influence of mammographic screening on the increasing burden of breast cancer in the state of Hawaii and to ascertain the contribution of screening to disparities across Hawaii's multiethnic population. Presumably, increases in breast cancer incidence attributed to mammography would be reflected in temporal increases in the diagnosis of smaller tumors and proportional decreases in larger tumors.

METHODS:

Statewide data from the Hawaii Tumor Registry, the statewide NCI SEER cancer registry, was evaluated in 22,288 breast cancer cases, including *in situ* (n=3,646) and invasive (n=18,642) tumor, diagnosed in women ages 40 and older in Hawaii between 1983 and 2011.

RESULTS:

Overall mean tumor size was 2.0 cm (1.4 for *in situ* and 2.2 cm for invasive cases). Mean tumor size was smallest in Japanese women (1.8 cm) followed by Whites and Chinese (2.0 cm), Koreans (2.1 cm), Filipina (2.2 cm), Native Hawaiians (2.3 cm), Other Asians (2.4 cm), and was largest in other Pacific Islanders (3.1 cm) ($p<0.0001$).

Overall, the proportion of breast tumors less than 2.0 cm increased from 54% of cases in 1983-1992 to 66% in 1993-2002 and decreased to 61% in 2003-2011 ($p<0.0001$). The proportion of tumors 5.0 cm or larger decreased from 8% of cases in 1983-1992 to 6% in 1993-2002 and increased to 8% in 2003-2011 ($p<0.0001$). From 1983-1992 to 1993-2002, significant decreases in tumor size were observed in Japanese, Filipina, Native Hawaiians, Whites, and Koreans. Tumor size was inversely correlated with age and positively correlated with grade. Mean tumor size was largest in ER-PR-tumors and smallest in ER+PR+ tumors. Racial/ethnic differences in tumors size remained after adjustment for age, grade, hormone receptor status, and time period.

CONCLUSION:

Hawaii's rising rates of breast cancer through 2002 were partly driven by increases in mammographic screening. However, the influence of screening appears to be less important in recent years. The persistence of breast cancer disparities in Hawaii's multiethnic population suggests differences in underlying risk factors and tumor heterogeneity in addition to screening behavior.

REFERENCES:

1. Maskarinec G, Wilkens L, Meng L. Mammography screening and the increase in breast cancer incidence in Hawaii. Cancer Epidemiology, Biomarkers and Prevention 1997; 6: 201-208.

Validation of Breast Cancer Polygenic Risk Scores in the Multiethnic Cohort

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Loic LeMarchand,[1] Yurii Shvetsov[1]
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INTRODUCTION

Over 100 single nucleotide polymorphisms (SNPs) associated with breast cancer risk have been identified to date. Some of these SNPs are ethnic-specific and do not replicate in other ethnicities. The relative risk associated with a single SNP is typically low. Due to this fact, several polygenic risk scores (PRS) have been proposed, combining known risk SNPs to examine their cumulative effect. These scores have been formulated for specific populations and their transferability to other populations is unknown.

OBJECTIVES

To examine breast cancer PRS in five main racial/ethnic groups within the Multiethnic Cohort (MEC) and evaluate differences in their predictive performance and their transferability across racial/ethnic groups. We hypothesized that predictive performance of the published PRS varies by score, sex, ethnicity, and/or tumor characteristics.

METHODS

The baseline questionnaire data and genome-wide genotyping data for 7071 female participants in the MEC breast cancer nested case-control study was used in the study. Genotype information on relevant SNPs was extracted and eleven PRS from published sources (1-6) were calculated using the available SNPs. For each PRS, its discriminatory performance was evaluated by computing the area under the receiver operating characteristic curve (AUC) statistic. Additionally, participants were classified into 5 strata based on PRS quintiles, and logistic regression was used to examine the association of the PRS with the risk of breast cancer. Models were adjusted for known breast cancer risk factors. Analyses were conducted for all races/ethnicities combined, as well as stratified by race/ethnicity.

RESULTS

The discriminatory performance of PRS differed by race/ethnicity. Most models performed well among White and Latino women, but poorly among African American women. Performance was affected by genotyping platform and the availability of SNPs required for PRS calculation. Performance also differed between two ethnicities with SNP data from the same genotyping platform (Native Hawaiians and Japanese Americans), suggesting that the observed ethnic differences are not exclusively due to different genotyping platforms or availability of SNPs. The Chan (1) and Wen ER-positive (5) were the top performing scores, with trends in breast cancer risk across score quintiles observed in 2 or more ethnicities. For the other PRS, no evidence of transferability across ethnic groups was observed.

CONCLUSION

Our results show limited or no transferability across races/ethnicities for the published breast cancer PRS. Further research is needed to establish unified PRS transferable across racial/ethnic groups.

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Partnering with Advocates to Assess Breast Density Patient Educational Materials

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INTRODUCTION:

Mammographic breast density increases lifetime risk of breast cancer and reduces the sensitivity of mammography.[1] Relative to White women, Black women are more likely to have dense breasts, yet experience more anxiety and have less knowledge about their density.[2]

OBJECTIVES:

This study aims to 1) identify preferred educational content, format and opportunities for cultural tailoring related to breast density information; and 2) characterize the readability and understandability of breast density information to improve the quality of breast density education for Black women.

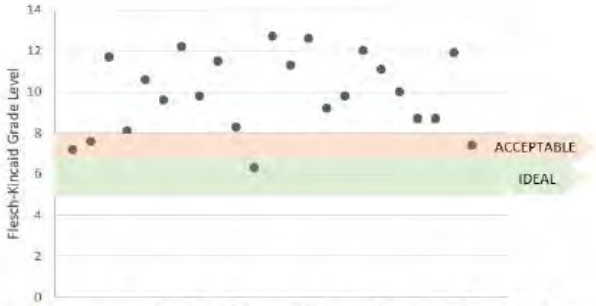
METHODS:

Members of the Pink & Black Education and Support Network, a group of Black breast cancer patients and survivors in Boston, were invited to discuss breast density materials. Women rated six elements of communication, indicating their relative importance. Ratings guided the discussion of materials from national breast cancer advocacy groups. We also compiled publically-available educational materials designed for women with dense breasts. Readability was evaluated using the Flesch-Kincaid and Dale-Chall New Readability metrics. Understandability was measured using the Patient Education Material Assessment Tool (PEMAT), where higher scores suggest patients will be able to understand and act on the information provided. Scores were rated by 2 coders and discrepancies resolved by the team.

RESULTS:

Nine Pink & Black members convened over 3 sessions. The most important elements of breast density education were: a) *knowing what I can do about dense breasts*, b) *being able to ask questions*, and c) *getting information quickly*.

Figure 1: Flesch-Kincaid Grade Level of Breast Density Education Materials (N=22)



The mean Flesh-Kincaid grade for the 22 breast density materials was 9.9 (6.2-12.7). Fifteen were assessed at Grade 11-12 on the New Dale-Chall score, with none scoring below Grade 9. The average PEMAT score was 66/100 (40-81). Consistent with readability scores, women suggested current materials used complex medical jargon and did not convey a clear definition of breast density. They advised briefing women about breast density in mammography waiting rooms prior to imaging using informational videos. To decrease anxiety, women desired information via peers or health navigators, rather than a doctor.

CONCLUSION:

We found that breast density education materials available to the public exceed the recommended reading level of 5-8th grade for health education materials, creating a barrier for patients' ability to use this information for breast cancer screening decision-making. Further, information is currently not delivered in a format that is concordant with women's preferences for information.

REFERENCES:

1. Pettersson A, Graff RE, Ursin G, et al. Mammographic density phenotypes and risk of breast cancer: A metaanalysis. J Natl Cancer Inst 2014;106.
2. Manning M, Albrecht TL, Yilmaz-Saab Z, Penner L, Norman A, Purrington K. Explaining between-race differences in African-American and European-American women's responses to breast density notification. Social Science & Medicine. 2017; 195:149-58.

What do women know and do about breast density?

Darcey E[1], Dench E[1], Keogh L[2], McLean K[1], Robertson M[1], Hunt EJ[1], Saunders C[3], Thompson S[4], Woulfe C[1], Wylie E[3,5], Stone J[1]

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INTRODUCTION:

Despite widespread consumer calls for women undergoing mammographic screening to be informed of their breast density, concerns remain as to how this can be interpreted and acted upon given the absence of evidence-based supplemental screening recommendations for women with dense breasts. The United States Congress has directed the Food and Drug Administration (FDA) to establish a national minimum standard for breast density notification as part of routine mammography reporting. Further evidence of what women know about breast density and how well women interpret breast density information provided by screening services will help inform and improve breast density notification standards.

OBJECTIVES:

To assess the knowledge and awareness of breast density and the post-screening actions/response of women who attended public mammographic screening at BreastScreen Western Australia.

METHODS:

Women who were notified they have dense breasts were compared to controls who had not been notified. Descriptive data analysis was used to summarize responses from 6,186 women. Thematic analysis was used to summarise qualitative data on how notified women understood the information provided, their emotional response, and their future screening intentions.

RESULTS:

Most screened women have heard of breast density (~60% of controls). Over 85% of women who have been notified that they have dense breasts knew that dense breast tissue makes it more difficult to see cancer on a mammogram, compared to 54% of controls. However, women are largely unaware that increased breast density is associated with increased risk of the disease (<25% of notified women compared to nearly 14% of controls). Half of women who are notified they have dense breasts within the BreastScreen Western Australia program appear to follow recommendations to consult their doctor. Of these, half were referred to supplemental screening with only 20% reporting having an ultrasound due to their breast density. Around 20% of women reported feeling anxious or confused post breast density notification however this emotional response does not appear to deter women from mammographic screening in the future. In fact, of the notified women who indicated that knowing their breast density made them feel anxious, 96% intended to have another mammogram with BreastScreen WA when they were next due (compared to 92% of controls).

CONCLUSION:

BreastScreen WA's main message that breast density reduces sensitivity of mammography to detect breast cancer appears to be getting though, with minimal impact on supplemental screening rates and/or anxiety levels within screening participants. Women are largely unaware that increased breast density is associated with increased breast cancer risk.

THURSDAY | JUNE 6, 2019

Diamond Head Luau Networking Event

After the last talk on Thursday, we have a networking event at the Diamond Head Luau, which also includes admission to the Waikīkī Aquarium before the show.

- **Diamond Head Luau**
  4:30 PM - 8:00 PM
  bus service from hotel
  In ancient Hawai'i, it was customary to celebrate special occasions with *'ohana* (family) and friends. At Diamond Head Luau, they continue this tradition with a menu that is locally grown and prepared right here in Hawai'i.
- **Waikīkī Aquarium**
  5:20 PM - 6:00 PM / walk
  The Waikīkī Aquarium - second oldest in the U.S. - showcases more than 500 marine species, and maintains more than 3,500 marine specimens. Public exhibits, education programs, and research focuses on the unique aquatic life of Hawai'i and the tropical Pacific.

TRANSPORTATION INSTRUCTIONS

Two buses are arranged to transport participants from the Prince Waikīkī to the Waikīkī Aquarium for the event.

Please be at the valet station right outside the hotel at 4:30 PM.

Don't be late.

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FRIDAY | JUNE 7, 2019
Breast Cancer Risk Assessment

REGISTRATION & BREAKFAST / BREAKOUT DISCUSSION

7:00 AM - 8:00 AM — Piʻinaio Foyer & Ballroom 2

HOUSEKEEPING

8:00 AM - 8:15 AM — Piʻinaio Ballroom 1

RISKS ASSESSMENT I

8:15 AM - 9:35 AM — Piʻinaio Ballroom 1
Moderator: Karla Kerlikowske

PLENARY TALK 6
Gertraud Maskarinec, MD, PhD | University of Hawaiʻi Cancer Center
Obesity and Breast Cancer Risk: The Multiethnic Story of Hawaii

POSTER TALK 6
Mikael Eriksson, PhD | Department of Medical Epidemiology and Biostatistics, Karolinska Institutet
A Clinical Model for Assessing the Individual Breast Cancer Risk in Mammography Screening

POSTER TALK 7
George Napolitano | Department of Public Health, University of Copenhagen
Birth cohort effect on breast density of Dutch women

COFFEE BREAK

9:35 AM - 10:05 AM — Piʻinaio Ballroom 2

RISKS ASSESSMENT I (CONT.)

10:05 AM - 11:25 AM — Piʻinaio Ballroom 1
Moderator: Karla Kerlikowske

PLENARY TALK 7
Solveig Hofvind, PhD | Cancer Registry of Norway, Oslo Metropolitan University
Digital breast tomosynthesis mammography and cancer detection - the To-Be trial

POSTER TALK 8
Katherine Callaway, PhD | Harvard Medical School/Harvard Pilgrim Healthcare Institute
Impact of Breast Density Legislation on Ultrasound Use, 2002-2016

LUNCH

11:25 AM - 12:25 PM Piʻinaio Ballroom 2

POSTER SESSION 2 (ODD-NUMBERED)

12:25 PM - 1:25 PM Piʻinaio Ballroom 2

P1. Andrew Maidment, PhD, FAAPM | University of Pennsylvania
Radiomic Texture Analysis in Digital Mammography Using an Anthropomorphic Phantom: Robust Feature Identification

P3. Samantha Puvanesarajah, PhD, MPH | Behavioral and Epidemiology Research Group, American Cancer Society
Correlates for multiple breast biopsies among women in Cancer Prevention Study-3

P5. Hannah Oh, PhD | College of Health Sciences, Korea University
Early-life and adult anthropometrics in relation to mammographic texture variation in the Nurses' Health Studies

P7. Gothami Hettiarachchi | Department of Radiology, University of Peradeniya
Breast density on mammography as a predictor of breast cancer: A Sri Lankan experience

~~**P9**. Inger Gram, MD, PhD | Department of Community Medicine, University of Tromsø~~
~~*Is it time to establish breast cancer as a smoking-related cancer?*~~

P11. Rebecca Kehm | Department of Epidemiology, Columbia University
A comparison of breast tissue composition between mothers and adolescent daughters using optical spectroscopy

P13. Jane Walter, PhD | University Health Network
Change in Breast Composition over Time Measured via Optical Spectroscopy in Women at Average and High-Risk of Breast Cancer

P15. Holly Harris, MPH, ScD | Public Health Sciences, Fred Hutchinson Cancer Research Center
Adolescent and early adulthood adherence to pro- and anti-inflammatory dietary patterns and effects on premenopausal mammographic density

P17. Lenora Loo, PhD | Cancer Epidemiology, University of Hawaiʻi Cancer Center
Molecular Profiling of Carcinoma In Situ to Predict Risk of Progression to Invasive Breast Cancer in a Multiethnic Population

P19. Sarink Danja, PhD | Cancer Epidemiology Program, University of Hawaiʻi Cancer Center
Racial/ethnic disparities in breast cancer and its risk factors: the Multiethnic Cohort Study

P21. Daniella Dougherty | School of Medicine, University of Adelaide, North Terrace
The potential utility of Shear Wave Elastography as a biomarker of the effects of interventions targeted at reducing Mammographic Breast Density

P23. Maria Luisa Garmendia, PhD | Institute of Nutrition and Food Technology, University of Chile
Effect of excessive gestational weight gain on daughters' breast density

POSTER SESSION 2 (ODD-NUMBERED)

12:25 PM - 1:25 PM — Pi‘inaio Ballroom 2

P25. Lothar Lilge, PhD | Department of Medical Biophysics, University of Toronto
Breast Chromophore Content as determined by Optical Breast Spectroscopy

P27. Omid Haji Maghsoudi, PhD | Department of Radiology, University of Pennsylvania
A deep learning approach for breast segmentation in digital mammography

P29. Rachel Lloyd | Centre for Genetic Origins of Health and Disease, Curtin University and University of Western Australia
Is early life growth associated with breast tissue composition in younger women?

P31. Lambert Leong | University of Hawai‘i Cancer Center
Iterative reconstruction approach to derive accurate local thicknesses of compressed breast in digital tomosynthesis

P33. John Hopper, PhD | NHMRC Senior Principal Research Fellow, University of Melbourne
New mammography-based measures of breast cancer risk

P35. Rulla Tamimi, ScD | Channing Division of Network Medicine, Brigham and Women’s Hospital and Harvard Medical School
Mammogram-derived texture features and risk of breast cancer

RISKS ASSESSMENT II

1:25 PM - 2:25 PM — Pi‘inaio Ballroom 1
Moderator: Nico Karssemeijer

PLENARY TALK 8

Jeffrey Tice, MD | University of California, San Francisco
Women Informed to Screen Depending On Measured of Risk (WISDOM): A Randomized Trial of Risk Assessment to Guide Breast Cancer Screening

POSTER TALK 9

Gretchen Gierach, PhD | National Cancer Institute
Alterations in Levels of Serum IGF-I and IGBFP-3 and Ultrasound Tomography Measures of Breast Density Following Tamoxifen Therapy

COFFEE BREAK

2:25 PM - 2:55 PM — Pi‘inaio Ballroom 2

RISKS ASSESSMENT II (CONT.)

2:55 PM - 3:55 PM

Pi‘inaio Ballroom 1
Moderator: Nico Karssemeijer

POSTER TALK 10

Erica Lee Argov | Mailman School of Public Health, Columbia University
Statins and Metformin Use and Mammographic Breast Density

PLENARY TALK 9

Wolfgang Buchberger, MD, MSc | Institute of Quality and Efficiency in Medicine, UMIT
Combined screening with mammography and ultrasound in a population-based breast cancer screening program

PANEL DISCUSSION AND QUESTIONS

3:55 PM - 4:25 PM

Pi‘inaio Ballroom 1

Obesity and Breast Cancer Risk: The Multiethnic Story of Hawaii

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Introduction

The risk to develop breast cancer varies considerably across ethnic groups. In general, incidence has been higher in Western countries than in Asia, but over decades many migrants have adopted the risk of their host population, a fact that argues against an exclusive genetic determination of risk and in favor of lifestyle and environmental factors. Migrants from Asia, and especially from Japan, to the US and to Hawaii have been an informative population to observe changes in breast cancer incidence and to explore possible risk factors that may be responsible for these trends in incidence.

Japanese Migration to Hawaii

During 1868-1924, more than 200,000 Japanese came to Hawaii from Japan. Whites developed more breast cancer than Japanese until 2000 when the incidence of Japanese in Hawaii reached similar rates as in whites. Breast cancer rates doubled among 1st generation migrants and tripled during the 2nd generation as compared to Japan. When mammography screening was introduced in the late 1980s, breast cancer incidence rates for all ethnic groups in Hawaii rose rapidly. Breast cancer incidence has been higher among Native Hawaiians and lower among Filipinas than whites, but the disproportionate mortality rates from breast cancer for these ethnic groups remain a concern.

Increasing Prevalence of Obesity

Excess body weight is considered the most important modifiable risk factor breast cancer and its prevalence has increasing at a rapid rate in all parts of the world. Within the MEC, obesity was a statistically significant predictor in all ethnic groups except Latinas (HR, 1.17; 95% CI, 0.99-1.38). The respective HRs for obese women as compared to the 20-<25 kg/m^2 category in white, African Americans, Native Hawaiians, and Japanese American were 1.33 (95% CI, 1.15-1.53), 1.21 (95% CI, 1.04-1.41), 1.35 (95% CI, 1.09-1.67), and 1.46 (95% CI, 1.23-1.72). A stronger association of obesity with breast cancer women of Asian ancestry than whites has been reported for many other investigations. It has been hypothesized that these ethnic differences may be due to body fact distribution, i.e., the higher ratio of visceral to subcutaneous adipose tissue (VAT/SAT) with its metabolic consequences often described in persons of Asian ancestry.

Mammographic Density in Hawaii

Mammographic density studies among Hawaii's ethnic groups have shown higher densities in women of Asian ancestry than whites due to their relatively small breast size. At the same time, breast density was higher among Japanese Americans in Hawaii than in Japan, reflecting the difference in breast cancer risk. In a subset of female MEC participants who underwent DXA and MRI imaging, mean mammographic density was (17.3±10.5%). It was highest in Japanese Americans (20.2±10.9%), intermediate in Native Hawaiians (16.7±9.5%), whites (16.1±9.9%), African Americans (16.1±11.9%), and lowest in Latinas (15.4±9.5%). While BMI, total body fat, VAT, and SAT were inversely related to breast density (r=-0.51, -0.52, -0.35, and -0.55; p<0.0001), the VAT/SAT ratio showed a positive association with breast density (r=0.10; p=0.01). After adjustment for relevant covariates, the association with breast density remained inverse for SAT (β=-0.004; 95% CI -0.005, -0.002; p<0.0001), disappeared for VAT (β=-0.0003; 95% CI -0.002, 0.002; p=0.78), but was strengthened for the VAT/SAT ratio (β=0.52; 95% CI 0.16, 0.88; p=0.005).

Conclusions

Increasing obesity rates but especially a higher VAT/SAT ratio appear to play an important role in changing breast cancer incidence rates in the multiethnic population of Hawaii.

Abbreviations

BMI=body mass index; CI=confidence interval; DXA=dual-energy x-ray absorptiometry; HR=hazards ratio; MRI=magnetic resonance imaging; SAT=subcutaneous adipose tissue; VAT=visceral adipose tissue

Authors and institutions

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

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Title

A Clinical Model for Assessing the Individual Breast Cancer Risk in Mammography Screening

Background. Mammography screening reduces breast cancer mortality but a large proportion of breast cancers are missed and detected at later stages. We developed a risk model that identifies women who are negative at screening but are likely to be diagnosed with breast cancer before or at next screen.

Methods. The study was based on the KARMA cohort, a prospective screening cohort including 70,877 participants including 1,025 incident cancers. A risk score was developed using mammographic features (density, masses, microcalcifications) and their asymmetry, age, menopausal status, body mass index, family history of breast cancer, three modifiable risk factors (current use of hormone replacement therapy, tobacco and alcohol) and a polygenic risk score including 313 SNPs. Absolute risks were estimated using Cox regression, national incidence rates, and competing risks. Two external cohorts were used for validation.

Results. The risk model with the highest discrimination reached an area under the curve of 0.75 (95% CI 0.74, 0.77) with good model fit (Hosmer-Lemeshow = 0.2). The model identified 50% of the cancers among the 19% women with highest risk. Using the image-based model only the 5% of women at highest risk had a 10-fold higher risk of being diagnosed with breast cancer compared to the average risk of breast cancer. The high-risk women were more likely to be diagnosed with invasive, larger, lymph node positive and stage 2 cancers. The models were validated in two independent datasets.

Conclusions. By combining mammographic features, lifestyle and family history factors, and a polygenic risk score we have generated a risk score of breast cancer that identifies women at high risk of breast cancer possibly in need of supplementary screening procedures.

Birth cohort effect on breast density of Dutch women

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INTRODUCTION:

High mammographic density is a well-known risk factor for breast cancer, however firm data on possible changes of breast density across birth cohorts are still missing.

OBJECTIVES:

The main objective of this study was the evaluation of a possible birth cohort effect on mammographic density. In turn, this would possibly provide a partial explanation to the observed increase in breast cancer incidence.

METHODS:

We analyzed volumetric breast measurements of the total breast volume and of the fibroglandular volume for the left and right breast separately. Mammograms were collected during a 13 year period (2003-2016) in a population-based breast cancer screening programme in the Netherlands. In total, our dataset contained information on 69,041 Dutch women, aged 48-76 and born in the period 1929-1966.

First, we studied the time trend of the percent dense volume (*PDV = (fibroglandular volume)/ (total volume)*) across consecutive birth cohorts of women in four distinct age-groups (50, 55, 60 and 70). In each age-group, a linear regression model of the PDV against year of birth has been applied. Outcome measures were the slope of the regression line and the p-value for t-test, determining whether the slope differs significantly from zero.

Second, we compared the proportions of women with highly dense breast (PDV $\geq$ 15.5%), stratified by 1-year age-group, in women born in the years 1946-1953 and 1959-1966. Relative risk with 95% confidence interval, and corresponding chi-squared test p-values were calculated.

RESULTS:

A linear regression model showed a statistically significant increase of PDV in different age groups, both for left and right breast. For the left breast we observed a statistically significant positive slope (Sl=0.04, p=0.003) in the 50 age group. For the right breast, the 50 and 70 age groups showed statistically significant regression slopes (Sl=0.09 and p<0.0001, Sl=0.05 and p=0.002, respectively), as well as the 55 age group, although with a p-value close to the significance threshold (Sl=0.04 and p=0.01).

A relative risk analysis showed that the proportion of women with highly dense breast was generally higher for the later-born women (group 1959-1966) compared to those born earlier (group 1946-1953). For the left breast we observed a statistically significant 26% increase in women aged 53. A similar increase appeared at ages 51, 52, 54 and 55, with p-values close to the significance threshold (p=0.02, 0.02, 0.02, 0.01, respectively). For the right breast, we obtained statistically significantly increases, ranging from 27% up to 48%, for all ages from 50 to 56.

CONCLUSION:

Our findings show an increase in the average PDV across birth cohorts. Furthermore, the proportion of women with highly dense breast was found to be higher in later-born than earlier-born cohorts.

REFERENCES:

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Int J Cancer. 2019 Feb 14. doi: 10.1002/ijc.32210

Digital breast tomosynthesis mammography and cancer detection - the To-Be trial

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INTRODUCTION:

The To-Be trial was a randomized controlled trial with tomosynthesis including synthetic mammograms (DBT) versus standard digital mammography (DM), performed in Bergen as a part of BreastScreen Norway, during 2016 and 2017. In the trial, we found lower recall rate in the DBT-arm, but no statistical significant difference in the rate of screen-detected breast cancer. However, mammo-graphic density, which is shown to be of influence for the sensitivity of a screening program, was not included in the analyses.

OBJECTIVES:

We aimed to describe the proportions of performance measures defined as consensus, recall, screen-detected and interval breast cancer for DBT and DM by mammographic density. Secondly, we wanted to analyze the risk of screen-detected breast cancer for women screened with DBT and with DM, also by mammographic density.

METHODS:

We explored three automated measures for mammographic density; Volpara density grade, volumetric breast density (VBD) and fibroglandular volume. We stratified analyzes by quintiles of VBD and screening technique and used Z- and t-tests to test for differences between the groups. All rates were estimated among those screened during the study period, except for interval breast cancer, where only women screened in 216 were included die to requirement of two years follow–up. A log-binomial regression model was fitted to provide the risk ratios (RR) of screen-detected cancers by mammographic density for DBT and for DM.

Table 1: Performance for DBT and DM by mammographic density

	DBT N = 14380		DM N = 14369		p-value*
	n	%	n	%	
Screen-detected breast cancer by quintiles of VBD[&]					
1st	13/2800	0.5 %	11/2724	0.4 %	0.73
2nd	12/2833	0.5 %	16/2818	0.6 %	0.44
3rd	20/2842	0.7 %	23/3006	0.8 %	0.78
4th	29/2928	1.0 %	23/2847	0.8 %	0.46
5th	21/2856	0.7 %	13/2910	0.5 %	0.15
NA[#]	0/121		1/64		
Consensus by quintiles of VBD[&]					
1st	106/2800	3.8 %	153/2724	5.6 %	<0.01
2nd	146/2833	5.2 %	193/2818	6.9 %	<0.01
3rd	188/2842	6.6 %	258/3006	8.6 %	0.00
4th	227/2928	7.8 %	224/2847	7.9 %	0.87
5th	230/2856	8.1 %	227/2910	7.8 %	0.72
NA[#]	11/121		5/64		
Recall by quintiles of VBD[&]					
1st	55/2800	2.0 %	89/2724	3.3 %	<0.01
2nd	71/2833	2.5 %	110/2818	3.9 %	<0.01
3rd	87/2842	3.1 %	136/3006	4.5 %	<0.01
4th	108/2928	3.7 %	116/2847	4.1 %	0.45
5th	118/2856	4.1 %	115/2910	4.0 %	0.73
NA[#]	11/121		5/64		
IC[°] for women screened in 2016 by quintiles of VBD[&]					
1st	1/1286	0.08 %	2/1243	0.16 %	0.54
2nd	1/1295	0.08 %	0/1335	0.00 %	0.31
3rd	1/1356	0.07 %	3/1438	0.21 %	0.35
4th	1/1463	0.07 %	5/1393	0.36 %	0.09
5th	3/1480	0.20 %	8/1495	0.54 %	0.14
NA[#]	0/105		0/41		

* Z tests for proportions [#]Information not available [°]Interval Breast Cancer
[&]Volumetric Breast Density

RESULTS:

The measurement of mammographic density differed for women screened with DBT versus DM. We identified higher consensus (3.8% vs 5.6%) and recall rates (2.0% vs 3.3%) in DM compared to DBT in quintile1, the fattiest breast. For DBT, we observed an increased risk of screen-detected breast cancer for women in the fourth density quintile (RR 2.27, 95%CI: 1.18 - 4.36).

CONCLUSION:

Results of automated measurements of mammographic density were challenging to compare across screening techniques. Using quintiles of volumetric breast density, DBT appeared to more accurate on fatty breasts. No differences in rates were observed for DBT vs DM for women with the highest density, quintile 4 and 5.

Table 2: Adjusted* risk ratio (RR) for screen-detected breast cancer in the DBT group

	RR	95% CI	p-value
Quintiles of Volumetric Breast D			
1st	1.00	-	-
2nd	0.94	0.43-2.06	0.88
3rd	1.61	0.80-3.24	0.18
4th	2.27	1.18-4.36	0.01
5th	1.18	0.88-3.55	0.11

*Adjusted for age and screening history

Impact of Breast Density Legislation on Ultrasound Use, 2002-2016

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INTRODUCTION:

Since 2009, 37 states have mandated women be notified if they have dense breasts with their screening mammogram report and in some states, women are encouraged to obtain supplemental screening with advanced breast imaging. While supplemental ultrasound may improve breast cancer detection, use also leads to more false-positive biopsies. Early clinic- and state-specific analyses have shown increases in ultrasound use following legislation; however, a multistate study showed mixed effects.

OBJECTIVES:

To investigate the population-level impact of state-specific breast density legislation on ultrasound use by comparing states with and without legislation from 2002-2016.

METHODS:

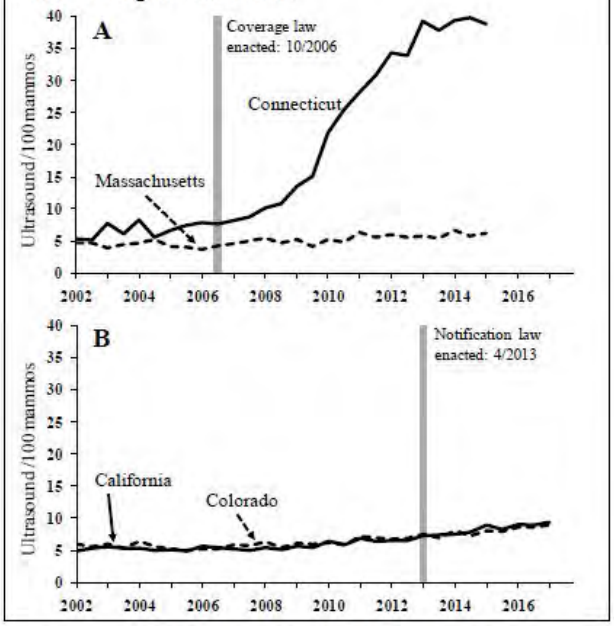
We used medical claims from a large national insurer to calculate state-level rates of ultrasound following a screening mammogram within 30 days for women aged 40-64 from 2002-2016. Biannual ultrasound rates per 100 mammograms were standardized by age and race. States with legislation were paired with states without based on proximity and trends in use prior to legislation. We used an interrupted time series with matched control series design and segmented regression to estimate trend and level changes in ultrasound use between pairs. State-specific effects were summarized as the average predicted increase in use at 1 and 3 years after legislation across control states.

RESULTS:

27 intervention states had at least 1 year of follow-up and 15 had at least 3 years. We found no increases in ultrasound use at 1 and 3 years post-enactment in over half the states (16/27 and 9/15, respectively). In states with positive effects at 3 years (n=6 of 15), ultrasound had increased on average by 3.8 additional exams per 100 mammograms (range 0.1-12/100). Effects were most pronounced in states with mandated insurance coverage (n=4) especially when coupled with notification laws as was the case in Connecticut. For example, despite similar rates at enactment, the average effect in Connecticut after 3 years was 12 additional screens/100 (Fig A) and 1/100 in California (Fig B), a state with a notification law alone.

CONCLUSION:

Figure: Biannual ultrasound use in 2 states and exemplar controls



In our multistate longitudinal study, breast density notification alone had a modest effect on ultrasound use following screening mammography at a population level. While this minimal effect may in part be due to uncertainty in the benefits and harms of supplemental ultrasound, the larger effects seen in states with mandated insurance coverage of supplemental ultrasound suggests other factors may also drive usage. Because supplemental ultrasound increases false-positive biopsies, further study of downstream intended and unintended consequences of legislation is needed.

Women Informed to Screen Depending On Measured of Risk (WISDOM): A Randomized Trial of Risk Assessment to Guide Breast Cancer Screening

[1]Tice JA; [1]Shieh Y; [1]Ziv E; [1]Acerbi I; [2]Eklund M; [1]Fiscalini AS; [1]van't Veer L; [1]Esserman L.
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INTRODUCTION:

Breast cancer screening guidelines vary widely in their recommendations in the United States and internationally. WISDOM is a preference-tolerant pragmatic study comparing annual versus screening tailored to a woman's personalized risk for invasive breast cancer.[1]

OBJECTIVES:

The goal of the WISDOM study is to determine if personalized screening vs. annual screening, is as safe, less morbid, enables prevention, and is preferred by women. The study is registered on ClinicalTrials.gov (NCT02620852).

METHODS:

Women 40 - 74 years of age with no history of breast cancer or DCIS, and no previous double mastectomy can join online at wisdomstudy.org. Participants can elect randomization or self-select a study arm and provide electronic consent and release for medical information using DocuSign. For all participants, the 5-year risk of developing invasive breast cancer is calculated using the Breast Cancer Screening Consortium (BCSC) model using clinical risk factors (age, family history, history of benign breast disease, race/ethnicity, BIRADS breast density). For participants in the personalized arm, DNA is collected from buccal cells and their BCSC risk is combined with a Polygenic Risk Score, based on a panel of single nucleotide polymorphisms and deleterious mutations identified by sequencing 9 genes (BRCA1, BRCA2, TP53, PTEN, STK11, CDH1, ATM, PALB2, and CHEK2). Each woman's estimated risk determines the study recommendations for the age to initiate mammography and the screening interval, counseling on chemoprevention, and MRI screening.[2]

RESULTS:

The WISDOM study is currently open to all eligible women in California, North Dakota, South Dakota, Minnesota and Iowa. Recruitment will continue through 2019.

CONCLUSION:

Our initial findings demonstrate that women will chose to be randomized in a preference tolerant pragmatic trial. Incorporating genetic variants into a validated clinical model is feasible and impacts risk classification compared to a model without genetic risk factors. Results at 5 years will determine if this classification improves screening outcomes.

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2. Shieh Y, Eklund M, Madlensky L, et al. Breast Cancer Screening in the Precision Medicine Era: Risk-Based Screening in a Population-Based Trial. *J Natl Cancer Inst.* 2017;109(5).

Alterations in Levels of Serum IGF-I and IGBFP-3 and Ultrasound Tomography Measures of Breast Density Following Tamoxifen Therapy

Gretchen L. Gierach[1], Manila Hada[1], Shaoqi Fan[1], Roni T. Falk[1], Ruth M. Pfeiffer[1], Michael Pollak[2], Peter Littrup[3,4], Lisa Bey-Knight[4], Vivian Linke[4], Michael S. Simon[4], David H. Gorski[4], Terrance Albrecht[4], Maeve Mullooly[5], Cody Ramin[1], Mengmeng Jia[1], Haythem Ali[6], Patricia Vallieres[6], Mark Sak[3], Mark E. Sherman[7], Nebojsa Duric[3,4]

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INTRODUCTION:

Data indicate that women whose mammographic breast density declines within 12-18 months after starting tamoxifen for chemoprevention or adjuvant treatment are more likely to experience positive clinical responses than those whose breast density does not decline,[1] but the mechanisms underlying these associations are unknown. Evidence from small clinical studies suggests that tamoxifen may reduce circulating insulin-like growth factor (IGF)-I,[2] a peptide hormone which is thought to play an important role in breast carcinogenesis.

OBJECTIVES:

We aimed to evaluate the influence of 12-months of tamoxifen therapy on serum levels of IGF-I and its binding protein-3 (IGFBP-3), which modulates IGF-I bioavailability. We further aimed to determine whether longitudinal changes in IGFs were associated with corresponding changes in ultrasound tomography measures of breast density over the same time period.

METHODS:

Serum IGF-I, IGFBP-3, and IGF-I:IGFBP-3 ratios were measured in duplicate by enzyme-linked immunosorbent assays at baseline and 12-months post-initiation of clinically-indicated tamoxifen therapy among 68 women, aged 30-70 years, enrolled in the Ultrasound Study of Tamoxifen at Karmanos Cancer Institute and Henry Ford Health Systems (Detroit, MI). Whole breast ultrasound tomography (UST) was used to assess change in sound speed, a surrogate of volumetric breast density,[3] between baseline and 12-months.

REFERENCES:

[1]Mullooly M, et al. *JNCI Cancer Spectr* 2018; 2(4).
[2]Lee O, et al. *Clin Cancer Res* 2014; 20(14).
[3]Sak M, et al. *Ultrasound Med Biol* 2017; 43.

RESULTS:

At the 12-month follow-up, circulating IGF-I, the IGF-I:IGFBP-3 ratio, and UST breast sound speed were all significantly reduced (**Table**). IGFBP-3 levels increased, albeit not statistically significantly.

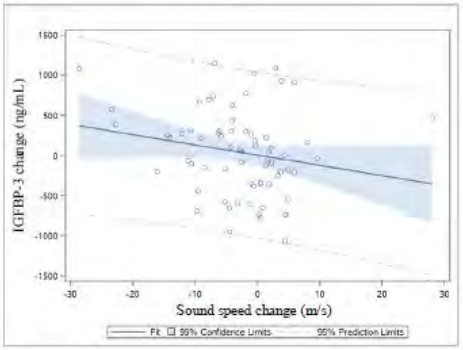
Table. Changes in IGFs and UST Breast Sound Speed from Baseline to 12-months Post-tamoxifen Treatment

Characteristic	Baseline Mean (SD)	12-month Follow-up Mean (SD)	Difference= (12-month - Baseline) Mean (SD)	P-value†
BMI (kg/m²)	30.4 (6.8)	30.5 (6.9)	0.04 (1.6)	0.83
IGF-I (ng/mL)	131.9 (40.2)	96.5 (31.2)	**-35.4 (31.4)**	**<0.0001**
IGFBP-3 (ng/mL)	3990.2 (795.6)	4032.2 (799.2)	42.0 (521.3)	0.51
IGF-I:IGFBP-3	0.12 (0.03)	0.09 (0.03)	**-0.03 (0.03)**	**<0.0001**
Sound speed (m/s)	1454.0 (14.5)	1451.2 (13.5)	**-2.89 (8.3)**	**0.005**

† P-values from paired t-test. P-values <0.05 are in bold font.

IGFBP-3 change was inversely correlated with sound speed change (r= -0.24, p=0.049), with increases in IGFBP-3 levels associated with decreases in sound speed over time (**Figure**). No statistically significant associations were observed for the relation of change in IGF-I or IGF-I:IGFBP-3 with sound speed changes.

Figure. Plot of IGFBP-3 Change by Sound Speed Change from Baseline to 12-month Follow-up



CONCLUSIONS:

These findings suggest that tamoxifen may exert its growth inhibitory effects in the breast, in part, by altering the IGF system. Findings may also provide mechanistic insights into relationships between tamoxifen, breast density changes, and breast cancer outcomes.

Statins and Metformin Use and Mammographic Breast Density

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INTRODUCTION:

Both metformin (used for diabetes treatment) and statins (used to lower blood cholesterol levels) have been linked to breast cancer suppression and are being proposed as potential therapeutics for breast cancer prevention.[1,2] Metformin has been associated with reduced cell growth and circulating estrogen levels, and has antiproliferative effects. Statins affect the production of cholesterols, which are used for hormone synthesis and in cell proliferation. Both of these hormonal mechanisms have been linked to mammographic breast density (MBD). Literature is inconclusive on the relationship between these medications and MBD.

OBJECTIVES:

We aimed to investigate the association between MBD and metformin or statin use.

METHODS:

We conducted a cross-sectional analysis of a predominantly Hispanic screening cohort (n=770). MBD measures were obtained from digital mammograms at enrollment using semi-automated method and Cumulus software. Clinical density BI-RADS were obtained from Electronic Medical Records. Data on medication use, and covariates were collected from in-person interviews at enrollment. BMI was calculated from measured height and weight. We compared the distribution of breast cancer risk factors among ever users of metformin and/or statin. We used linear regression to test the association of medication use with percent density (PD), cm^2 dense area (DA) and cm^2 nondense area (NDA), and logistic regression to test the association of high density BI-RADS (category C+D vs. A+B), adjusted for age, BMI, education, race, menopausal status, age at first live birth, and insulin use. Sensitivity analyses examined co-medication of metformin and statin, interaction between either medication and menopausal status or BMI.

RESULTS:

There was a high prevalence of statin (27.0%) and metformin use (13.4%) in this cohort. Statin use was inversely associated with high density BI-RADS (adjusted OR 0.5, 95% confidence interval (CI): 0.3, 0.78), PD (adjusted β -6.2, 95% CI: -8.8, -3.6) and DA (adjusted β -8.7, 95% CI: -14.7, -2.6); and positively associated with NDA (adjusted β 23.3, 95% CI: 13.1, 33.4). Metformin use was inversely associated with PD and positively associated with NDA, but not when further adjusted for statin use. Compared to nonusers of either medication, statin use alone or in combination was inversely associated with PD and DA (e.g., adjusted β -7.0, 95% CI: -9.8, -4.17 and adjusted β -6.8, 95% CI: -10.7, -2.9, respectively, for PD) and positively with NDA (adjusted β 25.2, 95% CI: 14.2, 36.3; adjusted β 28.2, 95% CI: 12.9, 43.5, respectively). Additive interaction by BMI and menopausal status was not observed in linear models nor in stratified analyses.

CONCLUSION:

Statin use was associated with lower mammographic breast density, measured through clinical radiologist assessment, and continuous relative and absolute measures of mammographically dense breast tissue. Observed associations between metformin use and MBD were driven by co-medication with statins.

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Combined screening with mammography and ultrasound in a population-based breast cancer screening program

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INTRODUCTION:

Mammography is the only screening modality that has been proven to reduce breast cancer mortality. However, its sensitivity varies greatly with breast density, and may be as low as 30% to 48% in extremely dense breasts. Data from various previous studies suggest that the addition of ultrasound screening to mammography for women with dense breasts increases cancer detection rates at the expense of lower specificity and lower positive predictive values.

OBJECTIVES:

The Tyrolean Breast Cancer Screening Program implemented hand-held ultrasound as a second-line screening procedure in addition to digital mammography. The purpose of this study was to evaluate the benefits and adverse effects of combined screening with mammography and ultrasound compared to mammography alone.

METHODS:

The study population included 66,680 women who underwent both mammography and bilateral breast ultrasound screening. Mammography and ultrasound screening results were recorded separately in a database. Linkage of cancer registry data with the screening database provided information on tumour characteristics (e.g., tumour size and stage) and therapy, and permitted identification of interval cancers.

Table 1: Outcome of screening

MA= mammography; US= ultrasound

	MA	MA+US
Cancer detection rate	3.5/1000	4.0/1000
Sensitivity	78.5%	90.6%
PPVof screening	11.7%	12.1%
PPV of assessment	33.3%	24.5%
PPV of biopsy	55.5%	43.3%

RESULTS:

Of the 66,680 women included in the study, 31,918 women (47.9%) had extremely dense or heterogeneously dense breasts, with proportions of 54.4%, 45.6% and 36.9% in the age groups 40-49, 50-59 and 60-69, respectively.
The overall sensitivity of mammography only was 61.5% in women with dense breasts and 86.6% in women with non-dense breasts, and the sensitivity of mammography and ultrasound combined was 81.3% in women with dense breasts and 95.0% in women with non-dense breasts.
Adjunctive ultrasound increased the recall rate from 10.5 to 16.5 per 1000 women screened, and increased the biopsy rate from 6.3 to 9.3 per 1000 women screened. The positive predictive value of biopsy recommendation was 55.5% (95% CI 50.6%-60.3%) for mammography alone and 43.3 (95% CI 39.4%-47.3%) for combined mammography plus ultrasound.

CONCLUSION:

The study results show that supplemental ultrasound screening in women at average risk of breast cancer leads to a moderate increase in cancer detection. The adverse effects in terms of recall rates and biopsy rates are comparable with those reported for population-based screening programs using mammography only.

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Radiomic Texture Analysis in Digital Mammography Using an Anthropomorphic Phantom: Robust Feature Identification

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INTRODUCTION: Studies have shown that breast density is an independent predictor of breast cancer risk.[1] Combining breast density with parenchymal radiomic feature calculations results in an even better assessment of risk, as was shown with case-control studies with ROC methods.[2] Given the multitude of radiomic features, there needs to be a way to identify the features that are generalizable across data sets; namely, the features that are robust to variability in image acquisition settings.

OBJECTIVES: 341 radiomic features were evaluated in an anthropomorphic phantom[3] ("Rachel", Gammex 169, Madison, WI) at different imaging acquisition settings. Specifically, we varied kV and mAs, which control the contrast and noise, respectively. Since the underlying texture of the phantom is unchanged, such calculations can be used to identify robust features as one would expect their variation across these settings to be small.

METHODS: 2D digital mammography (DM) images of the phantom were acquired with the Hologic Selenia Dimensions system using a W/Rh target/filter combination and cranial-caudal (CC) views. At each kV between 27 and 35, an auto-time image was acquired, and the mAs was varied in factors of $2^{1/2}$ (1.4) above and below the auto-time setting. In total, there were 49 combinations of kV and mAs. Each acquisition was repeated twice. Texture descriptors were then calculated from raw images using a lattice-based texture pipeline.[2] The window size and the distance between adjacent windows were both set to 6.3 mm. Raw DM images (CC views) in 1,000 women with negative screening exams at Penn were also analyzed. We focused specifically on the subgroup with thickness between 40 and 60 mm, since this thickness range is comparable to the phantom (50 mm thick). For the purpose of robustness calculations, the technique settings in the phantom were limited to six combinations of kV and mAs that were representative of settings used in the women with 40 to 60 mm thickness.

To quantify the robustness of each feature, the range of values obtained for different technique settings was normalized by the middle 90% of the clinical distribution.

$$\text{Imaging Acquisition Robustness} = \frac{\text{Range of Values in Phantom}}{c_{95} - c_5}$$

Here, c_{95} and c_5 denote the 95th and 5th percentile in the clinical distribution. This metric provides a sense of the spread of texture descriptors in the phantom scaled to the spread of the clinical distribution. This metric should be as small as possible to demonstrate that there is minimal variation across technique settings. We also analyzed the variation between the two lateralities of each patient.

$$\text{Intra-Human Variation} = \frac{\text{Median Difference Between Lateralities}}{c_{95} - c_5}$$

This metric should also be as small as possible, as the parenchymal texture variation within a woman's breasts (who has generally similar bilateral parenchymal patterns) should be smaller compared to the variation across the population (where there's larger parenchymal variability).

RESULTS: A scatter plot can be used to illustrate the imaging acquisition robustness and intra-human variation for each feature. Each data point should ideally be as close to the origin as possible. Thresholds were introduced based on distance from the origin (circular arcs Fig.1). These thresholds correspond to features with very good, good, moderate, and poor robustness (Table 1).

Figure 1. Scatter plot of robustness thresholds for 341 radiomic features.

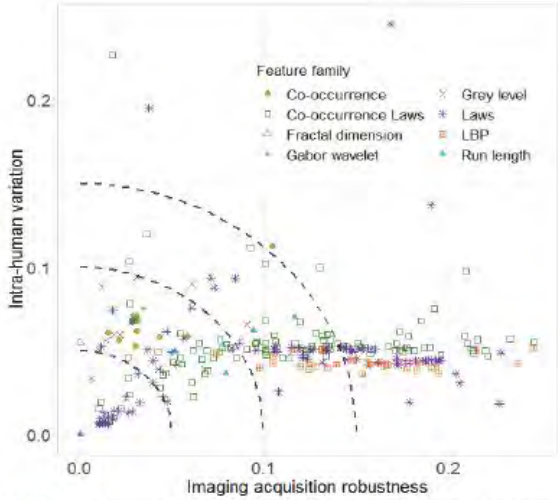

Table 1. Summary of % features for each robustness category.

Feature Family (Number of Features)	Very Good	Good	Moderate	Poor
Co-occurrence (7)	0%	85.7%	0%	14.3%
Co-occurrence Laws (120)	5%	20.8%	29.2%	45%
Fractal Dimension (2)	0%	50%	50%	0%
Gabor Wavelet (32)	0%	100%	0%	0%
Grey Level (12)	8.3%	75%	16.7%	0%
Laws (125)	16%	12%	16%	56%
LBP (36)	0%	2.8%	13.6%	66.7%
Run Length (7)	28.6%	42.9%	28.6%	0%

CONCLUSION: We develop a method to identify robust radiomic features in DM. In future work, a case-control study will be needed to validate our feature-selection results and optimize the choice of thresholds in Fig. 1.

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Correlates for multiple breast biopsies among women in Cancer Prevention Study-3

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INTRODUCTION:

The number of breast biopsies a woman has had is thought to be a representation of changes in the breast, some of which could lead to breast cancer. Although a small proportion of women will have multiple biopsies[1], this group of women is at elevated risk of breast cancer[2]. However, no studies have characterized women with multiple biopsies in detail.

OBJECTIVES:

Among women in the Cancer Prevention Study-3 (CPS-3) cohort, using a cross-sectional study design, we 1) describe the demographic characteristics and screening patterns of women who underwent zero, one, or two or more breast biopsies and 2) examine associations between known and suspected breast cancer risk factors and number of breast biopsies (0, 1, ≥2).

METHODS:

CPS-3 is a prospective cohort study that recruited both men and women from 35 states, Washington D.C., and Puerto Rico from 2006-2013. 147,968 women were available for analysis because they completed the baseline survey and the first follow-up survey in 2015 which queried breast biopsies. After exclusions, 145,532 women remained in the analytic set. On the 2015 survey, women were able to indicate individual years of biopsy, mammography, and MRI from 2007-2015; women were able to mark multiple years. Multivariate polytomous logistic regression models were used to calculate odds ratios and corresponding 95% confidence intervals. Models were adjusted for race, income, educational attainment, insurance status, family history of breast cancer (FHBC), menopausal status, smoking status, menopausal hormone therapy (MHT) use, oral contraceptive (OC) use, body mass index (kg/m^2), parity, age at menarche, and physical activity (METs/week). To account for differences in screening patterns by age, analyses were stratified by age at 2015 survey (<40 , 40-50, and >50 years).

RESULTS:

Most women were White (88%), had at least a college education (52%), and reported at least one screening during the 2007-2015 time period (84%). The average age at time of 2015 survey completion was 51.9 years. Of the women included in this study, 8.9% (N=13,061) reported 1 breast biopsy and 1.9% (N=2,801) reported ≥ 2 biopsies from 2007-2015. Screening patterns differed by biopsy number and by age group. Overall, screening use was higher among women with 1 or ≥2 biopsies, compared to women with no biopsies, a trend that persisted among women <40 years and women 40-49. However, screening rates were similar across all biopsy groups for women > 50 years. Factors associated with biopsy differed by age group. Among women <40, compared to women with no biopsies, women with FHBC were more likely to report either 1 (OR=2.39, 95% CI:1.97-2.91) or ≥2 (OR=1.93, 95% CI:1.24-3.11) biopsies and Black women more likely to report 1 biopsy (OR=1.75, 95% CI: 1.19-2.58). Similar trends were observed among women 40-50; women with FHBC had higher odds of reporting either 1 (OR=1.70, 95% CI:1.54-1.87) or ≥2 (OR=1.62, 95% CI:1.33-1.98) biopsies and Black women were more likely to report 1 (OR=1.22, 95% CI:0.99-1.49) or ≥2 biopsies (OR=1.76, 95% CI:1.21-2.56). In addition, women 40-50 who were current OC users were less likely to report either having 1 biopsy (OR=0.74, 95% CI:0.63-0.88) or ≥ 2 biopsies (OR=0.68, 95% CI: 0.48-0.97) compared to never users. Among women >50, race and FHBC were associated with increased odds of both 1 or ≥2 biopsies. Unlike other age groups, women >50 that were former estrogen-only MHT users were less likely to report ≥ 2 biopsies (OR=0.77, 95% CI: 0.65-0.91) compared to never MHT users while current estrogen+progestin users were more likely to have had 1 biopsy (OR=1.12, 95% CI: 1.00-1.26).

CONCLUSIONS:

We observed that factors associated with more intense screening (FHBC and MHT use) were also related with number of biopsies. Relationships between number of biopsies and OCs and number of biopsies and race need further study.

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Early-life and adult anthropometrics in relation to mammographic texture variation in the Nurses' Health Studies

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INTRODUCTION:

Anthropometrics such as height[1] and body fatness[2] are associated with breast cancer risk possibly through influencing development of breast tissue structures and determining breast density. Texture features indicate the heterogeneity in patterns of breast density that are not captured by current mammographic density measurements (e.g., percentage of mammographic density [PMD]). The V metric, a summary measure of spatial variation in gray intensity values on a mammogram, is positively associated with breast cancer risk, independent of PMD[3]. However, it is unknown whether anthropometrics are associated with the V, independent of PMD.

OBJECTIVES:

Using automated techniques of texture measurement, we examined the associations of early-life and adult anthropometrics (childhood and adolescent body fatness, BMI at age 18 years, current adult BMI, and adult height) with V among pre- and postmenopausal women in the Nurses' Health Study (NHS) and the NHSII.

METHODS:

We conducted an analysis among 1,700 premenopausal (mean age: 45.9 years) and 1,947 postmenopausal (mean age: 58.0 years) women who served as controls in a nested case-control study of breast cancer within the NHS and NHSII. Prior to mammogram, participants recalled their body fatness at ages 5, 10, and 20 years using a 9-level pictogram (level 1: most lean), BMI at age 18, current adult BMI, and height. V is an automated measure that captures grayscale variation in digital mammographic images. Linear regression models were used to estimate beta coefficients (ß) and 95% confidence intervals (CIs) for the relationships between anthropometrics and V, adjusting for age, potential confounders, and PMD. All analyses were stratified by menopausal status at time of mammogram.

RESULTS:

V and PMD were positively correlated (Spearman r=0.49-0.63). Higher average body fatness at ages 5-10 years (Level ≥4.5 vs. 1) was significantly associated with lower V in premenopausal (ß=-0.38, 95% CI=-0.53 to -0.24) and postmenopausal (ß=-0.26, 95% CI: -0.38 to -0.13) women, adjusting for potential confounders, current BMI and PMD. Similar inverse associations were observed with average body fatness at ages 10-20 years, and BMI at age 18 years. Current BMI and height were not associated with V after adjustment for PMD.

CONCLUSION:

Our data suggest that early-life body fatness may reflect lifelong impact on breast tissue architecture beyond breast density (dense vs. nondense tissue).

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Breast density on mammography as a predictor of breast cancer: A Sri Lankan experience

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INTRODUCTION:

Breast cancer ranks the highest among all the cancers of women worldwide, including Sri Lanka[1]. Mammographic breast density is an important risk factor of breast cancer among many other risk factors and it is considered a predictor of breast cancer. Mammographic breast density can be measured by using qualitative and quantitative methods. To date, there is no study has been carried out in Sri Lanka analyzing the correlation between breast cancer and mammographic breast density parenchymal patterns, particularly based on their quantitative measurements. Therefore, it is important to quantitatively analyze the breast density to investigate whether there is an association between breast cancer and breast density in Sri Lankan women with a unique cultural and social background.

OBJECTIVES:

The study was designed to quantify the mammographic breast density and to find out the association between breast density and risk of breast cancer in a group of Sri Lankan women.

METHODS:

The subjects were retrospectively selected from each mammographic facility in three pre-determined provinces of Sri Lanka, namely Central, Southern and Western. Cases were 119 BI-RADS management category 5/6 mammograms of cancer-free side of the breast in histologically proven breast cancer patients. Controls were 136 age and time matched asymptomatic group of females with BI-RADS category 1 mammograms. All the mammograms were Full Field Digital 2D Mammograms (FFDM) and we quantitatively analyzed them for BI-RADS breast density categories[2] by using image J software (version 1.46r) for following mammographic features: total area of dense tissue, total area of adipose tissue, total area of the breast and percent breast density. Odds ratio with confidence interval was calculated to assess the breast cancer risk associated with breast density. Two subjects with >50% breast density category were excluded in the analysis.

Table 1: Case-control correlation for mammographic breast density

		Cancer		Total	OR
		No	Yes		2.316
Breast density percentage	<25	92 -68.10%	55 -46.60%	147	(CI=95% 1.411-3.81)
	25-50	43 -31.80%	63 -53.40%	106	*p<0.05*
Total		135	118	253	

RESULTS:

Subjects were in the age range of 20 to 80years with a mean age of 53 years. Comparison of breast density with breast cancer between <25% and 25–50% categories were statistically significant; $p<0.05$ and Odds Ratio; 2.31(CI 95%; 1.47–3.81) Table 1.

CONCLUSION:

There was a 2.3 fold significantly higher risk of getting breast cancer among 25-50% breast density category compared to <25% breast density category in our group of Sri Lankan women.

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Is it time to establish breast cancer as a smoking-related cancer?

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WITHDRAWN

A comparison of breast tissue composition between mothers and adolescent daughters using optical spectroscopy

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INTRODUCTION:

Growing research, both in animal models and epidemiologic cohorts, supports the role of the early life environment in altering breast cancer risk trajectories.[1] However, most of the data on changes in normal breast tissue composition comes from mammographic data in women over 40 years. There is currently limited prospective data on breast development and composition in adolescent girls. A few studies have shown a correlation in breast density between mothers and daughters (10-30 years) using MRI (%water ρ=0.28)[2] and DXA (absolute fibroglandular volume ρ=0.56)[3]. However, the heritability of other structural and metabolic components of the breast has yet to be characterized. Such information may provide unique insights on breast development and breast cancer risk.

OBJECTIVES:

We examined the correlation of breast tissue composition between mothers and adolescent daughters as measured by optical spectroscopy (OS), a novel and non-invasive measurement tool. OS provides a broader compositional view of the breast compared to mammography, MRI and DXA because it captures variation in the amount of water, lipid, oxy-hemoglobin (HbO_2), deoxy-hemoglobin (Hb), and collagen (coll.), as well as overall cellular and connective tissue density in the breast.[4-5]

METHODS:

Study Sample – We measured breast tissue compositions by OS in 117 mother-daughter dyads from the Columbia Center for Children's Environmental Health (CCCEH) birth cohort.[6] Mothers were recruited to the CCCEH in NYC from 1998-2006, when women were in their third trimester of pregnancy. Women were eligible if they were 18-39 years, residents of Northern Manhattan or the South Bronx, self-reported as a non-smoker, and self-identified as African American or Dominican. Girls were 11-19 years at OS; mothers were 31-55 years.

Measures – OS measured red and near-infrared light transmission of 7 wavelengths (650-1060 nm) at 6 source-detector distances in each breast quadrant resulting in 24 overlapping tissue volumes. Spectra were corrected for dark signal and instrument throughput variations. Principal component analysis reduced spectral data and generate PC scores for each participant, which were averaged over both breasts. Percent body fat was measured by bioimpedance (Omron Handheld HBF-360C).

Statistical Analysis – To compare OS PC scores between mothers and daughters, we calculated Spearman correlation coefficients (ρ) and performed multiple linear regression analyses adjusted for ethnicity, age, and % body fat.

Table 1: Correlation between OS PC Scores in Mothers and Adolescent Daughters

OS PC	Total % Variance	Correlation of OS PC Loads and Chromophore Spectra: Hb	HbO_2	Lipid	Water	Coll.	ρ^a	Linear Regression Models: Unadjusted β (95% CI)	Adjusted[b] β (95% CI)
1	91.8	-0.95	0.98	0.52	0.66	-0.76	0.58	0.43 (0.31, 0.54)	0.41 (0.25, 0.57)
2	97.6	0.85	-0.90	-0.47	-0.86	0.52	0.58	0.51 (0.36, 0.64)	0.51 (0.38, 0.64)
3	98.8	0.45	-0.29	-0.19	0.39	0.78	0.62	0.58 (0.44, 0.72)	0.57 (0.43, 0.72)
4	99.3	0.02	-0.14	0.56	0.21	0.11	0.51	0.59 (0.44, 0.75)	0.57 (0.41, 0.73)
5	99.7	-0.13	-0.22	-0.63	0.27	0.01	0.37	0.30 (0.12, 0.48)	0.38 (0.19, 0.58)
6	99.9	0.04	0.05	-0.07	0.07	-0.09	0.40	0.19 (0.03, 0.36)	0.10 (-0.07, 0.27)
7	100	-0.15	-0.05	-0.13	-0.11	-0.26	0.24	0.13 (-0.04, 0.29)	0.16 (-0.01, 0.33)

[a]Spearman correlation coefficient, all correlations had a p-value <0.05.

[b]Adjusted for age, ethnicity and % body fat of mothers and daughters.

RESULTS:

Seven PCs explained 100% of the spectral variations; with multiple chromophores contributing to each PC (Table 1). Spearman correlations were 0.51-0.62 for the first 4 OS PCs, covering >99% of the spectral variations. Adjusting for age, ethnicity and percent body fat did not appreciably alter associations.

CONCLUSION:

Breast tissue composition is correlated between mothers and their adolescent daughters. This includes, but is not limited to, breast density.

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Change in Breast Composition over Time Measured via Optical Spectroscopy in Women at Average and High-Risk of Breast Cancer

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INTRODUCTION:

Optical spectroscopy (OS) is a low-cost, non-imaging method for measuring breast composition, including breast density, which is safe to use on women of any age with any frequency[1]. As a result, OS is a useful tool for measuring breast composition in younger women, for whom mammography is not routinely advisable, and for repeated measures of breast composition for assessing rate of change in breast tissue with aging or during breast cancer (BC) risk-altering events.

OBJECTIVES:

A longitudinal, prospective cohort study was carried out at the Princess Margaret Cancer Centre in Toronto, Canada measuring breast OS parameters over a period of ~4 years in women at elevated risk of BC and in age-matched women with low or average BC risk. The change in OS-measured breast composition with age as well as the rates of change in breast composition over time in individual women were compared between the two BC risk groups.

METHODS:

Study Group: High-risk women were recruited from the high-risk BC screening programs through three local screening centers. Low- and average-risk women (Gail score <1.67 at study start) were recruited from the regular screening populations of these screening centers or from the general population of local women younger than regular screening age. Mean age at study start was 49 years (23-64.3 years for high-risk, 24.7-68.3 years for low-/average-risk).

Data Collection: OS measurements were made at 8 semi-annual visits over ~4 years using a broadband, spectrometer-based OS system. Light transmission at four positions on each breast was quantified, correcting for the dark signal and system response to a reference standard for each participant visit. A questionnaire was completed to obtain information relevant to BC risk such age, pregnancy history, anthropomorphic data and family history of breast and ovarian cancer. Mammograms were obtained when available and density (MD) was calculated using an automated density thresholding program (LIBRA[2]).

Analysis: Principal Components (PC) Analysis was performed on the spectra from the first visits for all women. The resulting PC loads were used to generate PC scores for all spectra. Linear regression was used to test for relationships between the PC scores and age or MD for either of the risk groups. Analysis of covariance was used to determine whether these relationships differed between the two groups.

RESULTS:

PC 1 and 4 scores were significantly correlated with age in both groups, however the rate of increase in PC 1 with age was higher in the low-risk than the high-risk group, while the rate of decrease in PC 4 with age was higher for the high-risk group than the low-risk group ($p<0.05$). As expected, MD showed a small but significant decrease with age (-0.5%/year, $p<0.001$). PC 1 and 3 had positive correlations with MD, while PC 4 showed a negative relationship (all $p<0.001$).

CONCLUSION:

OS breast composition parameters show significant changes with age which are different between the low or average-risk and high-risk groups. Rates of change of OS parameters with age for individual women will be calculated and also compared between risk groups.

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Adolescent and early adulthood adherence to pro- and anti-inflammatory dietary patterns and effects on premenopausal mammographic density

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INTRODUCTION:

Emerging evidence supports the importance of experiences during early life and before first birth in shaping breast cancer risk, particularly in regards to premenopausal breast cancer. In previous research in the prospective Nurses' Health Study II (NHSII), we observed an increased risk of premenopausal breast cancer among women who consumed a dietary pattern characterized by inflammation during adolescence and early adulthood. However, the mechanisms beyond this association are not understood. Further, there is limited research on the influence of dietary factors on breast density, a strong predictor of breast cancer risk.

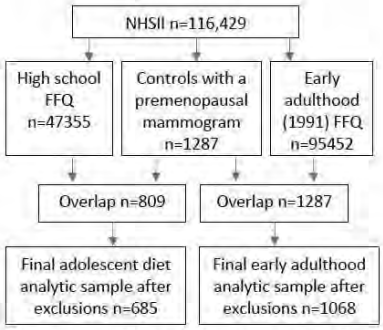
OBJECTIVES:

To examine the association between adolescent and early adulthood pro- and anti-inflammatory dietary patterns and premenopausal mammographic density (MD).

METHODS:

Dietary assessment: NHSII participants completed a food frequency questionnaire in 1998 about their high school diet (HS-FFQ) and an FFQ in 1991 (early adulthood). The pro-inflammatory pattern (IP) has been previously identified in a subset of women using reduced rank regression based on associations with inflammatory markers (CRP, IL-6, and TNFα receptor 2). The anti-inflammatory dietary measure was based on the Alternative Healthy Eating Index (AHEI), which quantifies diet based on intake levels of 11 components: fruits, vegetables, red/processed meat, nuts/legumes, whole grains, sugar sweetened beverages, polyunsaturated fatty acids (FA), *trans* fats, long-chain omega-3 FAs, sodium, and alcohol.

Mammographic density measurement: Absolute dense area, absolute non-dense area, and percent MD were calculated using digitized analog film mammograms from premenopausal women with no history of cancer (analytic sample size described in figure). Generalized linear models were used to evaluate the association between quintile of dietary pattern and the three MD phenotypes.



RESULTS:

Consuming an adolescent dietary pattern characterized as pro- or anti-inflammatory was not associated with percent density, absolute dense area, or non-dense area (Table 1). Similarly, consumption of these patterns in early adulthood was not associated with any of the three MD phenotypes (data not shown).

Table 1. Mean percent mammographic density by quintile of dietary pattern score (n=685)

	Adolescent diet	
Quintile	AHEI	IP
1	42.4 (39.9-45.0)	39.5 (37.4-41.7)
2	39.8 (37.2-42.4)	41.2 (38.6-43.8)
3	39.6 (37.1-42.2)	42.4 (40.1-44.7)
4	40.5 (38.2-42.9)	42.3 (39.8-44.8)
5	42.2 (39.7-44.6)	38.5 (35.4-41.6)
P_{trend}	0.85	0.91

Adjusted for BMI at age 18, adolescent physical activity, adolescent and adult alcohol intake, age at menarche, age at first birth, parity, benign breast disease, and family history of breast cancer.

CONCLUSION:

Our findings suggest that the association between adolescent and early adulthood inflammatory patterns and premenopausal breast cancer risk is unlikely to be mediated through effects on mammographic density.

Funding: This work was supported by the Breast Cancer Research Foundation.

Molecular Profiling of Carcinoma In Situ to Predict Risk of Progression to Invasive Breast Cancer in a Multiethnic Population

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INTRODUCTION:

According to the American Cancer Society's estimates for 2019, there will be approximately 268,600 new cases of invasive breast cancer and 62,930 new cases of carcinoma in situ (CIS, a non-invasive form of breast cancer) diagnosed in 2019. CIS is heterogeneous with variable etiology and course of progression to invasive breast cancer. In addition, there are racial/ethnic differences in risk of progression to invasive breast cancer following a prior CIS diagnosis [1].

OBJECTIVES:

To identify risk stratification profiles predictive of progression from CIS to invasive breast cancer in Hawaii's multiethnic population. A retrospective study (Hawaii Tumor Registry) comparing CIS patients progressing ("cases") versus not progressing ("controls") to invasive breast cancer. Using established predictors of CIS progression based on the Van Nuys Prognostic Index, we evaluated the added value of other elements including demographic, clinical and pathologic factors, and genome-wide gene expression profiles to identify CIS patients at highest risk of progression to invasive cancer.

METHODS:

Conditional logistic regression [2] of DCIS progression status were fit where strata was defined by age and treatment-matched sets of cases and controls. Odds ratios (OR) and 95% confidence intervals (CI) were the main measures of association. For gene expression analysis, RNA was extracted from formalin-fixed paraffin-embedded tissue and analyzed with the high resolution Affymetrix Clariom™ D microarray. Analysis of variance (ANOVA) was used to identify differentially expressed genes (coding and non-coding) between cases and controls.

RESULTS:

A total of 4,438 women were diagnosed with CIS breast cancer in Hawaii (1973-2012), with 520 (11.7%) subsequently diagnosed with a 2nd primary breast cancer (*in situ* or invasive). Women ≥50 yrs old were at lower risk of developing a 2nd primary diagnosis of invasive ipsilateral breast cancer compared to women <50 yrs. Native Hawaiian women were at higher risk of a 2nd primary diagnosis of invasive ipsilateral breast cancer compared to White women.

For gene expression profiling, we analyzed CIS controls (n=25) and cases (n=13) and identified at total of 233 differentially expressed coding and non-coding genes (p-value < 0.0001) that distinguish CIS breast tumors that progressed to a 2nd primary invasive breast cancer.

CONCLUSION:

Younger women (<50 yrs) were at higher risk of developing a 2nd ipsilateral invasive breast cancer. There were racial/ethnic differences in risk of progression to develop a 2nd ipsilateral invasive breast cancer, with Native Hawaiian women having the highest risk. Both coding and non-coding genes were differentially expressed in CIS tumors that progressed to invasive breast cancer compared to CIS tumors that did not.

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Racial/ethnic disparities in breast cancer and its risk factors: the Multiethnic Cohort Study

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INTRODUCTION:

Incidence of breast cancer and its subtypes differs substantially by race/ethnicity[1]. Though the impact of hormone-related factors on breast cancer risk has been well-studied[2], data on racial/ethnic minorities, especially Native Hawaiian women, remain relatively scarce.

OBJECTIVES:

To examine racial/ethnic differences in breast cancer risk and associations with hormone-related factors among 90,087 postmenopausal non-Hispanic White, African American, Native Hawaiian, Japanese American, and Hispanic women in the Multiethnic Cohort (MEC) Study.

METHODS:

Participants completed a baseline questionnaire, providing information on hormone-related factors. During a median follow-up of 20 years, 5,608 incident invasive breast cancer cases were identified by linkage to tumor registries. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between, (1) race/ethnicity and breast cancer risk and (2) hormone-related factors and breast cancer risk overall and for across racial/ethnic group. Models were adjusted for baseline age and body mass index (BMI), type of menopause, parity, and ages at menarche, menopause, and first birth.

RESULTS:

Native Hawaiian women had a 38% higher risk for ER positive (ER+) breast cancer than White women (see table), whereas risk was 40% lower in Hispanic women. African American women had a 17% lower ER+ disease risk, but a 44% higher risk of ER negative (ER-) disease. These results were unchanged after adjustment for hormone-related factors.

In the full population, risk of ER+ breast cancer increased with postmenopausal hormone (PMH) use, higher BMI, and higher age at natural menopause. When stratifying by race/ethnicity, BMI was associated with risk of ER+ disease only in Japanese Americans (30 vs <25kg/m^2 HR 1.59 [CI 1.29-1.96]) and Native Hawaiians (HR 1.48 [CI 1.16-1.90]). An older age at natural menopause increased ER+ breast cancer risk among Whites (≥55 vs <45yrs HR 1.59 [CI 1.17-2.16]) and Japanese Americans (HR 1.42 [CI 1.06-1.91]). PMH use significantly increased ER+ disease risk by 20-40% in all racial/ethnic groups except Native Hawaiians. We saw no associations with ER− disease.

Table. Age-adjusted associations between race/ethnicity and risk of ER+ and ER- breast cancer

	ER+	ER-
White	1.00 (Ref.)	1.00 (Ref)
African American	0.83 (0.76-0.90)	1.44 (1.24-1.66)
Native Hawaiian	1.38 (1.24-1.54)	1.12 (0.89-1.40)
Japanese American	0.94 (0.87-1.02)	0.89 (0.77-1.04)
Hispanic	0.60 (0.55-0.66)	0.98 (0.84-1.14)

CONCLUSION:

We confirm the higher ER+ breast cancer risk in Native Hawaiians and lower risk in Hispanics previously reported in the MEC[3]. Although we see different associations across racial/ethnic groups for several hormone-related factors with risk of ER+ disease, these do not appear to explain the observed racial/ethnic differences in breast cancer risk.

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The potential utility of Shear Wave Elastography as a biomarker of the effects of interventions targeted at reducing Mammographic Breast Density

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INTRODUCTION:

High mammographic breast density (MBD) is a major independent and modifiable risk factor for breast cancer. The response to cancer risk reduction treatment has previously been assessed by clinical palpation, mammography, ultrasound and MRI. High MBD tissue is associated with an increased number of cells, collagen, extracellular matrix and proteoglycan expression[1,2]; these factors also influence the elasticity of the tissues. Shear wave elastography (SWE) is a medical imaging technique that produces a quantitative elasticity value of the imaged tissue in real time.

OBJECTIVES:

As functional tissue changes occur before global structural alterations, we aimed to determine if breast elasticity, as measured by SWE, is a rapidly changing biomarker of MBD.

METHODS:

This clinical trial was a single center, open label, non-randomized trial of 8 premenopausal women with (>15.5%) MBD on a combined hormonal intervention to reduce MBD. Elasticity (kPa) was measured using SWE at baseline, 1, 3, 6 and 12 months. MBD and total fibroglandular volume (TFV) was measured using VolparaDensity™ software at baseline and 12 months. A second study was conducted using 4 repeat breast elasticity measurements every 2 weeks with healthy subjects to act as the control group. Paired T-tests were used to determine the changes in breast elasticity and correlation analyses were used to examine correlations between SWE and MBD variables.

RESULTS:

%VBD had a relative decrease of 14.75% (95% CI -1.20 to 30.69%, P=0.065). TFV decreased 41.86% (95% CI 29.61 to 53.91%, P=<0.005). Breast elasticity decreased by 30.04% (95% CI 12.93 to 47.10%, P=0.001).

The control group had no statistically significant changes across the 4 repeat elasticity measures.

Table 1: Correlations between mammography variables and breast elasticity

Correlation Analysis	R Value	p-value
Changes in kPa and %VBD	0.25	0.551
Changes in kPa and TFV	0.74	0.094
Changes in kPa (1 month) and TFV at 12 months	0.50	0.313

CONCLUSION:

Breast elasticity decreased with a hormonal intervention that also decreased MBD and TFV and these changes were strongly correlated. These results show promise that breast tissue elasticity may be used as an early biomarker to determine breast tissue changes with hormonal intervention used to decrease breast cancer risk.

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Effect of excessive gestational weight gain on daughters' breast density

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INTRODUCTION:

Breast density (BD) is one of the most important risk factors for breast cancer (BC). Excessive gestational weight gain (EGWG) in mothers has been related to several outcomes in the offspring; however, the effect of EGWG on the daughters´ BD at the end of puberty has not been explored.

OBJECTIVES:

We aimed to assess the association between EGWG according to the 2009 recommendations of the Institute Of Medicine (IOM) 2009 and daughters' breast composition (% of fibroglandular volume (%FGV) and absolute fibroglandular volume (AFGV)) at the end of the onset of puberty (breast Tanner stage 4 (Tanner B4)).

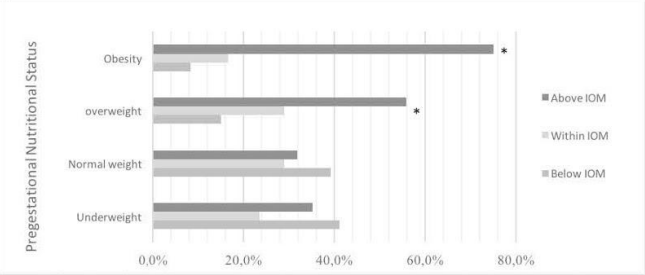
METHODS:

We included 341 girls and their mothers from an ongoing cohort of 400 low-income Chilean girls born in 2002-2003. Maternal gestational weight gain (GWG) was self-reported in 2007, and in 2010 we performed digital mammography to measure BD. In daughters, we collected data on anthropometry (weight and height) and breast composition by dual X-ray absorptiometry (DXA) at Tanner B4 (80th percentile of %FGV and AFGV). The relationship between EGWG and breast composition was estimated through logistic regression models.

RESULTS:

The mean GWG was 13.7 kg (SD=6.9 kg). Compared to pregestational normal weight women, a larger proportion of women overweight and obesity weight exceeded the recommended GWG (58.8% vs. 31.8%, respectively, p<0.05) **(Figure 1)**. Median %FGV and AFGV in daughters were 39% and 79.5cm^3, respectively. We did not observe an association between EGWG and %FGV; however, daughters of women who had EGWG had higher risk of having an AFGV above p80 (adjusted OR 2.02; 95%CI 1.16–3.53) at Tanner B4 than daughters of the mothers who had a GWG within the recommended range **(Table 1).**

Figure 1: Accomplishment to IOM gestational weight gain recommendations in relation to pre-gestational nutritional status.



*Statistically significant results (Fisher's test p <0.05) for excessive GWG in women with pre-pregnancy nutritional status with overweight and obesity versus normal.

Table 1: Association between excessive gestational weight gain and breast composition. Logistic regression models.

	AFGV OR 95%CI >P80/<P80	%FGV OR 95% CI >P80/<P80
Crude model	1.74 (1.12-2.70)*	0.63 (0.40-0.98)
Adjusted model**	2.02 (1.16-3.53)*	0.82 (0.40-1.65)

*Model was statistically significant (p value <0.05).
** Adjusted by maternal variables: education, parity, %FGV, gestational diabetes mellitus; and by girls variables at Tanner B4: BMI Z-score and presence of menarche).

CONCLUSION:

Daughters of women who had EGWG had higher AFGV. This finding may be explained by metabolic and hormonal exposures in utero, which might be modifiable in early life and reduce BC risk in adulthood.

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Breast Chromophore Content as determined by Optical Breast Spectroscopy

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INTRODUCTION:

Various medical imaging and non-imaging techniques have been used to determine breast tissue composition and thus potential breast cancer risk. Mammographic breast density (MBD) quantifies the combined quantity of glandular and connective tissue, MRI the water content and ultrasound the change in acoustic impedance. Less well known techniques such as electrical impedance, quantify the interstitial quantify the amount of free water, lymphatics and glandular tissue. While only mammographic density has demonstrated predictive value for breast cancer risk, it provides limited mechanistic information about the contribution of connective versus glandular tissue to a women breast cancer risk.

Optical methods such as TiBS[1] or frequency-domain diffuse optical tomography[2] have the advantageous to obtaining molecular (water, lipid, collagen, hemoglobins) and structural information (difference in light scattering) of the breast tissue. While frequency-domain diffuse optical tomography is capable of generating spatial distribution maps of these measures, TiBS provides only volume average data about these measures.

OBJECTIVES:

Extract quantitative assessment of the major tissue chromophores, from spectrally steady state transmission measurements.

METHODS:

Look up tables for light absorption as function of absorption μ_a, reduced light scattering coefficient μ_s' and the source-detector distances (d) were created. The five chromophore concentrations including hemoglobin (oxy and deoxy), collagen, lipids and water as well as the tissue average reduced light scattering coefficient μ_s' were obtained by minimization techniques using the following constrains:

$$\mu_a(\lambda,d)=(\Sigma\varepsilon_i(\lambda)c_i)d$$

$$\mu_s'=a(\lambda/600)^{-b}$$

whereby, c_i, are the five chromophore concentrations, $\varepsilon_i(\lambda)$ the molar extinction coefficients. a and b are the scattering amplitude and scattering powers for a particular tissue. Hence, the 7 unknowns are extracted from a matrix of up to 13 wavelength (635 nm to 1050 nm) and 6 source-detector distances (up to 12 cm).

RESULTS:

Figure 1 shows the contribution of the 2 dominant near infrared absorbers as quantified from a predominantly post-menopausal population separated based on physician quantified MBD over a single source detector distance. Further analysis as function of age, and MBD, when available, is ongoing and will be presented during the meeting.

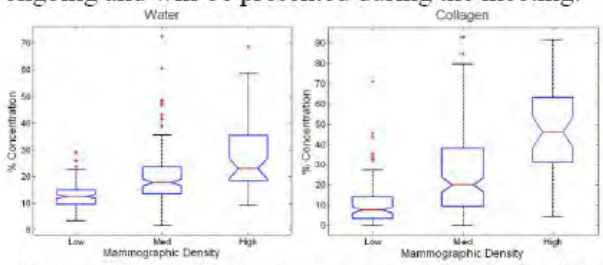

Figure 1 Water and collagen concentration [rel %] as function of mammographic breast density

CONCLUSION:

Determining the tissue chromophore concentrations from the measured data has two advantages. First, fitting by minimization allows to utilize also the source-detector distance as an additional constrain and hence analysis is less vulnerable to missing wavelength data. Second, breast composition can be compared directly between individual women and ratio's of the tissue chromophores and the light scattering amplitude be associated with MBD also in the populations where x-ray based density measures are not obtainable.

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A deep learning approach for breast segmentation in digital mammography

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INTRODUCTION:

Various factors can increase the risk of developing breast cancer. Studies have shown that the relative amount of breast fibroglandular tissue, referred to as the percent breast density (PD), is an important risk factor as measured on digital mammograms (DM).

In estimating PD, the pectoralis muscle located behind the breast, especially in the medial-lateral oblique view (MLO), should be segmented from the breast tissue to accurately estimate the total breast region. Methods have been developed to automatically measure breast PD from DM images, typically considering the pectoral muscle to be a straight line to simplify the segmentation algorithm [1]. However, the pectoral muscle is generally not a straight line, and therefore, more accurate segmentation of pectoral muscle is a key step in refining the measurement of PD.

OBJECTIVES:

We have developed and tested a robust method to accurately segment the pectoral muscle and the breast area using a deep learning approach.

METHODS:

In this study, 102 raw MLO-view DM images were used of the left breast of 102 women with negative routine screening mammograms. A histogram equalization method, involving log-normalization of the original raw DM intensity values, was first applied [2]. In addition, the Otsu thresholding method was used to mask the background. The resulting thresholded area (showing the breast and pectoral muscle) was normalized between 1 to 255 (0 assigned to background).

After these preprocessing steps, the images were manually segmented into the pectoral and breast regions, to obtain ground truth for segmentation. Five-fold cross-validation was then used to generate independent training and test sets where a U-Net [3] architecture was trained and evaluated for 50 epochs to segment the pectoralis muscle, the breast glandular tissue, and the background regions. The rationale for using the U-Net architecture was that it has been shown to achieve good performance in small number of epochs, while alleviating overfitting for limited sample sizes such as in our study.

Segmentation was evaluated using the dice coefficient, weighted dice, sensitivity, and specificity, calculated based on the performance of segmentation to segment the breast area. The background was excluded from these measures (background is always set to zero, Figure 1).

Figure 1: Examples of segmentation results for two DM scans are shown in each row of panel (a). The left, middle, and right columns show the original image, normalized image after preprocessing steps, and the segmented regions, respectively. The panel (b) shows the loss function and accuracy measure (dice) results for training vs. validation.

(a) (b)

RESULTS:

The mean dice was 95.66% with a standard deviation of 1.11% in five-fold cross-validation, with no obvious evidence of model ovefitting (Fig.1). However, sensitivity, specificity, and weighted dice (based on area for segmentation of the breast glandular tissue from the pectoralis muscle) showed an average of 89.01%, 68.12%, and 81.7%, respectively.

CONCLUSION:

Deep learning can be used to segment the pectoralis muscle for DM images, as a fundamental first step to estimate breast PD. The low specificity value shows the need for increasing the number of training cases. The future works will extend the method for various vendors and image format (raw and processed).

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Is early life growth associated with breast tissue composition in younger women?

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INTRODUCTION:

Critical periods of high fibroglandular tissue proliferation occur during fetal life and again at puberty, making these early life periods potential windows of vulnerability for carcinogen exposure. Higher birth weight (suggesting rapid prenatal growth) and rapid height growth at puberty strongly predict later life breast cancer risk[1]. Worldwide, changes in infant and childhood diet have led to increasing adiposity which impacts growth, puberty and estrogen exposure[2]. Despite strong experimental evidence that these early life exposures affect mammary tumorigenesis, there are limited human data[3]. Breast density is the optimal intermediate endpoint because: (i) it is the strongest predictor of breast cancer; (ii) it is thought to represent cumulative exposure to risk; (iii) it tracks from early adult years; hence, (iv) high-risk women can be identified at an earlier age – a key aspect for targeting prevention. Our team has developed Transillumination Breast Spectroscopy (TiBS), a quick, low-cost and safe measure that uses visible and near infrared light to measure breast tissue composition.

We have obtained TiBS measures on volunteers from The Western Australian Pregnancy Cohort (Raine) Study, one of the largest successful prospective cohorts of pregnancy, childhood, adolescence and now early adulthood available anywhere in the world. The Raine Study comprises 2,900 mothers recruited prior to 18-weeks' gestation from 1989-1991. Extensive pregnancy, neonatal, childhood, adolescent and young adult data have been collected, including a large volume of anthropometric measures from birth to 27 years.

OBJECTIVES:

We propose to investigate the distribution in young women of breast tissue composition and its determinants, including early life growth measures within the Raine Study.

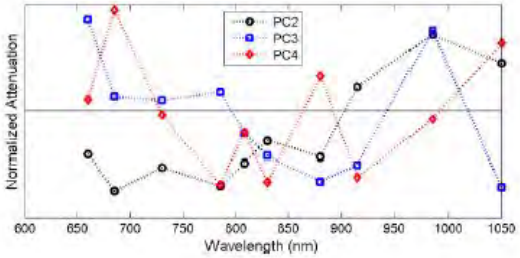
METHODS:

We measured TiBS-breast density in 486 female volunteers aged 27 years without history of breast cancer or breast surgery, sourced via the Raine Study. Principal component (PC) analysis was used to quantify the breast tissue composition via TiBS and the PCs representing dense breast tissue will be examined for their correlation with known breast density determinants and early life growth curves, produced using SuperImposition by Translation And Rotation (SITAR) models.

RESULTS:

Available anthropometric measures include birth weight and length, weight and crown to heel lengths at ages 1, 2 and 3 and height and weight for ages 5, 8, 10, 13, 16, 20, 23 and 27. A preliminary PC analysis on spectra from the first 265 women yielded PC vectors consistent with those from previous studies and application of the PC vectors to previous study data indicates that PCs 2, 3 and 4 (Figure 1) are associated with breast density.

Figure 1. PC load vectors for PCs 2, 3 and 4



Results describing the association of the PC scores with breast density determinants and early life growth will be presented at the meeting.

CONCLUSION:

Understanding what influences TiBS-measured breast density in young women will not only build on the knowledge base that currently only exists for older women, it will also help inform future follow-up studies that could monitor changes in a woman's breast density over time and indicate novel possibilities for monitoring the effectiveness of preventive interventions and targeted breast screening.

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Iterative reconstruction approach to derive accurate local thicknesses of compressed breast in digital tomosynthesis

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INTRODUCTION:

Accurate and local breast thickness measures enable lesions to be characterized by their lipid, water, and protein content through a dual-energy 3-compartment model while still in situ to better assess malignancy status.[1] Previous work for full-field digital mammography required an in-image calibration phantom adhered to the compression paddle to describe thickness, tilt, and warp.[2]

OBJECTIVES:

Our purpose is to describe invasive breast cancer in terms of lipid, water, and protein content using dual-energy tomosynthesis. We show these parameters can be estimated by using an iterative reconstruction approach on the sinograms resulting in a model of the breast characteristics including local breast thickness, compression paddle tilt, and warp.

METHODS:

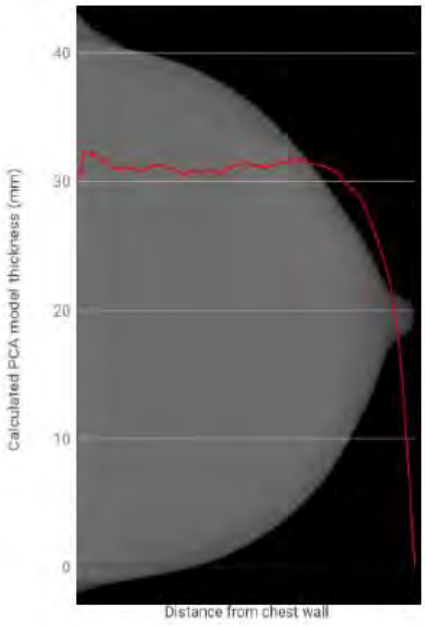
Virtual breast objects (VBO) of known geometries, defined using only five unique parameters (thickness, width, density, warp, and tilt), were constructed in simulation with MATLAB and their corresponding sinograms generated. Breast thicknesses from 1 to 80 mm and chest wall to nipple distances from 1 to 200 mm were generated to sample the space. Single coronal sinograms for training and validation sets of 9600 and 1920 VBO's, respectively, were constructed. Principal component analysis (PCA) was used to generate a model which explains the relationship between the five parameters and the sinograms. Clinical DICOM header thicknesses in 24 tomosynthesis exams were also compared to the local model estimates.

RESULTS:

We found that 25 PCA components explained greater than 99% of model variance. A comparison between iterative reconstructed models and phantom measures is ongoing. A mean thickness difference (DICOM - model) of 24 breasts was found to be 2.80 mm (SD = 2.95 mm, Min/Max=-12/11 mm). The PCA model captured the local thickness decline from the chest wall to the nipple.

CONCLUSION:

We demonstrate a method to capture local breast thickness using an iterative reconstruction method in the sinogram space. The model was able to describe paddle warp and tilt. Phantom calibration of the model is ongoing and accurate local breast thicknesses were seen when compared to DICOM values in clinical images. This method can be implemented on commercial tomosynthesis systems without modification. Future studies will utilize these thickness measures with dual-energy tomosynthesis to create voxels lipid, water, and protein contents instead of greyscale values alone.



REFERENCES:

1. Drukker et al., Medical Physics, Vol 41, No. 3, 2014
2. Marlkov et al., Medical Physics, Vol. 36, No. 12, 2009;

New mammography-based measures of breast cancer risk

[1]Hopper, John; [2]Nguyen TL; [1]Schmidt DF; [2]Makalic E
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INTRODUCTION:

Conventional mammographic density, the white or bright areas on a mammogram (Cumulus), is associated with risk of breast cancer, including interval and screen-detected cancers. We challenged the paradigm and found two new risk factors by: (i) redefining mammographic density as the bright, or brightest regions on the mammogram (we call the latter Cirrocumulus[1]); and (ii) applying machine learning to textural patterns (we call this measure Cirrus[2]).

OBJECTIVES:

To estimate the risk gradients for multiple mammography-based measures of breast cancer risk when fitted together and combined.

METHODS:

We measured Cumulus, Cirrocumulus and Cirrus for: (i) 669 cases and 2629 matched controls from the Melbourne Collaborative Cohort Study (MCCS); (ii) 384 cases and 1314 controls from Australian breast cancer family studies (ABCFS). We estimated odds ratio per standard deviation adjusted for age and BMI (OPERA)[3] and area under ROC curve (AUC) ~ Φ(log (OPERA)/1.414); Φ is a Normal (0,1) df.

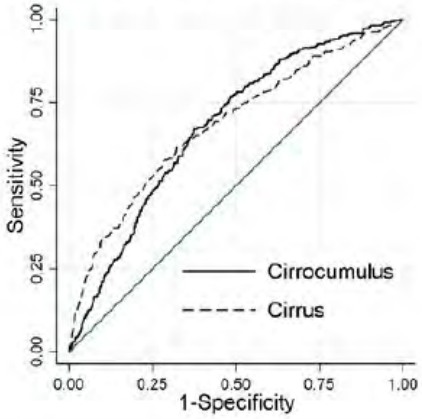
RESULTS:

Table 1: OPERAs (95% CIs) from fitting Cumulus (%), Cirrocumulus and Cirrus together.

Outcome	Cumulus (%)	Cirro	Cirrus
Interval (MCCS)	**1.73** (1.21-2.47)	*1.09* (0.80-1.48)	**1.73** (1.39-2.16)
Screen-detected (MCCS)	*0.78* (0.64-0.96)	**1.36** (1.14-1.64)	**1.59** (1.39-1.82)
All cases (ABCFS)	*0.89* (0.72-1.10)	**1.54** (1.27-1.86)	**1.61** (1.35-1.92)

For ABCFS, the AUCs were: Cirrocumulus: 0.68; Cirrus: 0.68; Combined: 0.71 cf. 314 SNP polygenic risk score[3]: 0.63. The equivalent OPERAs are 1.86, 1.86, 2.16 cf. 1.61.

Figure 1: Receiver Operating Characteristic (ROC) curve for Cirrocumulus and Cirrus for Australian case-control study



CONCLUSION:

Conventional mammographic density predicts risk of interval cancer, better as a percentage, most likely due to its role in masking tumours. Mammographic density defined by higher pixel brightness thresholds is more likely to be causally-related to intrinsic risk and does better at identifying women at higher than average breast cancer risk. Textural features are also more likely to be causally-related to intrinsic risk and do better at identifying women at lower than average breast cancer risk. Conventional mammographic density adds little or no information on intrinsic risk to these two measures. In differentiating women who will or will not get breast cancer on a population basis, the combination of these new mammography-based risk measures does >50% better than does all the known genetic risk factors.

REFERENCES:

1.Nguyen TL et al. *Br Cancer Res* 2018;20:152.
2.Schmidt DF et al. *JNCI Cancer Spectrum* 2018;2:pky057.
3.Hopper JL. *Am J Epidemiol* 2015;182:863-7.
4.Mavaddat N et al. *Am J Hum Genet* 2019; 104:21-3.

Mammogram-derived texture features and risk of breast cancer

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INTRODUCTION:

Mammographic density is one of the strongest risk factors for breast cancer. The most widely accepted measure of mammographic density is based on the percentage of dense tissue on a mammogram (percent mammographic density or percent MD). However, there is additional information in mammographic images that is not captured by current MD measurements including heterogeneity in patterns of breast density, often referred to as 'texture'. More recent research suggests that textural features on a mammogram are associated with breast cancer risk independent of percent MD.

OBJECTIVES:

We propose to test the hypothesis that mammogram derived texture features are associated with risk of breast cancer, independent of percent MD and established breast cancer risk factors, in two large prospective cohort studies.

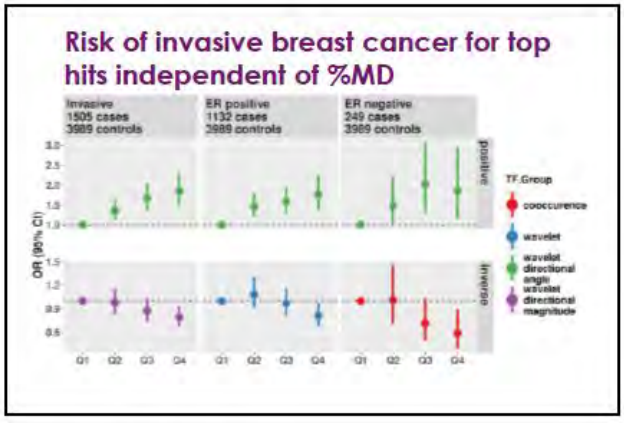
METHODS:

We extracted 593 texture features from screening film mammograms of Nurses' Health Studies (NHS) and NHS II participants (881 breast cancer cases and 1904 controls) and ensured that mammograms from cases were always pre-diagnostic. Texture features were calculated based on: contrast, correlation, co-occurrence, Fourier, wavelet and Laws filtering. Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were estimated for the association between each texture feature and breast cancer risk using logistic regression and adjusting for the following covariates taken at the time of the mammogram: age, BMI, menopausal status, hormone therapy use, and percent MD.

RESULTS:

115 extracted texture features were significantly associated with risk of breast cancer independent of percent MD and following Bonferroni correction. Two Fourier texture features were positively associated with breast cancer risk and 113 texture features (100 correlation and 13 Fourier) were inversely associated with breast cancer risk. For example, the strongest measure associated with increased risk was estimated for a Fourier texture feature with OR = 1.33 (95% CI = (1.19, 1.49)) per 1 standard deviation (SD) increase in the texture feature, while the strongest inverse association was estimated for six (highly correlated) correlation texture features with OR = 0.62 (95% CI = (0.53, 0.74)) per 1 SD increase in the texture feature.

Figure 1: Relative risk estimates for top features associated with breast cancer risk independent of % MD



CONCLUSION:

Multiple texture features derived from mammograms are associated with breast cancer independent of percent MD. Future work will evaluate the contribution of these texture features into breast cancer risk prediction models.

In and Around Waikīkī

TRANSPORTATION

Prince Waikīkī Shuttle
The hotel provides a regular shuttle to Waikīkī from the lobby. View routes and schedules here.

Rental Cars
Check for Waikīkī locations of the rental companies below if you want to rent for just a day or two. There are also convenient locations at the airport for when you arrive.

Alamo
Budget
Dollar
Enterprise

TheBus
All the places mentioned in this guide are along or near the Hawai'i bus system routes. Ask your concierge or use Google Maps to check bus routes and schedules before heading out. They also provide a Waikīkī Guide for visitors.

TheBus – ADULT (18 years and over)
One-Way Fare: $2.75 | 1-Day Pass: $5.50
Ask your bus operator for the 1-Day Pass before placing your money in the farebox. Valid 12:00 a.m. – 2:59 a.m. the next day, for up to 27 hours of unlimited rides.

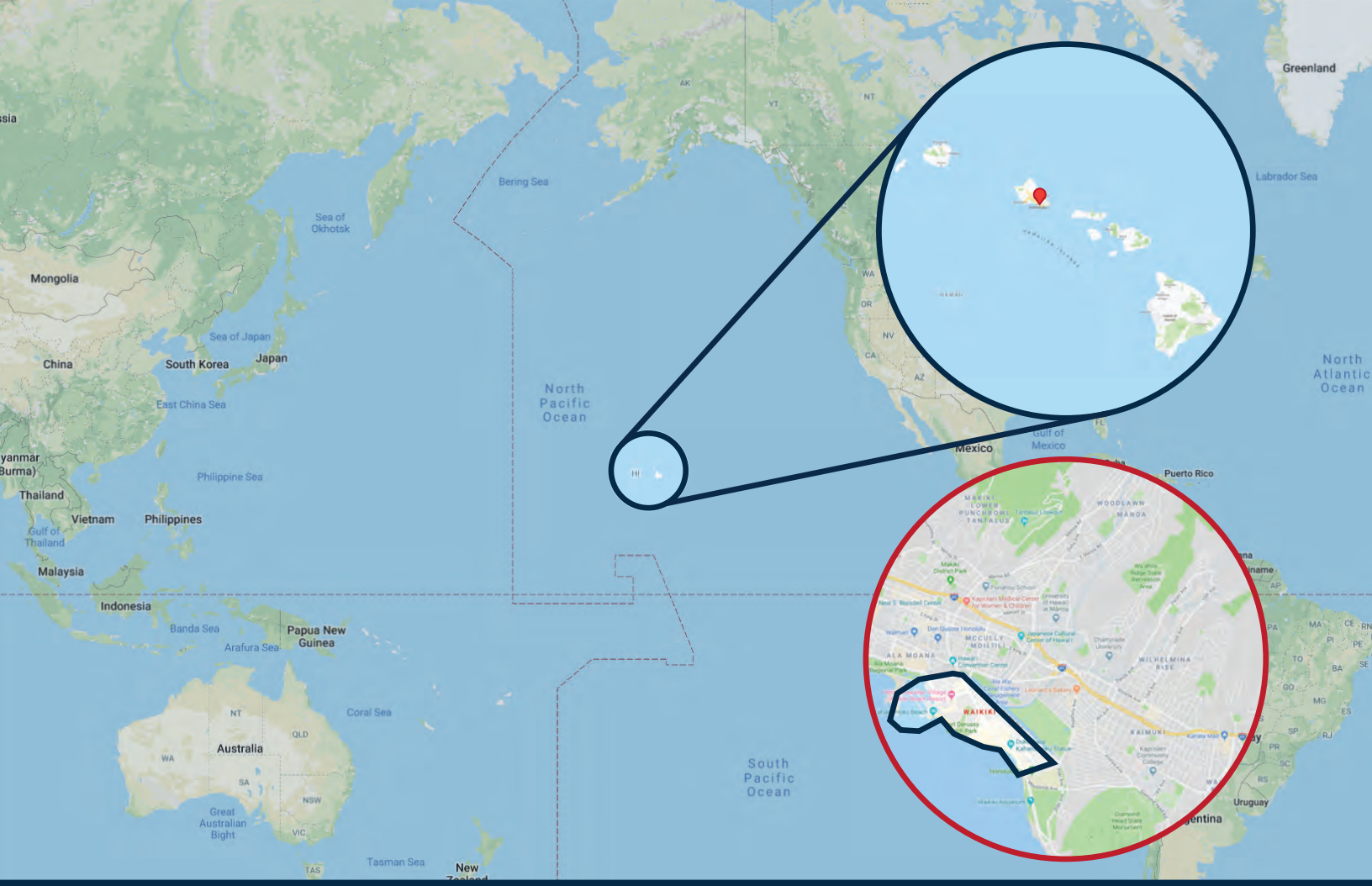
TheBus – YOUTH (17 years and under)
One-Way Fare: $1.25 | 1-Day Pass $2.50
Ask your bus operator for the 1-Day Pass before placing your money in the farebox. Valid 12:00 a.m. – 2:59 a.m. the next day, for up to 27 hours of unlimited rides.

From the airport you can take bus numbers 19 and 20, and stop at Ala Moana Bl + Hobron Ln. You can also mention to the bus driver that you're going to Prince Waikīkī and they will let you know when to get off.

Uber/Lyft
Using their respective mobile apps, you can use Uber or Lyft to travel between the airport and hotel, and anywhere else on the island.

Taxis
Charlie's Taxi: 1-877-531-1333 (toll free number)

TheCab: 1-800-422-2222


Greenland
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Sea of Okhotsk
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East China Sea
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North Atlantic Ocean
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Thailand
Vietnam
Philippines
Gulf of Thailand
Malaysia
Indonesia
Banda Sea
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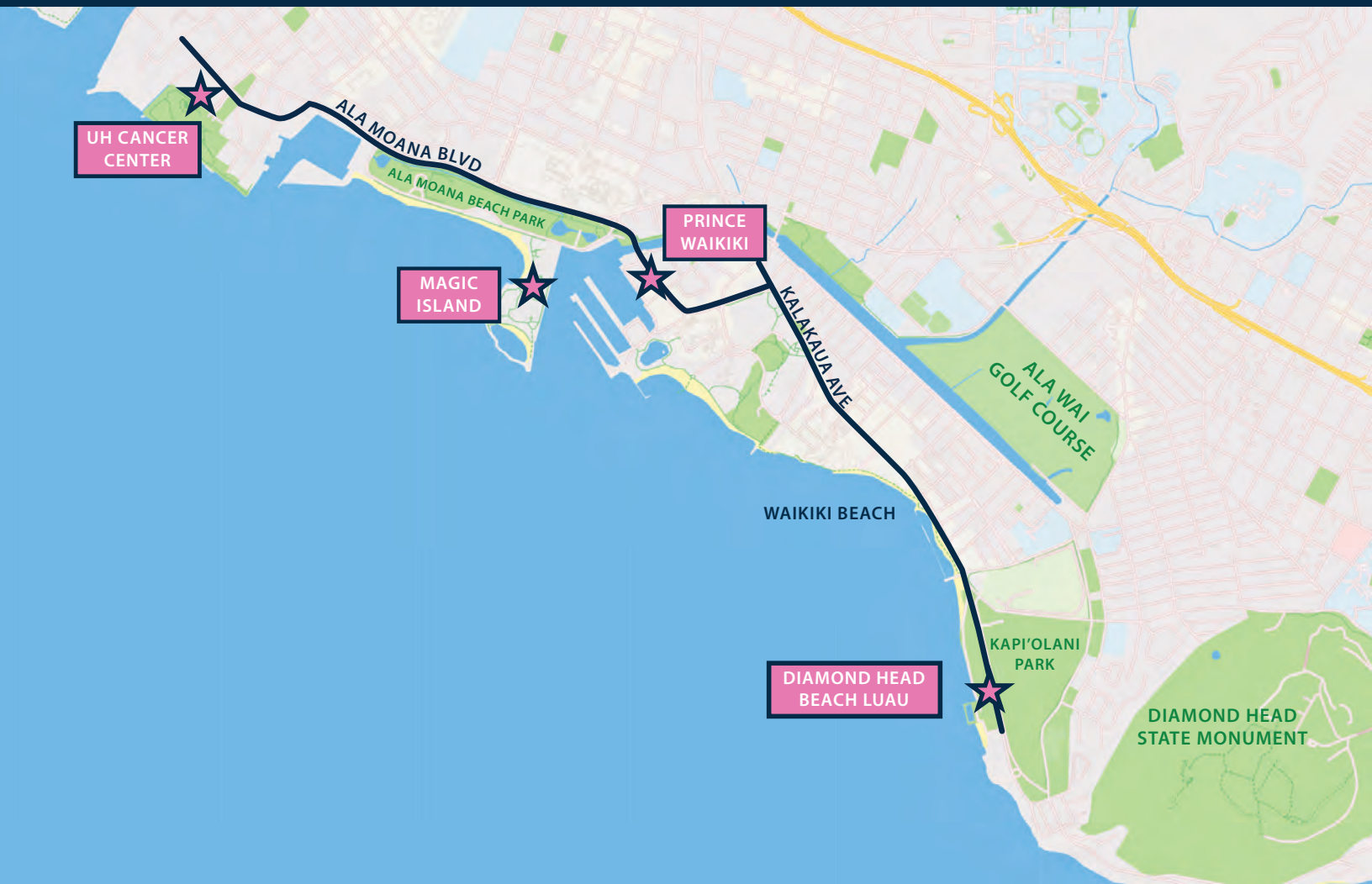
UH CANCER CENTER
ALA MOANA BLVD
ALA MOANA BEACH PARK
MAGIC ISLAND
PRINCE WAIKIKI
KALAKAUA AVE
ALA WAI GOLF COURSE
WAIKIKI BEACH
KAPI'OLANI PARK
DIAMOND HEAD BEACH LUAU
DIAMOND HEAD STATE MONUMENT

CULTURAL SITES

‘Iolani Palace
‘Iolani Palace is a living restoration of a proud Hawaiian national identity and is recognized as the spiritual and physical multicultural epicenter of Hawai‘i. Built in 1882 by King Kalakaua, Iolani Palace was the home of Hawaii’s last reigning monarchs and served as the official royal residence and the residence of the Kingdom’s political and social life until the overthrow of the monarchy in 1893.

Shangri La
Shangri La is a center for Islamic arts and cultures, offering guided tours, residencies for scholars and artists, and programs with the purpose of improving understanding of the Islamic world. Built in 1937 as the Honolulu home of American heiress and philanthropist Doris Duke (1912-1993), Shangri La was inspired by Duke’s extensive travels throughout North Africa, the Middle East, and South Asia and reflects architectural traditions from India, Iran, Morocco and Syria.

Honolulu Museum of Art
Honolulu Museum of Art is an art museum in Honolulu, Hawai‘i. The museum is largest of its kind in the state, and was founded in 1922 by Anna Rice Cooke. The museum has one of the largest single collections of Asian and Pan-Pacific art in the United States. Have lunch in their open-air café surrounded by gardens, a waterfall, and spectacular sculptures by Jun Kaneko. On Sunday enjoy their special brunch menu.

SHOPPING

Ala Moana Shopping Center
The world’s largest open-air shopping mall with more than 350 shops and restaurants to explore. It is just a short walk from the Prince Hotel.

International Market Place
International Market Place is Waikīkī’s premier retail, dining and entertainment destination. The open-air center features over 75 stores, ten restaurants on the incredible Grand Lanai, and Hawaii’s first Saks Fifth Avenue.

Royal Hawaiian Center
Royal Hawaiian Center offers 310,000 square feet of delight for Hawai‘i shoppers. With its more than 110 shops and restaurants, the Center is one of Hawaii’s largest shopping malls. There are boutiques, sporting-good stores, Hawaii’s top surf shops, jewelry stores, craft shops and practically everything else conceivable — all in the very center of Waikīkī.

DINING

Duke's Waikīkī
Popular option known for its beachfront location, surf 'n' turf, tiki vibe & umbrella drinks.

Marukame Udon
Guests order at the counter at this casual Japanese restaurant specializing in noodle soup.

Da Cove Health Bar
Casual cafe offering healthy eats, including smoothies, wraps & kava, with live music in evenings.

Roy's Waikīkī
High-end chain serving notable chef Roy Yamaguchi's Hawaiian fusion fare in a contemporary setting.

Merriman's Honolulu
Merriman's is driven by our long-standing commitment to Hawai'i Regional Cuisine. We support local farmers, ranchers and the local economy while offering fresh, authentic cuisine at its peak flavor.

Da Ono Hawaiian Food
No-frills, family-owned eatery draws locals with a menu of traditional Hawaiian plates.

Eggs n Things
Casual eatery with traditional breakfast/brunch staples featuring area-sourced ingredients & syrups.

Bombay Palace
Tranquil halal restaurant at the Discovery Bay Center for grilled kebabs & biryanis, plus other Pakistani & North Indian fare.

Phuket Thai
Restaurant serving Thai soups & curries in an airy dining room with a bar & outdoor seating.

BARS

Yard House
Sports-bar chain with a huge menu of New American fare & an extensive list of draft beers.

Maui Brewing Co., Waikīkī
MBC is based on Maui, with its production brewery, full-service restaurant and tasting room in Kihei, as well as pubs in Lahaina (Maui) and Waikīkī (O‘ahu).

LIVE MUSIC

Blue Note Hawai‘i
Hawai‘i branch of the iconic NYC music venue, with big-name jazz, blues & local artists, plus dinner.

Mai Tai Bar
Open-air bar atop the Ala Moana Mall known for tropical-drink happy hours, local fare & live music.

The most comprehensive portfolio of breast health products

Whether it's the ability to employ personalized screening, or to perform diagnosis, biopsy, staging, treatment planning and monitoring, and surveillance, GE Healthcare has an innovative solution. In addition, our products enable radiologists to personalize care to each woman depending on her age, breast density, size, medical history, risk factors, and personal preferences. In other words, the right solution for the right patient at the right time.

Learn more about our breast health portfolio at: **gehealthcare.com/breasthealth**

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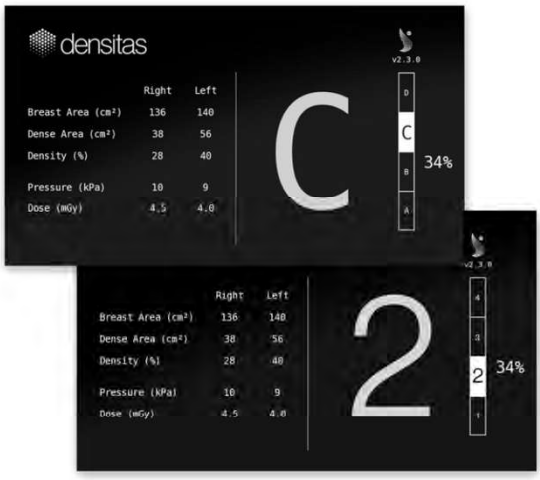
van Gils, Carla	Professor of Clinical Epidemiology of Cancer, *University Medical Center Utrecht*
Vu, Sophia	Clinical Research Supervisor, *California Pacific Medical Center Research Institute*
Walter, Jane	Postdoc, *University Health Network*
Warner, Erica	Assistant Professor of Medicine, *Massachusetts General Hospital*
Wolfgruber, Thomas	Postdoc, *UH Cancer Center*
Wong, Michael	Graduate Researcher, *University of Hawai'i*
Zhou, Qi	Research Manager, *GE Healthcare*
Zhu, Xun	Postdoc, *UH Cancer Center*

densitas



Standardized, Efficient Workflows

We generate automated, standardized, and reproducible breast density measures from the same routinely archived standard digital mammograms that radiologists evaluate, all without disrupting radiologist productivity or reading workflow.

Improved Quality

We support compliance with the Mammography Quality Standards Act EQUIP (US), CAR Mammography Accreditation Program (Canada) and EUREF (EU) guidelines for identifying errors and tracking mammography quality performance indicators and corrective actions, including closed-loop training of mammographers.

Patient-specific Care

We augment radiologists' practice with individualized patient-specific breast density and image quality assessments to increase confidence in their breast screening followup recommendations.

Researchers

Our density and quality algorithms are built to work with "for presentation" images. This allows for less work and lower cost to collect, store, and process images for research purposes.

Contact us at info@densitas.health to find out about our research support program!

BACK COVER - The Makawalu Vortex sculpture at the entrance of the UH Cancer Center was carved by local artist Jerry Vasconcellos from *pohaku* quarried from Koʻolau, the same source that produced the lava that formed Honolulu. The sculpture symbolizes the core mission of the UHCC - to ease suffering, to comfort, to heal, and to discover. The Native Hawaiian concept of *makawalu*, meaning "eight eyes" refers to thinking using multiple perspectives and drawing information from many sources. The two large *pohaku* from Kailua placed on both sides of the path symbolize drawing energy from the surroundings and radiating it outward.