RISE UP for BC Session 4

Risk Prediction and Biomarkers for Prevention Trials

Session 4: Risk Prediction and Biomarkers for Prevention Trials

Co-Chairs

Dr. Adetunji Toriola, MD, PhD, MPH
Professor of Surgery (Division of Public Health Sciences)
William H. Danforth Washington University Physician-Scientist Scholar
Co-Lead, Cancer Prevention and Control Program
Siteman Cancer Center, Washington University School of Medicine

Dr. Laura Fejerman, PhD, MSc,
Professor, Department of Public Health Sciences
Placer Breast Cancer Endowed Chair
Associate Director, Community Outreach and Engagement
University of California Davis Comprehensive Cancer Center

Advocate

Ricki Fairley

CEO and Co-Founder of TOUCH: The Black Breast Cancer Alliance.

- *In January 2022, she started the When We Tri(al) Movement to change the game on Black women participating in clinical trials to improve outcomes for Black women with breast cancer, resulting in 17,000 Black women in clinical trial portals in the past year.*
- *In January 2023, she founded the For The Love of My Gurls Campaign to drive awareness and action, now having reached over 375,000 young Black women.*
- *In 2023, she launched the first ever advocacy led nurse navigator outreach program for pharmaceutical company clinical trials to elevate the inclusion and participation of Black women.*
- *In 2024, Ricki expanded TOUCH BBCA globally to the UK and Africa by serving as the Co-Investigator, leading the Patient Advocacy Work Package for the Cancer Grand Challenge Team SAMBAI.*

Presenters selected from abstract review

Dr. Mark Powell MD MPH
Visiting Scientist, Buck Institute for Research on Aging
Senior Researcher, Zero Breast Cancer

Dr. Suleeporn Sujichantararat (Yui), PhD
Postdoctoral Scholar
Department of Radiology, University of Washington, Seattle, WA

Dr. Mustapha Abubakar, MD, PhD
Division of Cancer Epidemiology and Genetics, National Cancer Institute, NCI, USA

Vagmi Luhar, Pre-Baccalaureate Research Fellow
Division of Cancer Epidemiology and Genetics (DCEG) at the National Cancer Institute, NCI, USA

Dr. Mikael Eriksson PhD,
Department of Medical Epidemiology and Biostatistics, Karolinska Instituet, Sweden

Identifying New Targetable Pathways for Breast Cancer Prevention in Premenopausal Women

Adetunji T. Toriola, MD, PhD, MPH
Professor of Surgery (Division of Public Health Sciences)
William H. Danforth Washington University Physician-Scientist Scholar
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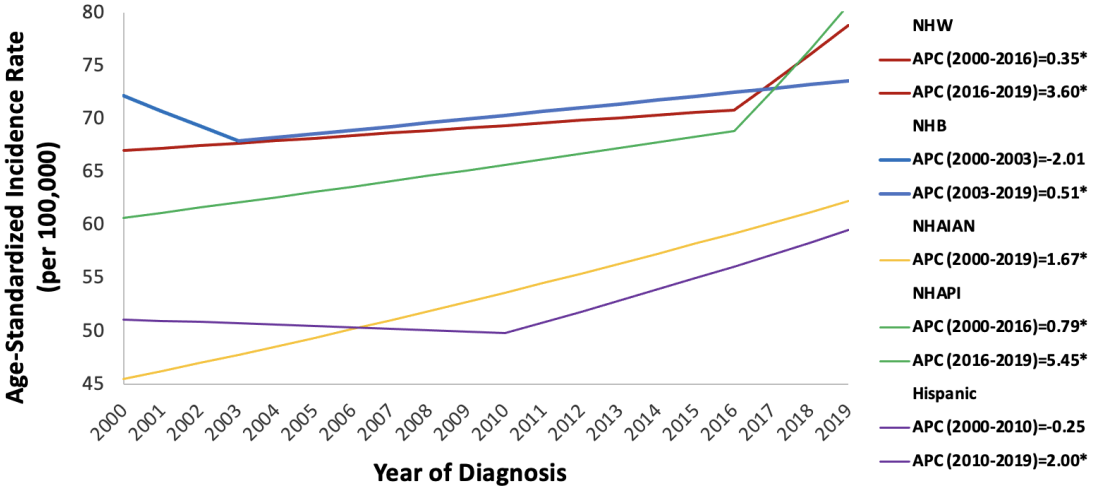
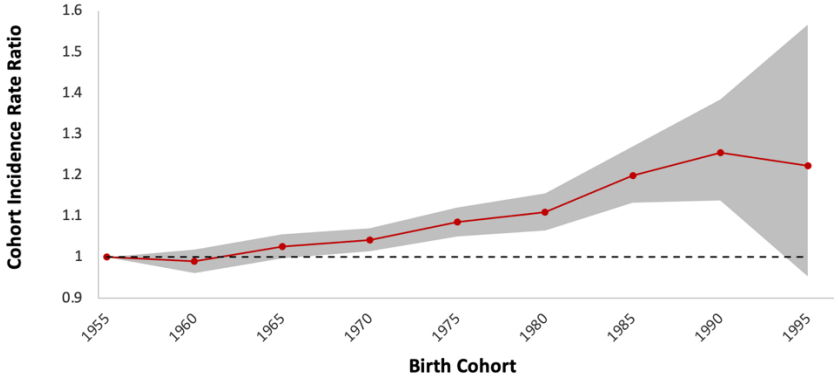
Rising Incidence Rates of BC in Premenopausal Women





Shuia Xu

Original Investigation | Public Health

January 26, 2024

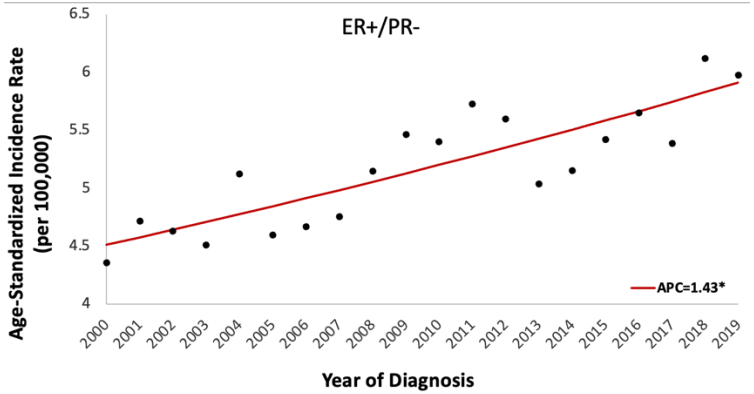
Breast Cancer Incidence Among US Women Aged 20 to 49 Years by Race, Stage, and Hormone Receptor Status

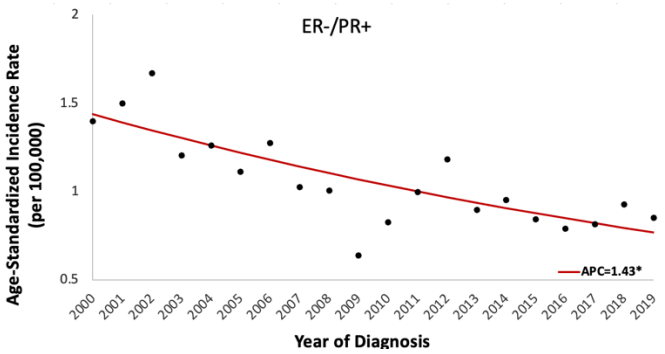
Shuai Xu, MPH[1]; Sara Murtagh, MD[2]; Yunan Han, MD[1]; Fei Wan, PhD[1]; Adetunji T. Toriola, MD, PhD, MPH[1]

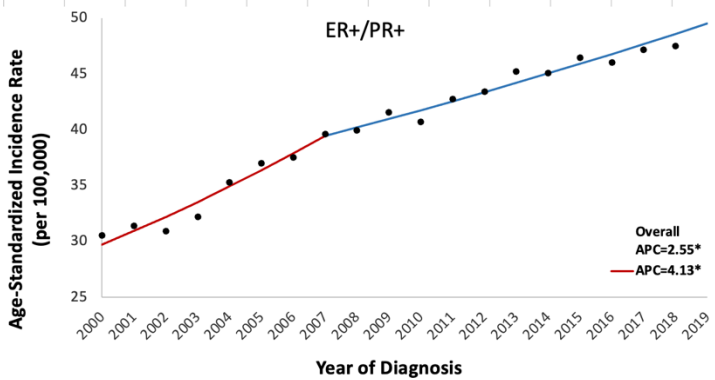
Author Affiliations | Article Information

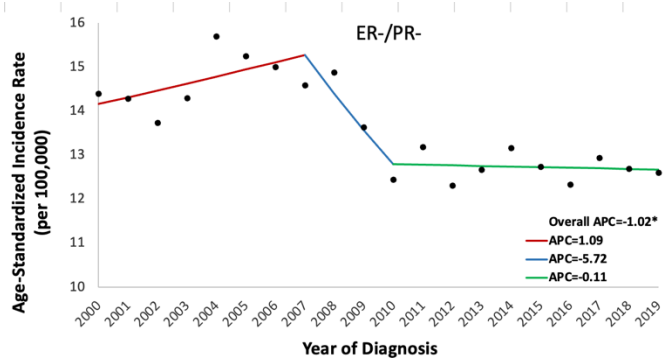
JAMA Netw Open. 2024;7(1):e2353331. doi:10.1001/jamanetworkopen.2023.53331

Trends in Premenopausal Breast Cancer Incidence by HR Status









Opportunities for Breast Cancer Prevention

1. Learn from the divergence in ER+ve tumors vs. ER-ve tumors.
2. Early-life factors and breast cancer risk later in life
   - Early-life adiposity
3. Apply genomic approaches to identify new targetable pathways and repurpose existing medications for prevention

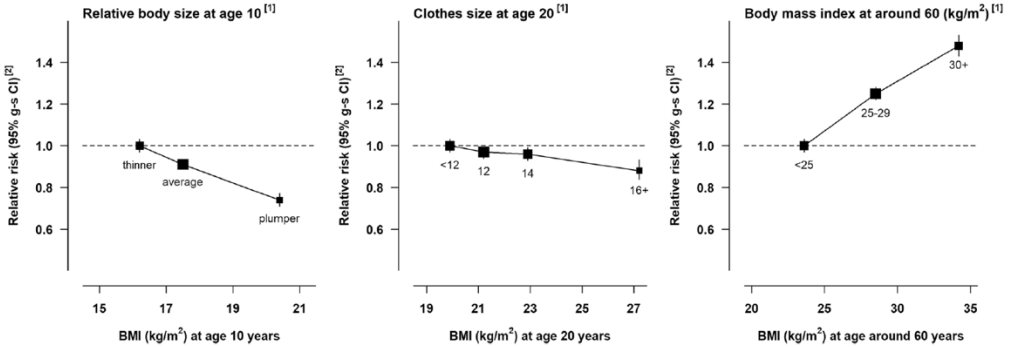
Lessons from the Divergence in Trends by HR Status

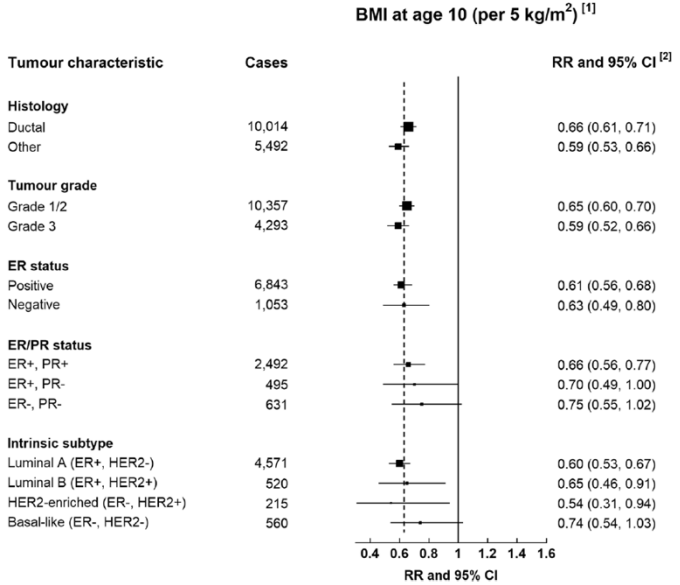
1. Physical activity
   - Stronger for ER-ve tumors and in premenopausal women than for ER+ve tumors - Wu Y et al. BCRT 2013

2. High vegetable intake
   - Inverse for ER-ve tumors but not ER+ve tumors - Jung S et al. JNCI 2013

3. Reproductive factors
   - More relevant for ER+ve tumors

Early-Life Adiposity and Breast Cancer Risk





Yang et al. BMC Med 2022

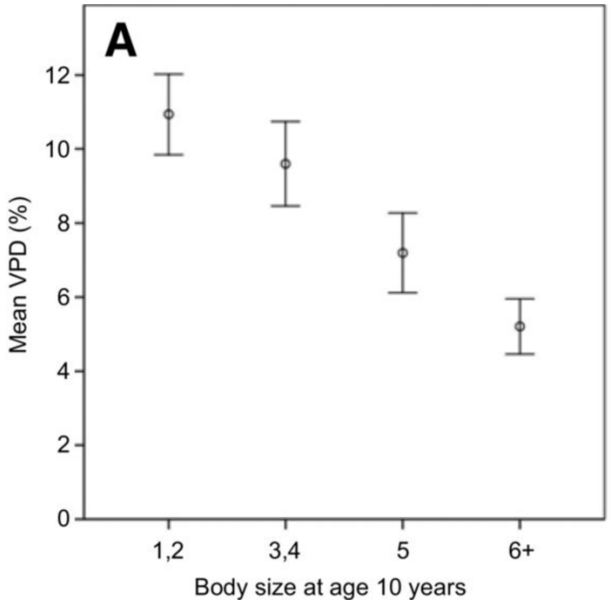
Early-Life Adiposity and MBD

Research Article

Cancer Prevention Research

Adiposity at Age 10 and Mammographic Density among Premenopausal Women

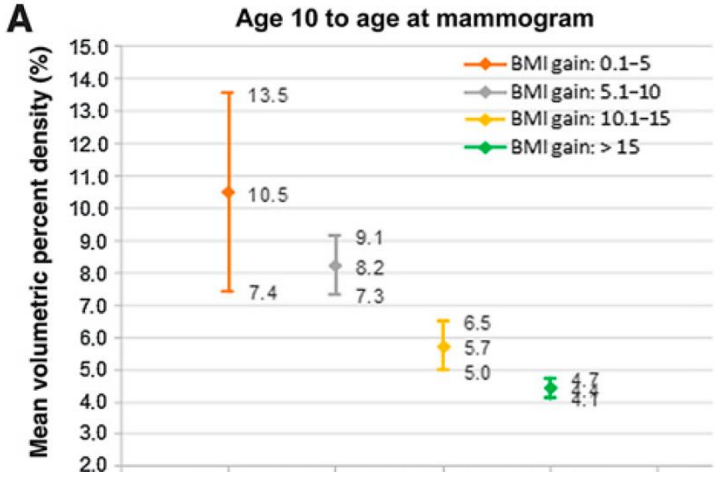
Aliya Alimujiang[1], Kellie R. Imm[1], Catherine M. Appleton[2], Graham A. Colditz[1], Catherine S. Berkey[3], and Adetunji T. Toriola[1]



CANCER PREVENTION RESEARCH | RESEARCH ARTICLE

Adiposity Change Over the Life Course and Mammographic Breast Density in Postmenopausal Women

Yunan Han[1,2], Catherine S. Berkey[3], Cheryl R. Herman[4], Catherine M. Appleton[5], Aliya Alimujiang[6], Graham A. Colditz[1,4], and Adetunji T. Toriola[1,4]



Early-Life Adiposity and BC – Direct Effect

OXFORD

JNCI J Natl Cancer Inst (2020) 00(0): djaa169

doi: 10.1093/jnci/djaa169
First published online 2 November 2020
Article

Early-Life Body Adiposity and the Breast Tumor Transcriptome

Jun Wang, PhD,[1,2,*] Cheng Peng, ScD,[3] Catherine Guranich, BS,[4] Yujing J. Heng, PhD,[5,6] Gabrielle M. Baker, MD,[5] Christopher A. Rubadue, MD,[5] Kimberly Glass, PhD,[3] A. Heather Eliassen, ScD,[3,7] Rulla M. Tamimi, ScD,[3,7,8] Kornelia Polyak, MD, PhD,[9,10] Susan Hankinson, ScD[3,4]

OXFORD

JNCI J Natl Cancer Inst (2020) 00(0): djaa173

doi: 10.1093/jnci/djaa173
First published online 2 November 2020
Editorial

Refining the Focus on Early Life and Adolescent Pathways to Prevent Breast Cancer

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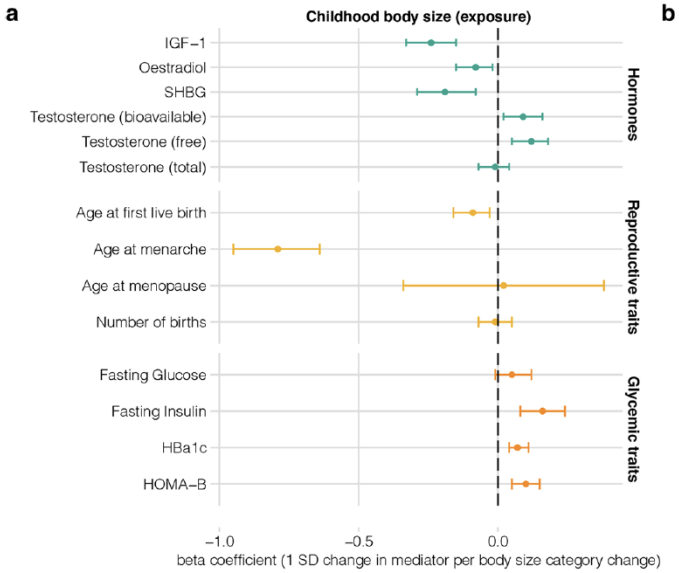
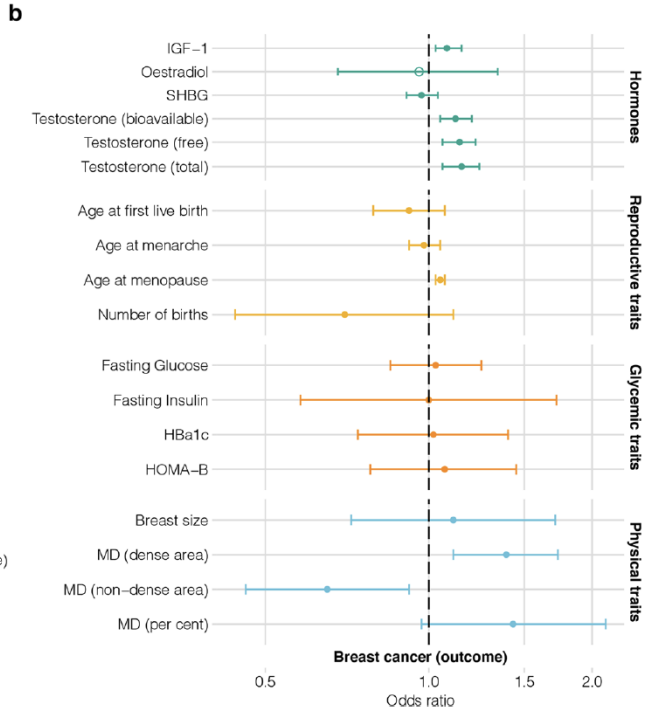
*Correspondence to: Graham A. Colditz, MD, DrPH, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8100, St Louis, MO, 63110, USA (e-mail: colditzg@wustl.edu).

Early-Life Adiposity and BC – Indirect Effect





communications biology
ARTICLE
https://doi.org/10.1038/s42003-022-03272-5 OPEN

Deciphering how early life adiposity influences breast cancer risk using Mendelian randomization

Marina Vabistsevits[1,2✉], George Davey Smith[1,2], Eleanor Sanderson[1,2], Tom G. Richardson[1,2,3,5], Bethan Lloyd-Lewis[4,5] & Rebecca C. Richmond[1,2,5]

Early-Life Adiposity and MBD – Direct Effect

RESEARCH ARTICLE

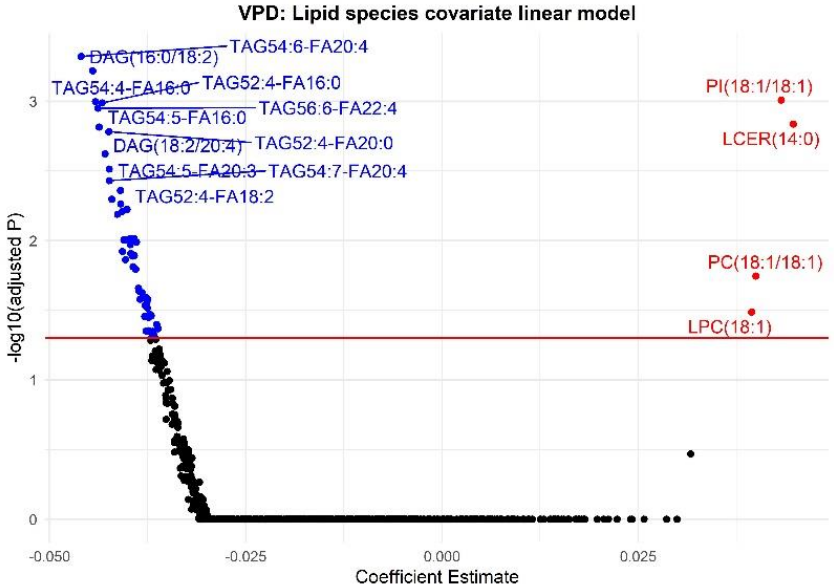
Cancer Medicine Open Access WILEY

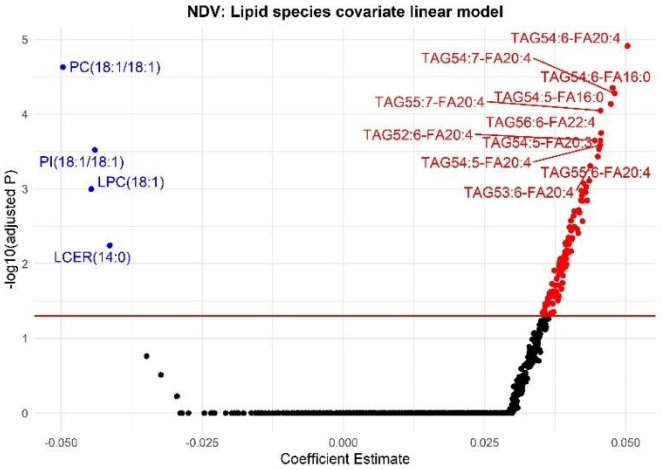
Changes in adiposity over the life course and gene expression in postmenopausal women

Yunan Han[1] | Graham A. Colditz[1,2] | Adetunji T. Toriola[1,2]

Genes[b]	Per 10 kg/m^2 BMI increase at age 10	
	Diff%[c]	95% CI
Growth factor-related genes		
BMP2	−1.3	−20.0, 21.6
IGF-1	−9.6	−29.9, 16.6
IGFBP-3	−2.3	−17.2, 15.4
FGF1	2.5	−5.5, 11.1
FGF12	−0.1	−8.0, 8.5
TGFB1	0.4	−7.8, 9.4
RANK pathway-related genes		
RANK	−7.5	−19.9, 6.7
RANKL	**−17.2***	**−30.8, −0.9**
TNFRSF13B	−11.1	−22.8, 2.4
TNFRSF18	1.5	−7.1, 10.8
OPG	−4.2	−15.8, 9.1
Sex hormone-related genes		
PRL	−4.3	−11.5, 3.4
PGR	0.3	−11.5, 13.7
ESR1	−3.9	−12.9, 6.1
STAT1	10.3	−3.8, 26.6
STAT5	3.7	−5.2, 13.3

Lipidomic Profiling of MBD





Getz KR

Getz….Toriola. Breast Cancer Research, 2023

Conclusions

- Understand biological mechanisms driving the associations of early-life factors with BC and deploy these early in life
- Apply new technologies to refine biomarker and pathway identification for targeted prevention
- Equity, equity, equity – diversity in study population

Acknowledgements

- Catherine Appleton
- Debbie Bennet
- Graham Colditz
- Cheryl Herman
- Rosy Luo

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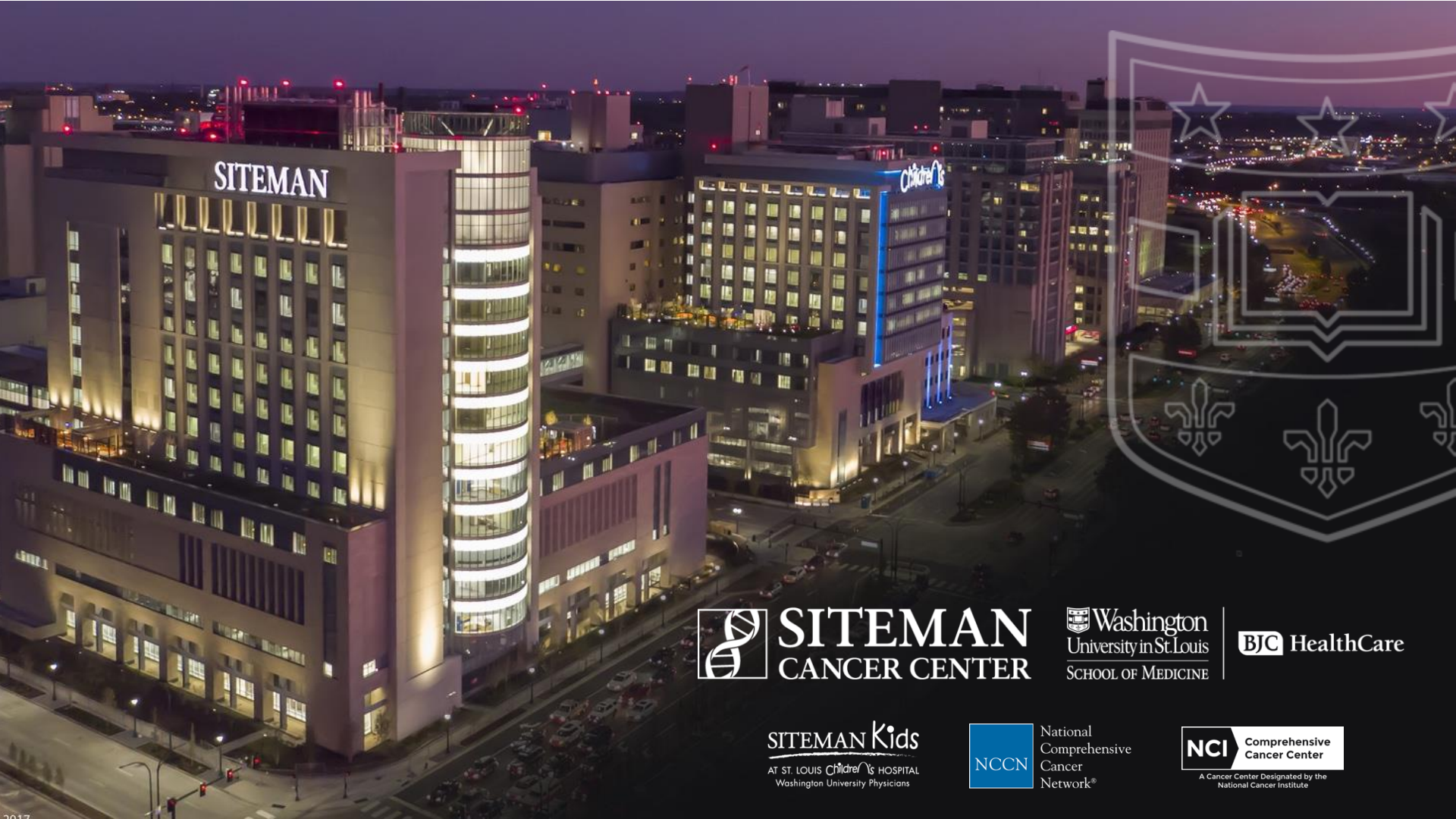
- NIH/NCI - R01CA246592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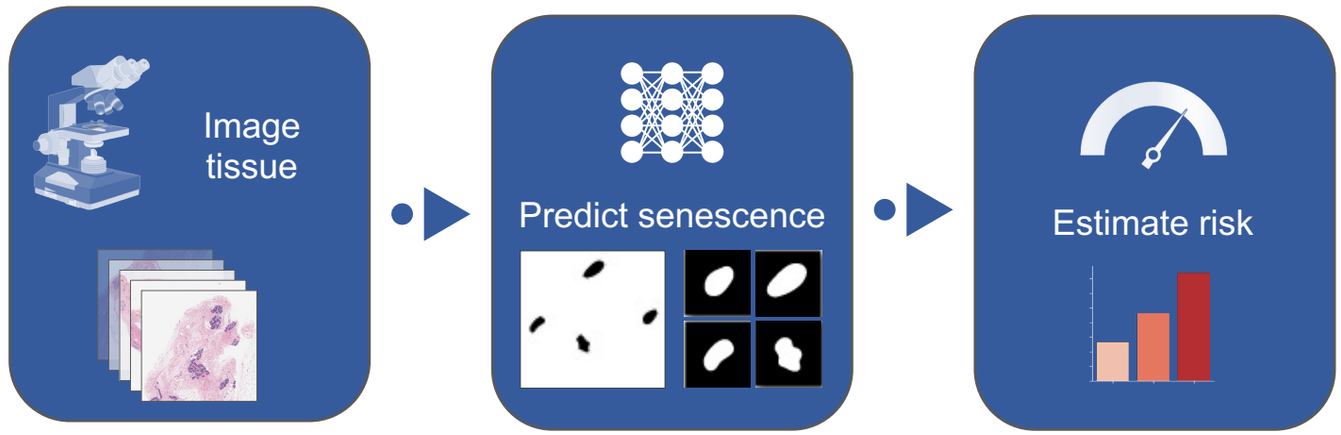
Washington University Physicians
NCCN
National Comprehensive Cancer Network®
NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Senescence-Based Deep Learning Predicts Breast Cancer Risk Using H&E Core Biopsy Images From Healthy Women

Mark Powell MD MPH[1]
Christopher Benz MD[1]
Indra Heckenbach PhD[2]
Morten Scheibye-Knudsen MD DMSc[2]

November 2024



1


2
UNIVERSITY OF COPENHAGEN

Cellular senescence: a complex phenotype

Characterized by irreversible cell cycle arrest and an inflammatory senescence-associated secretory phenotype (SASP)

Complex state – can impact cancer risk in both positive and negative ways

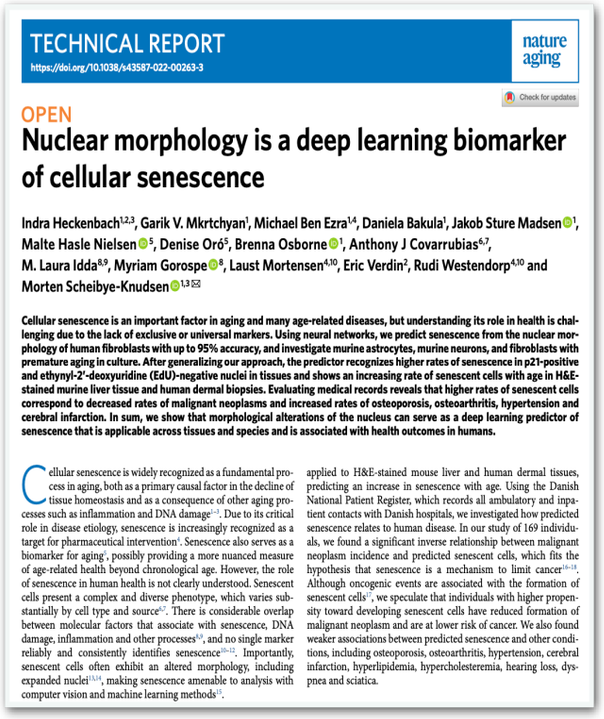
Difficult to identify – lacks universal and specific markers

No current way to evaluate role of senescence in large observational studies

Can deep learning detect senescence?

Use known inducers of senescence in tissue culture such as radiation and drugs and then apply deep learning

Subtle changes in nuclear morphology such as area and convexity can be utilized to detect senescent cells from standard H&E image



TECHNICAL REPORT
https://doi.org/10.1038/s43587-022-00263-3
nature aging
Check for updates

OPEN

Nuclear morphology is a deep learning biomarker of cellular senescence

Indra Heckenbach[1,2,3], Garik V. Mkrtchyan[1], Michael Ben Ezra[1,4], Daniela Bakula[1], Jakob Sture Madsen[1], Malte Hasle Nielsen[5], Denise Oró[5], Brenna Osborne[1], Anthony J Covarrubias[6,7], M. Laura Idda[8,9], Myriam Gorospe[8], Laust Mortensen[4,10], Eric Verdin[2], Rudi Westendorp[4,10] and Morten Scheibye-Knudsen[1,3]

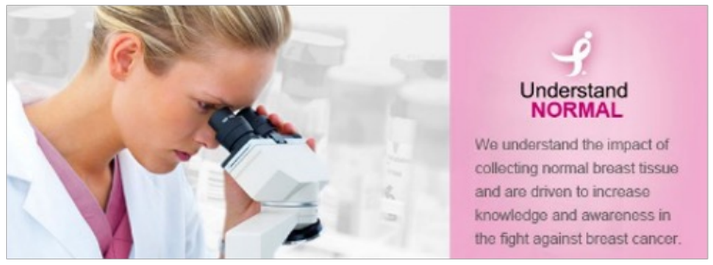
Cellular senescence is an important factor in aging and many age-related diseases, but understanding its role in health is challenging due to the lack of exclusive or universal markers. Using neural networks, we predict senescence from the nuclear morphology of human fibroblasts with up to 95% accuracy, and investigate murine astrocytes, murine neurons, and fibroblasts with premature aging in culture. After generalizing our approach, the predictor recognizes higher rates of senescence in p21-positive and ethynyl-2′-deoxyuridine (EdU)-negative nuclei in tissues and shows an increasing rate of senescent cells with age in H&E-stained murine liver tissue and human dermal biopsies. Evaluating medical records reveals that higher rates of senescent cells correspond to decreased rates of malignant neoplasms and increased rates of osteoporosis, osteoarthritis, hypertension and cerebral infarction. In sum, we show that morphological alterations of the nucleus can serve as a deep learning predictor of senescence that is applicable across tissues and species and is associated with health outcomes in humans.

Cellular senescence is widely recognized as a fundamental process in aging, both as a primary causal factor in the decline of tissue homeostasis and as a consequence of other aging processes such as inflammation and DNA damage[1–3]. Due to its critical role in disease etiology, senescence is increasingly recognized as a target for pharmaceutical intervention[4]. Senescence also serves as a biomarker for aging[5], possibly providing a more nuanced measure of age-related health beyond chronological age. However, the role of senescence in human health is not clearly understood. Senescent cells present a complex and diverse phenotype, which varies substantially by cell type and source[6,7]. There is considerable overlap between molecular factors that associate with senescence, DNA damage, inflammation and other processes[8,9], and no single marker reliably and consistently identifies senescence[10–12]. Importantly, senescent cells often exhibit an altered morphology, including expanded nuclei[13,14], making senescence amenable to analysis with computer vision and machine learning methods[15].

applied to H&E-stained mouse liver and human dermal tissues, predicting an increase in senescence with age. Using the Danish National Patient Register, which records all ambulatory and inpatient contacts with Danish hospitals, we investigated how predicted senescence relates to human disease. In our study of 169 individuals, we found a significant inverse relationship between malignant neoplasm incidence and predicted senescent cells, which fits the hypothesis that senescence is a mechanism to limit cancer[16–18]. Although oncogenic events are associated with the formation of senescent cells[17], we speculate that individuals with higher propensity toward developing senescent cells have reduced formation of malignant neoplasm and are at lower risk of cancer. We also found weaker associations between predicted senescence and other conditions, including osteoporosis, osteoarthritis, hypertension, cerebral infarction, hyperlipidemia, hypercholesteremia, hearing loss, dyspnea and sciatica.

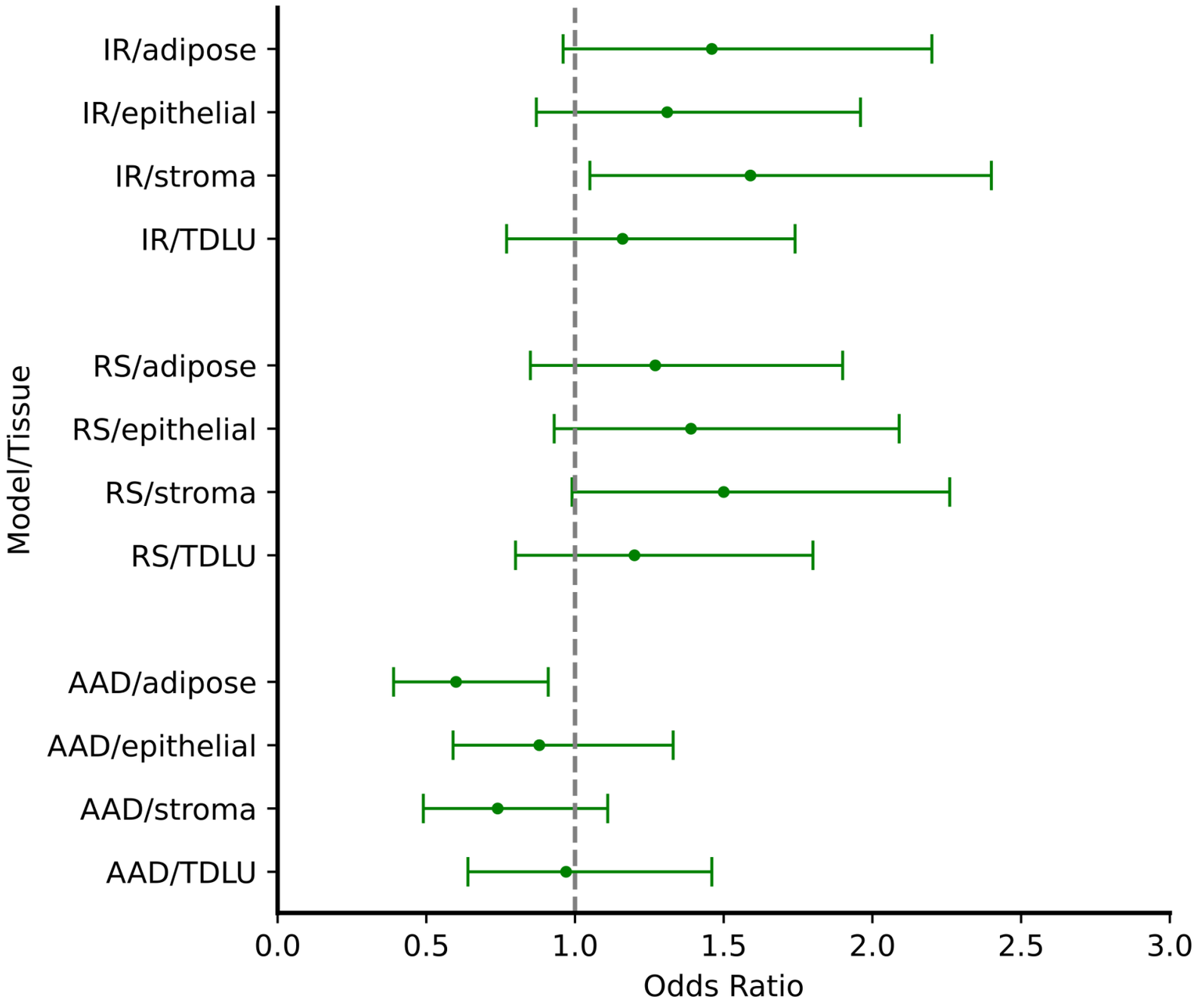
3 models: IR (radiation), RS (replicative senescence), and AAD (drug induced by antimycin, atazanavir-ritonavir, doxorubicin) applied to 4 breast tissues: adipose, stroma, TDLU and non-TDLU epithelium

Normal breast tissue from the Komen Tissue Bank



- **KTB provides H&E-stained images from entry biopsy with associated data**
- **4382 individuals with no prior history of breast disease enrolled 2009-2019 and followed through May 2024**
- **Median age 45, 69% NH White, 18% NH Black, 9% Hispanic, 4% Asian**
- **99 breast cancer cases diagnosed on average 4.8 years after biopsy, 13 additional cases and detailed path reports since initial publication**

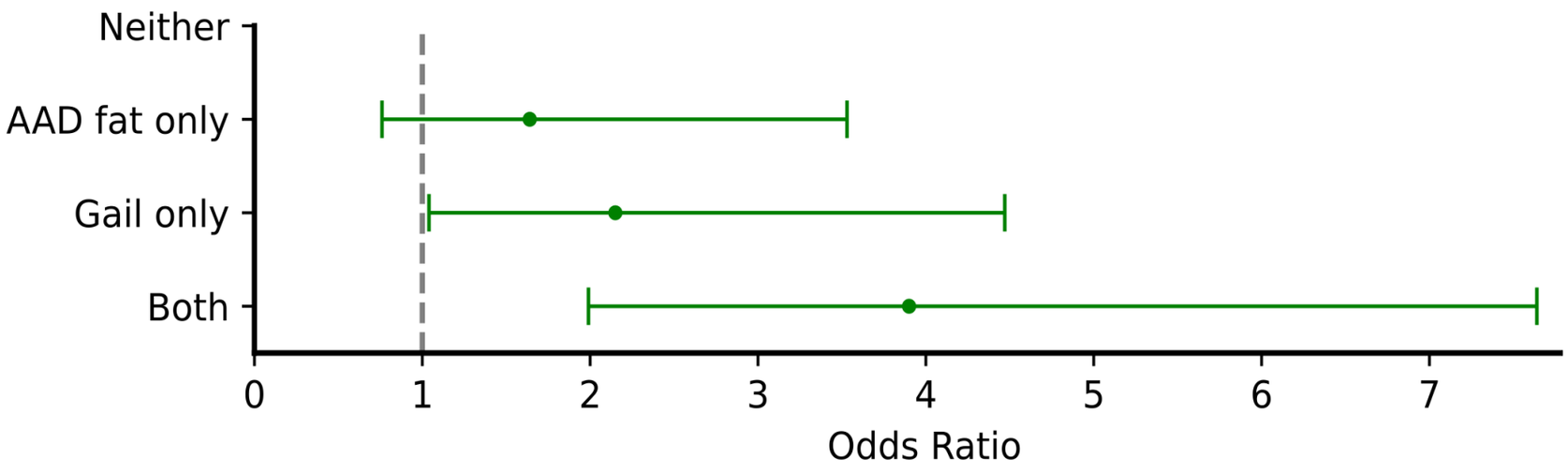
Senescence scores are associated with breast cancer risk



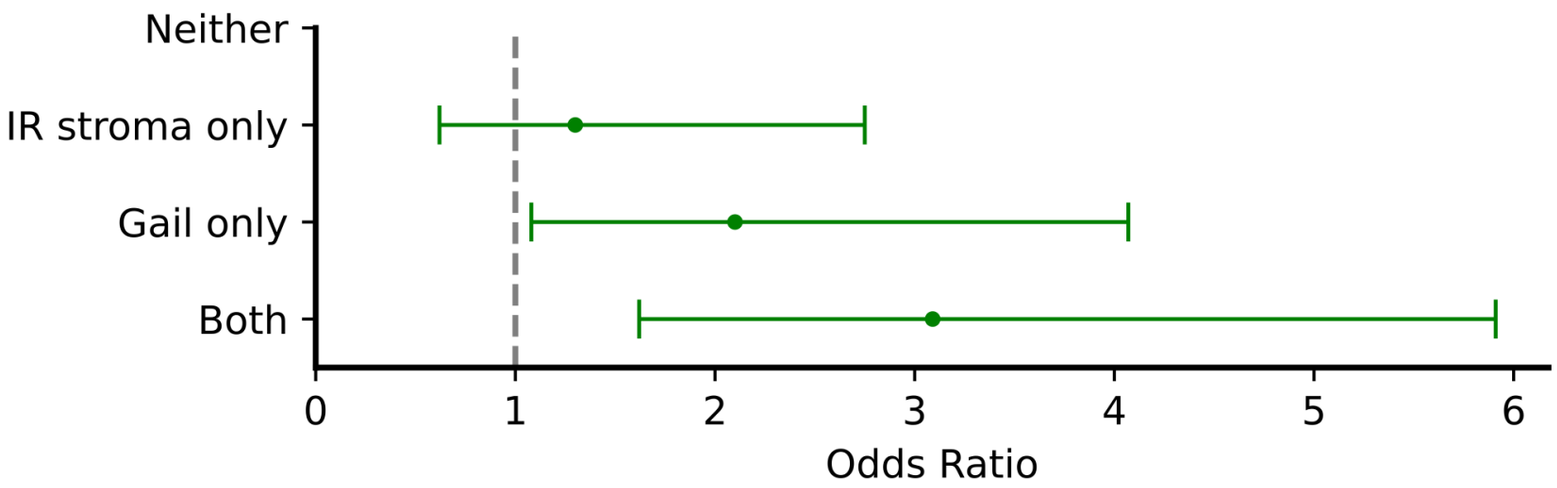
Odds Ratio	95% CI	P value
1.46	0.96 – 2.20	0.08
1.31	0.87 – 1.96	0.20
1.59	1.05 – 2.40	0.03
1.16	0.77 – 1.74	0.47
1.27	0.85 – 1.90	0.25
1.39	0.93 – 2.09	0.11
1.50	1.00 – 2.26	0.05
1.20	0.80 – 1.80	0.37
0.60	0.39 – 0.91	0.02
0.88	0.59 – 1.33	0.55
0.74	0.49 – 1.11	0.14
0.97	0.64 – 1.46	0.88

All analyses are adjusted for age, race/ethnicity, age menarche, parity, family history, BMI, alcohol and tobacco use

Senescence scores add to predictive value of Gail model



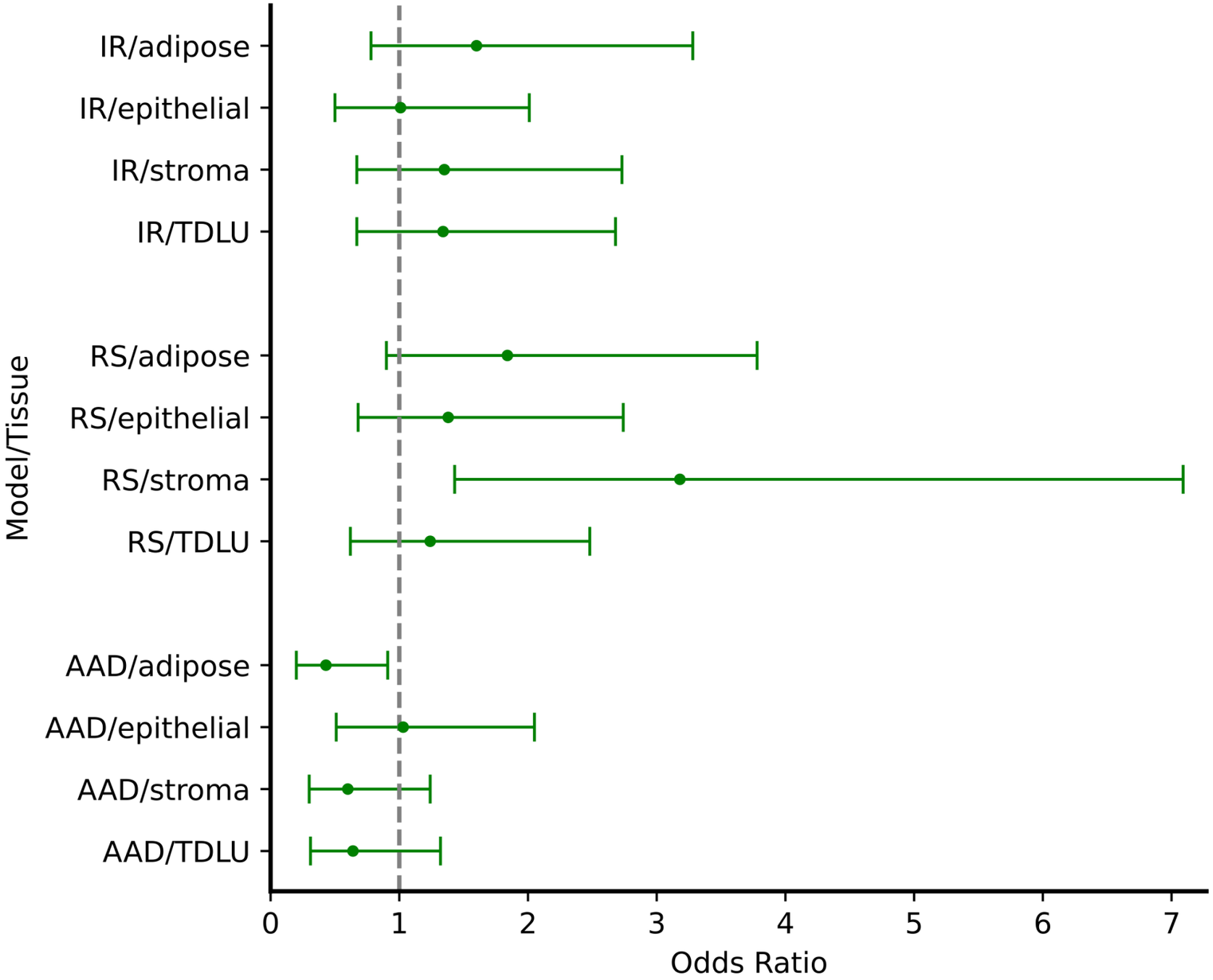
	Odds Ratio	95% CI	P value
Neither			
AAD fat only	1.64	0.76 – 3.53	0.21
Gail only	2.15	1.04 – 4.47	0.04
Both	3.90	1.99 – 7.64	0.0001



	Odds Ratio	95% CI	P value
Neither			
IR stroma only	1.30	0.62 – 2.75	0.48
Gail only	2.10	1.08 – 4.07	0.03
Both	3.09	1.62 – 5.91	0.0006

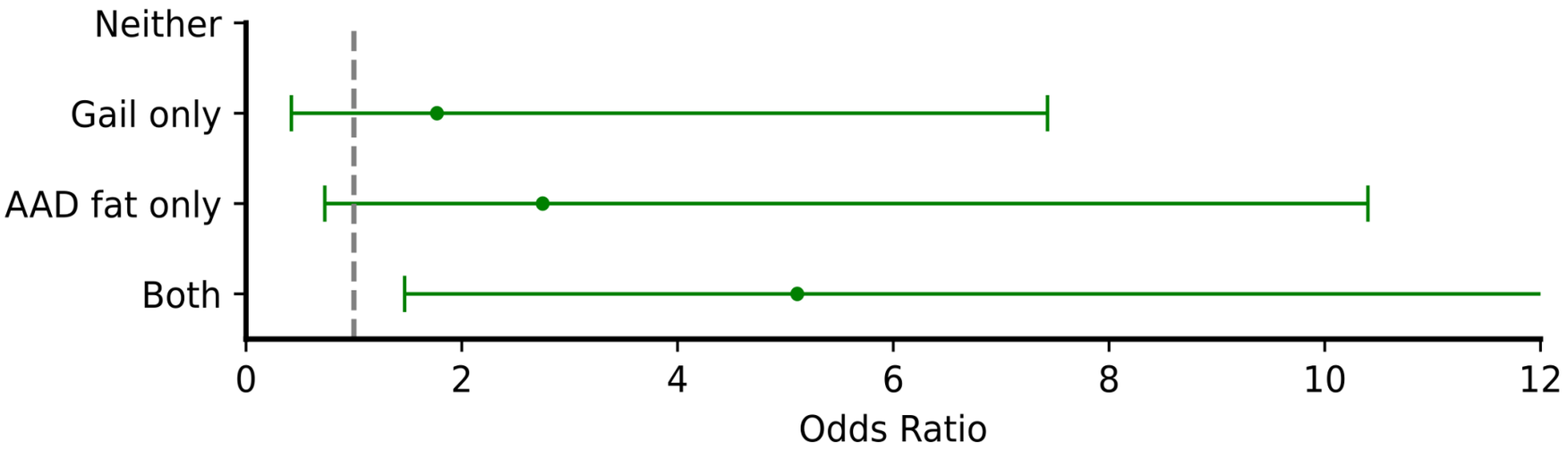
Gail scores are based on age, race/ethnicity, age at first birth, age of menarche, family history in first degree relative, and history of prior breast biopsies

Senescence scores are associated with risk of DCIS (n = 36)

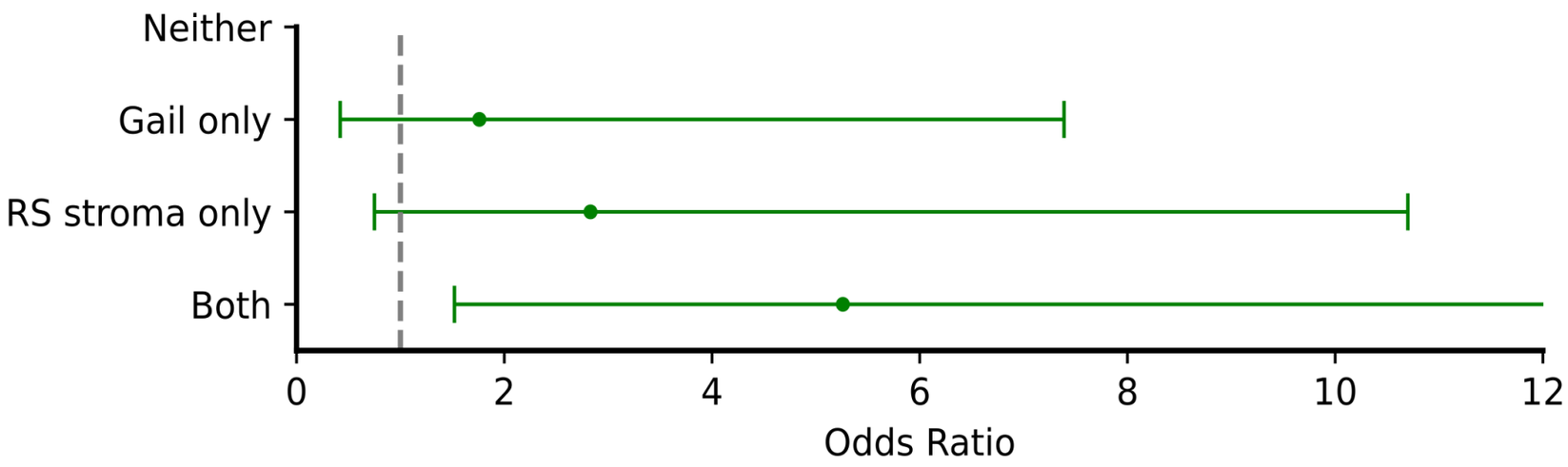


	Odds Ratio	95% CI	P value
IR/adipose	1.60	0.78 – 3.28	0.20
IR/epithelial	1.01	0.50 – 2.01	0.98
IR/stroma	1.35	0.67 – 2.73	0.40
IR/TDLU	1.34	0.67 – 2.68	0.41
RS/adipose	1.84	0.90 – 3.78	0.10
RS/epithelial	1.38	0.68 – 2.74	0.37
RS/stroma	3.18	1.43 – 7.09	0.005
RS/TDLU	1.24	0.62 – 2.48	0.54
AAD/adipose	0.43	0.20 – 0.91	0.03
AAD/epithelial	1.03	0.51 – 2.05	0.93
AAD/stroma	0.60	0.30 – 1.24	0.17
AAD/TDLU	0.64	0.31 – 1.32	0.23

Senescence scores combined with Gail scores for DCIS



	Odds Ratio	95% CI	P value
Gail only	1.77	0.42 – 7.43	0.43
AAD fat only	2.75	0.73 – 10.4	0.14
Both	5.11	1.47 – 17.7	0.01



	Odds Ratio	95% CI	P value
Gail only	1.76	0.42 – 7.39	0.44
RS stroma only	2.83	0.75 – 10.7	0.13
Both	5.26	1.52 – 18.3	0.009

Conclusions and Future Directions

- **Senescence scores generated by deep learning models may be a new biomarker for predicting breast cancer risk**

- **Use in predicting future risk of invasive cancer in women with BBD looks promising especially in high-risk women with proliferative changes**

- **The scores may represent ability of a woman's breast tissue to resist the development of breast cancer**

- **Potential applications may exist for predicting prognosis in women with DCIS or early-stage invasive cancer**

- **Can be added to traditional risk factors and have been shown to increase predictive value when added to MIRAI mammography algorithm**

Thank you!

Stromal Inflammation as a Driver of Parity-related Breast Cancer Etiologic Heterogeneity

Implications for Precision Prevention in a Sub-Saharan African Population

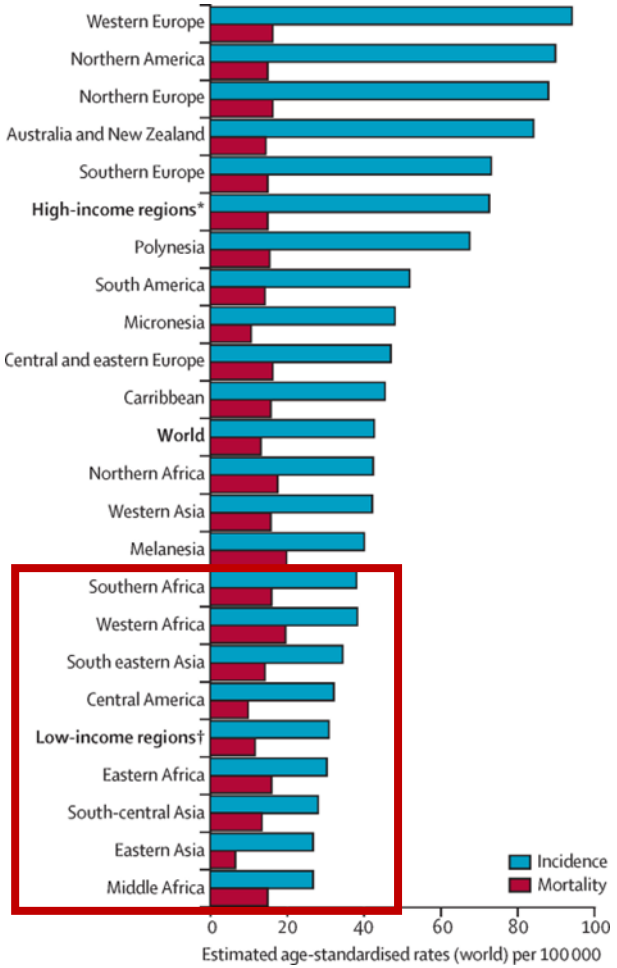
Mustapha Abubakar, M.D., Ph.D.
Earl Stadtman Investigator
NIH Distinguished Scholar (2022)
Integrative Tumor Epidemiology Branch (ITEB)
Division of Cancer Epidemiology and Genetics

Background: Breast cancer in Sub-Saharan Africa

- A leading cause of cancer-related morbidity and mortality

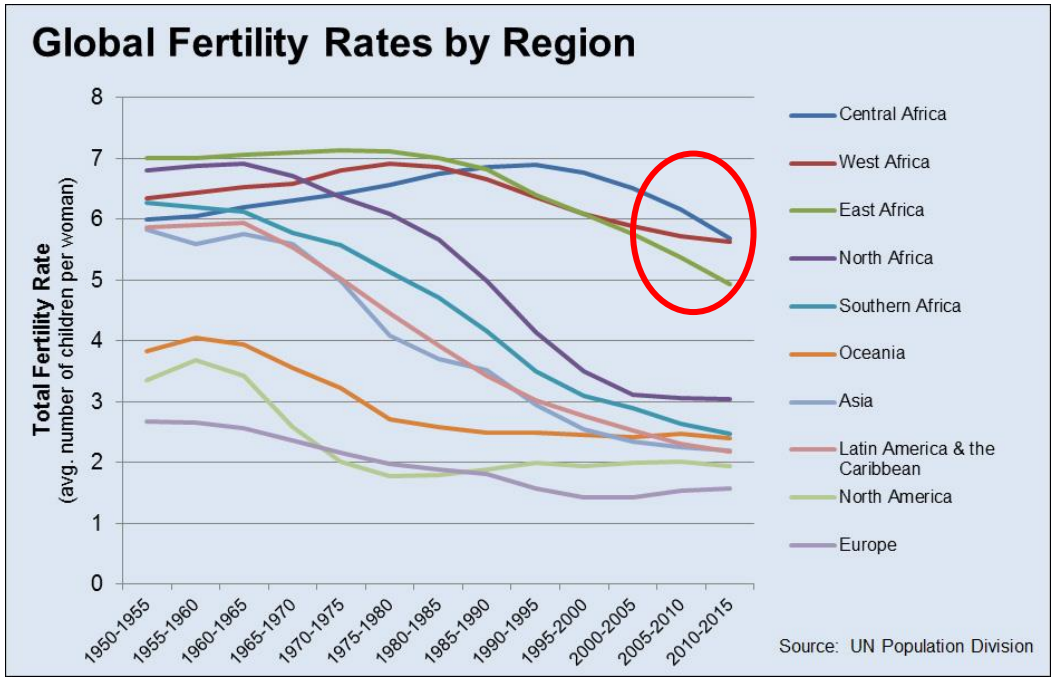
- Disproportionately high mortality rates:
  - Late stage at presentation
  - Limited access to screening, diagnostic and treatment services
  - Manpower shortages

  - Aggressive tumor biology
    - Younger age
    - Family history
    - Multiparity

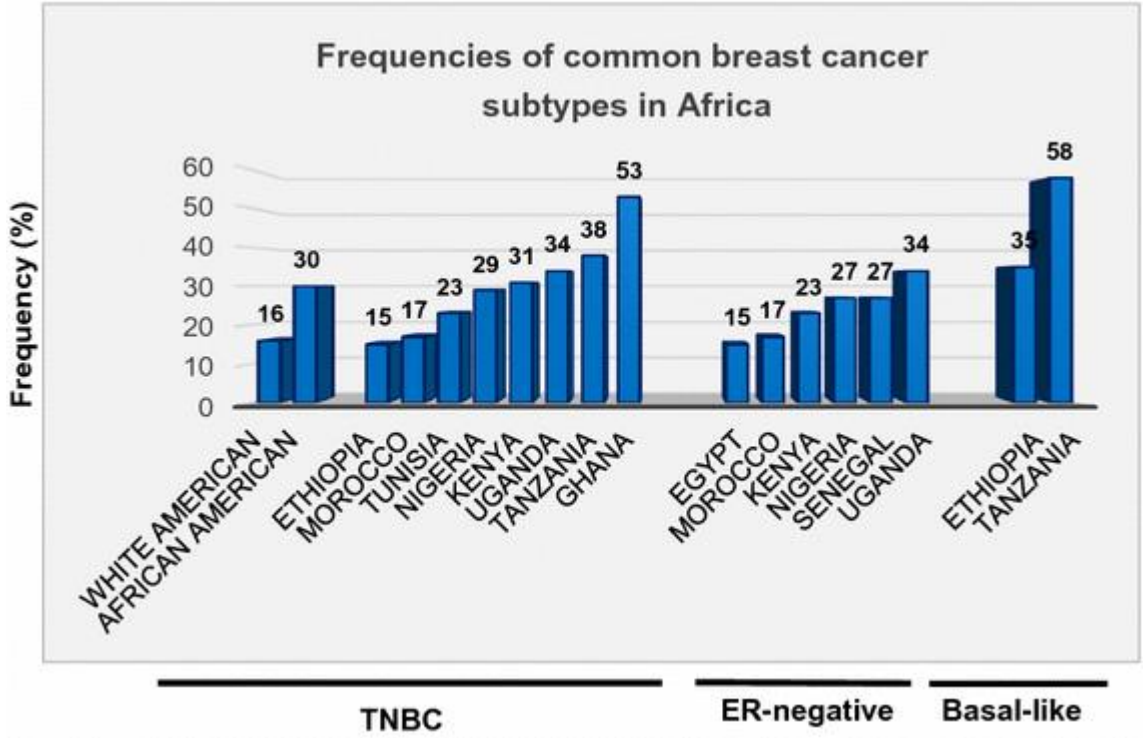


Brewster et al, Lancet. 2014

Higher parity rates in parallel with higher proportions of aggressive breast tumor phenotypes among sub-Saharan African women



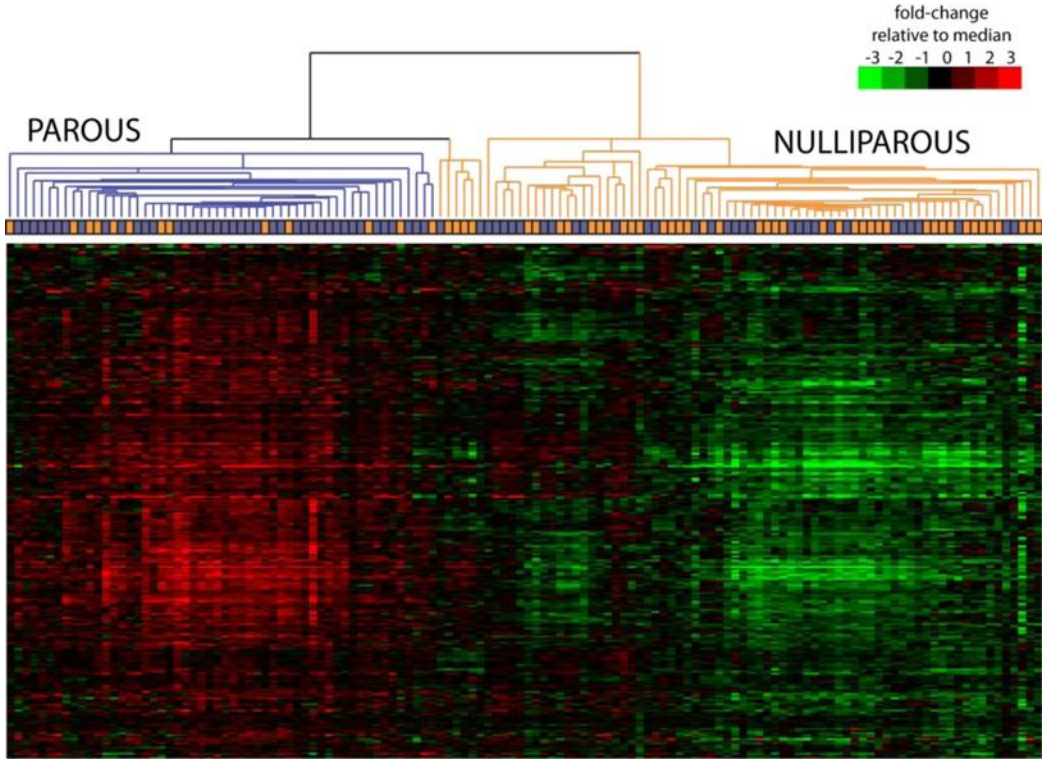
Avg. 5 children per woman in most of sub-Saharan Africa



Lukong et al, BCRT. 2017

Complex relationship of parity and breast cancer risk

- Varies by ER status
  - Reduced risk for ER+
  - Increased risk for ER-/basal-like
- Attenuating effect of breastfeeding (ER-)
- Underlying mechanisms?
  - Aberrant lobular involution
  - Chronic inflammation



Upregulation of genes in immune, inflammation and wound response pathways in parous breast tissues.

Rotuno et al, BCR. 2017

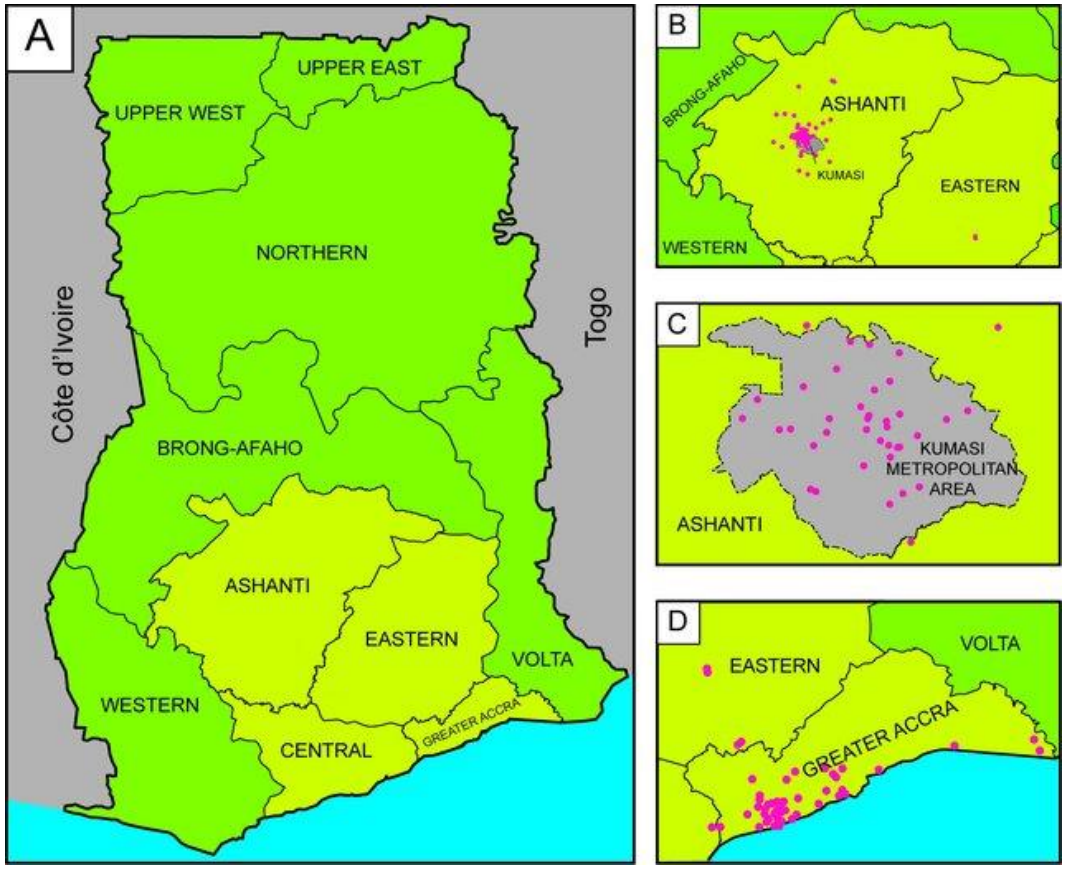
Millikan et al, BCRT. 2008; Palmer et al, CEBP. 2011; Figueroa et al, IJC. 2020; Jung et al, JNCI. 2022

Aim

To investigate the associations between parity-related factors and risk of breast cancer subtypes defined by degree of stromal inflammation, overall and by tumor estrogen receptor (ER) status

Study population: Ghana Breast Health Study (GBHS)

- Population-based case-control study (2013-2015)
- Cases (invasive breast cancer patients)
- Population controls recruited from Ashanti, Central, Eastern, and Greater Accra Regions
- Current analysis: 790 cases and 2,095 controls



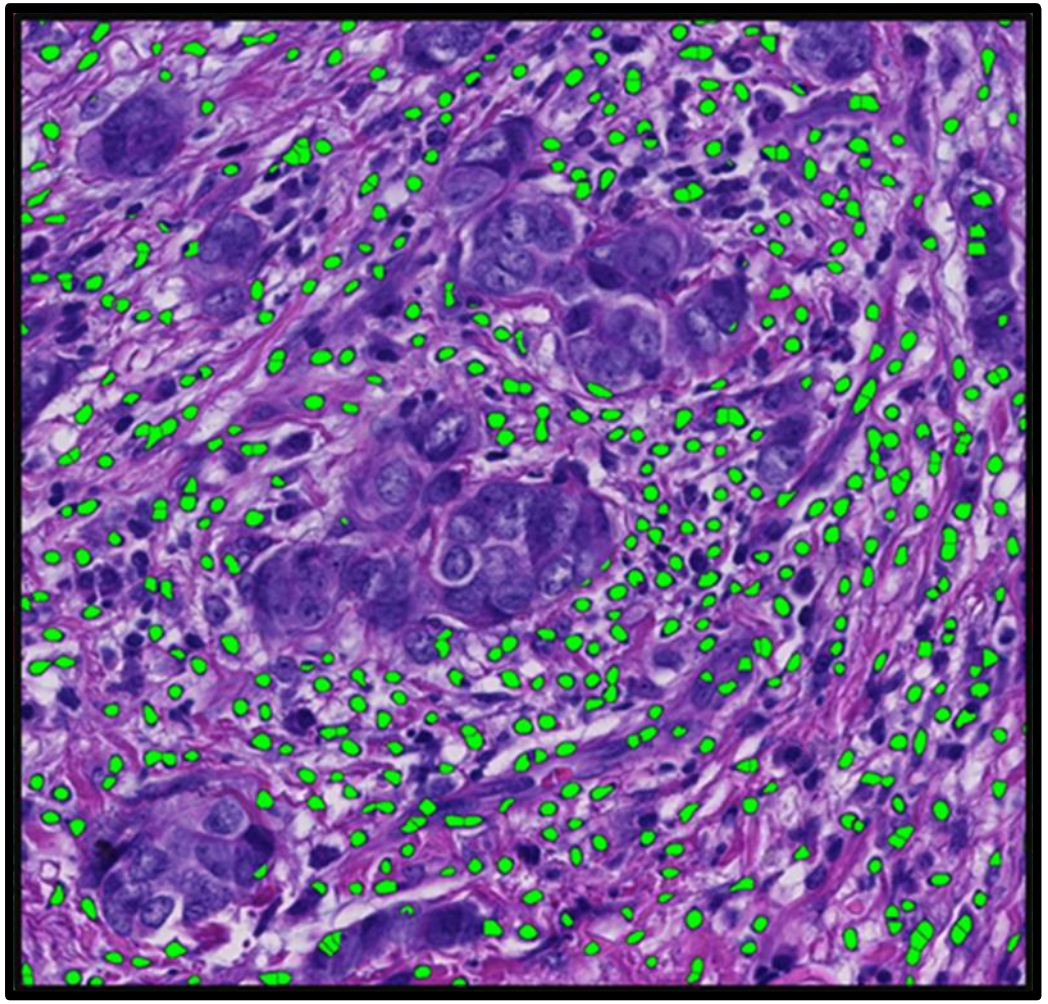
Nyante et al, PLOS ONE. 2019

Exposures

- Detailed questionnaire-based risk factors (demographic, lifestyle, and environmental factors)
- Exposures of interest: parity (nulliparous, parous), number of children, breastfeeding duration, time since last childbirth, joint parity/breastfeeding
- Other exposures: age at menarche, body size, menopausal status, family history, etc.

Brinton et al, IJC. 2017; Figueroa et al, IJC. 2020

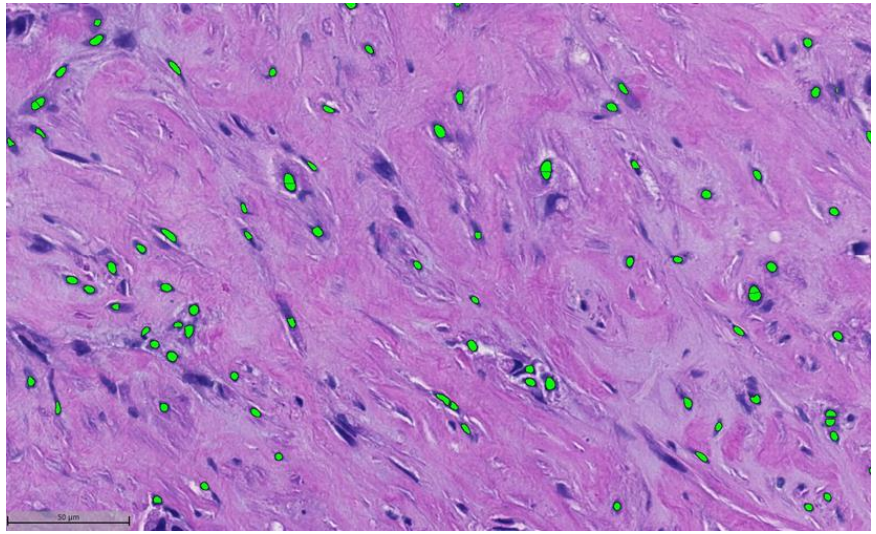
Characterizing stromal inflammation on standard H&E images using machine learning



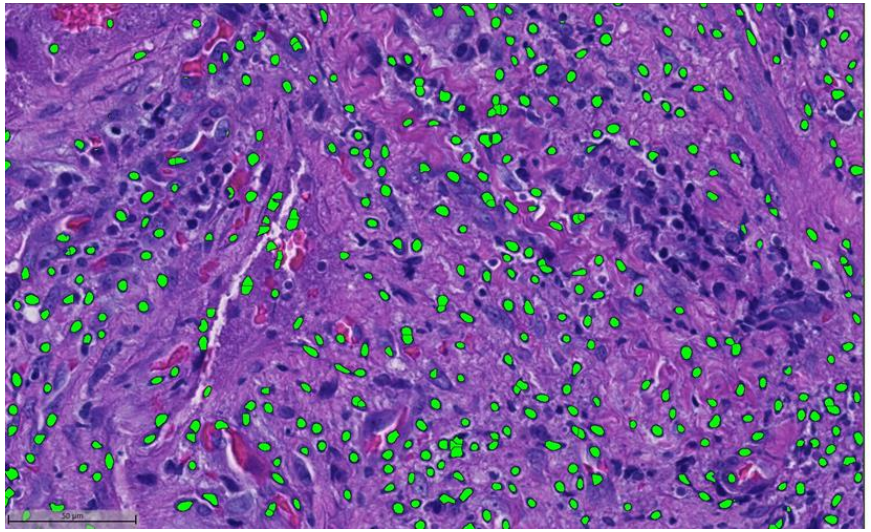
- Excellent agreement with two pathologists (r=0.75-0.93 for intra-tumoral & peri-tumoral stromal cellularity)
- Stromal cellular density = % of stroma area occupied by nucleated stromal cells

Abubakar et al, CEBP. 2024

Defining low-grade and high-grade stromal inflammation-based subtypes of breast cancer



Low-grade stromal inflammation (LGSI)
<30%

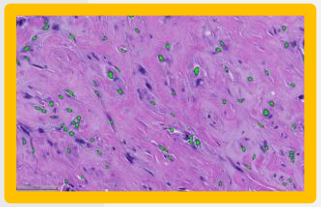


High-grade stromal inflammation (HGSI)
≥30%

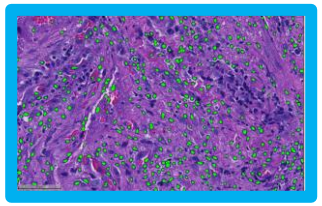
Park et al, Ann Oncol. 2019; Loi et al, JCO. 2019

Analytical approach

- Associations of parity-related factors with risk of inflammation-based breast cancer subtypes



Low-grade stromal inflammation (LGSI)

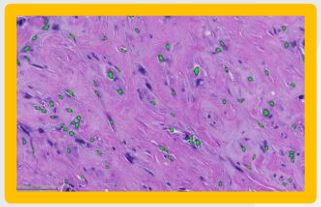


High-grade stromal inflammation (HGSI)

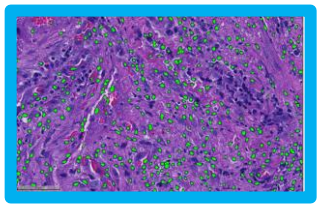
- **Overall** (ER+/ER-)
- **≤50 years** (ER+/ER-)
- **>50 years** (ER+/ER-)

Results 1: Associations of parity-related factors with risk of inflammation-based breast cancer subtypes

- Overall
- By ER status

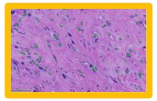
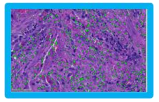


Low-grade stromal inflammation (LGSI)



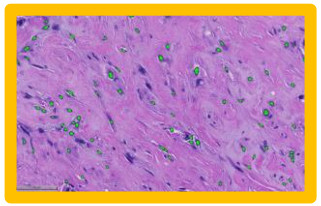
High-grade stromal inflammation (HGSI)

Frequencies of parity-related variables differed by inflammation-based subtypes

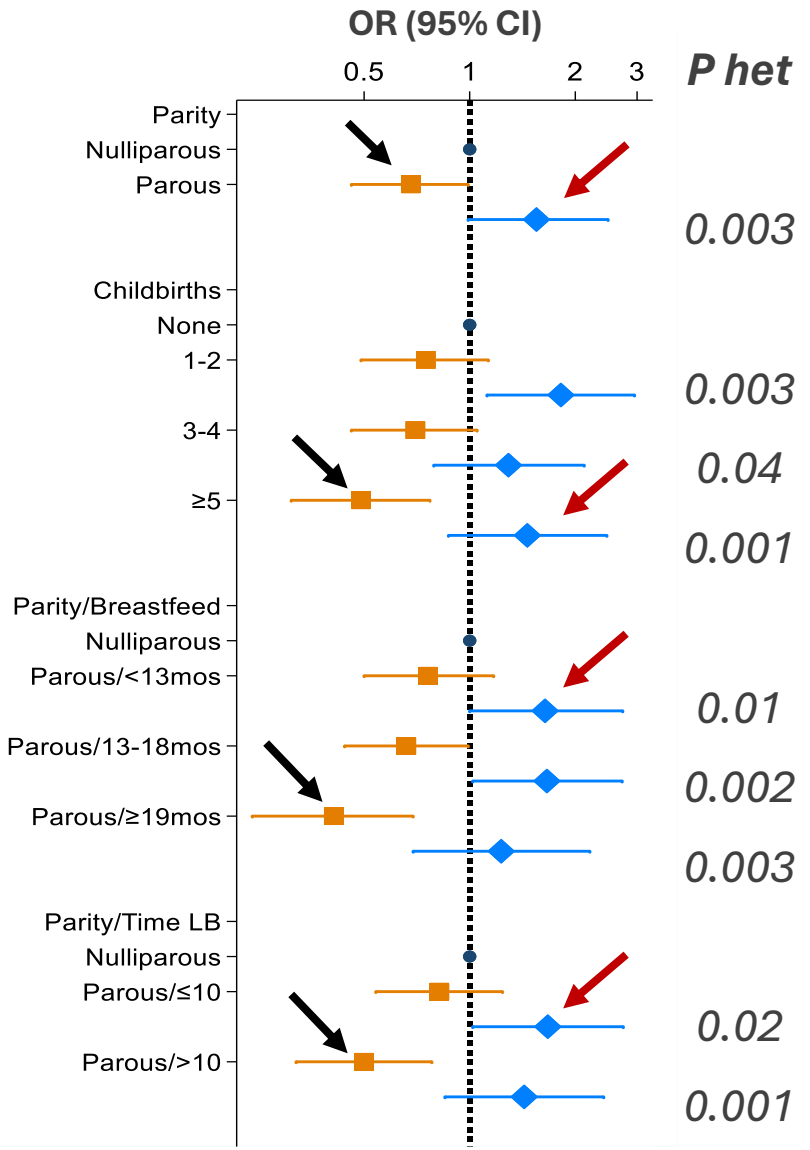
Characteristic	 Low-grade Inflammation	High-grade Inflammation 	
	n=394	n=395	P-value
Parity			
Nulliparous	45 (11.4)	25 (6.3)	
Parous	348 (88.6)	369 (93.7)	0.01
Number of children			
Nulliparous	45 (11.5)	25 (6.3)	
1-2	98 (24.9)	115 (29.2)	
3-4	140 (35.6)	118 (30.0)	
≥5	110 (28.0)	136 (34.5)	0.009
Breastfeeding, months			
<13	129 (34.3)	110 (29.5)	
13-18	203 (54.0)	211 (56.6)	
≥19	44 (11.7)	52 (13.9)	0.31
Joint parity/breastfeeding (months)			
Nulliparous	45 (12.0)	25 (6.7)	
Parous/<13	84 (22.3)	85 (22.8)	
Parous/13-18	203 (54.0)	211 (56.6)	
Parous/≥19	44 (11.7)	52 (13.9)	0.08
Parity/time since last birth, years			
Nullparous	45 (12.6)	25 (6.9)	
Parous/≤10	118 (32.9)	111 (30.6)	
Parous/>10	195 (54.5)	227 (62.5)	0.01
Family history			
None	371 (95.4)	352 (90.5)	
Yes	18 (4.6)	37 (9.5)	0.008

Case-control analysis revealed etiologic heterogeneity of inflammation-based subtypes by parity

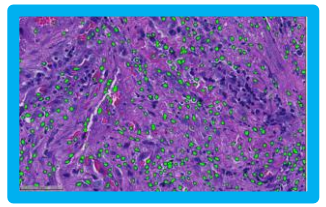
Reduced risk



Low-grade stromal inflammation (LGSI)

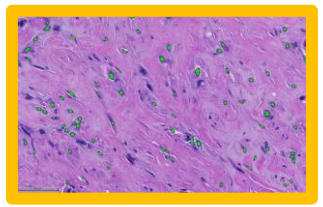


Increased risk

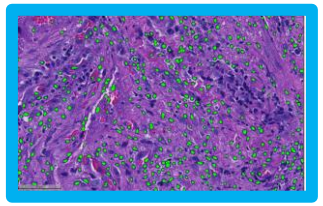


High-grade stromal inflammation (HGSI)

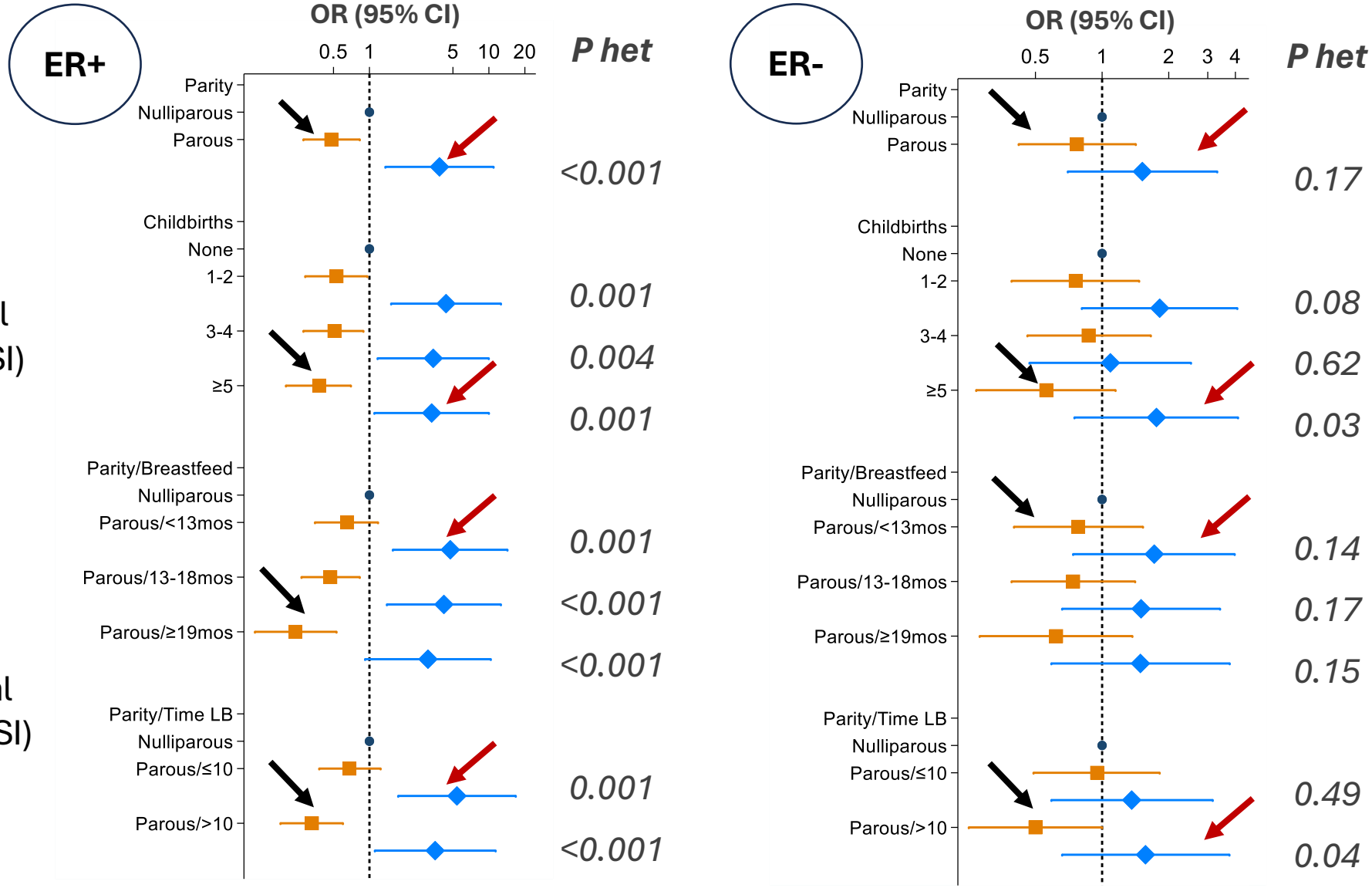
Inflammation-based subtyping refines parity-related etiologic heterogeneity by estrogen receptor status



Low-grade stromal inflammation (LGSI)

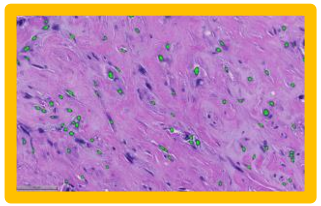


High-grade stromal inflammation (HGSI)

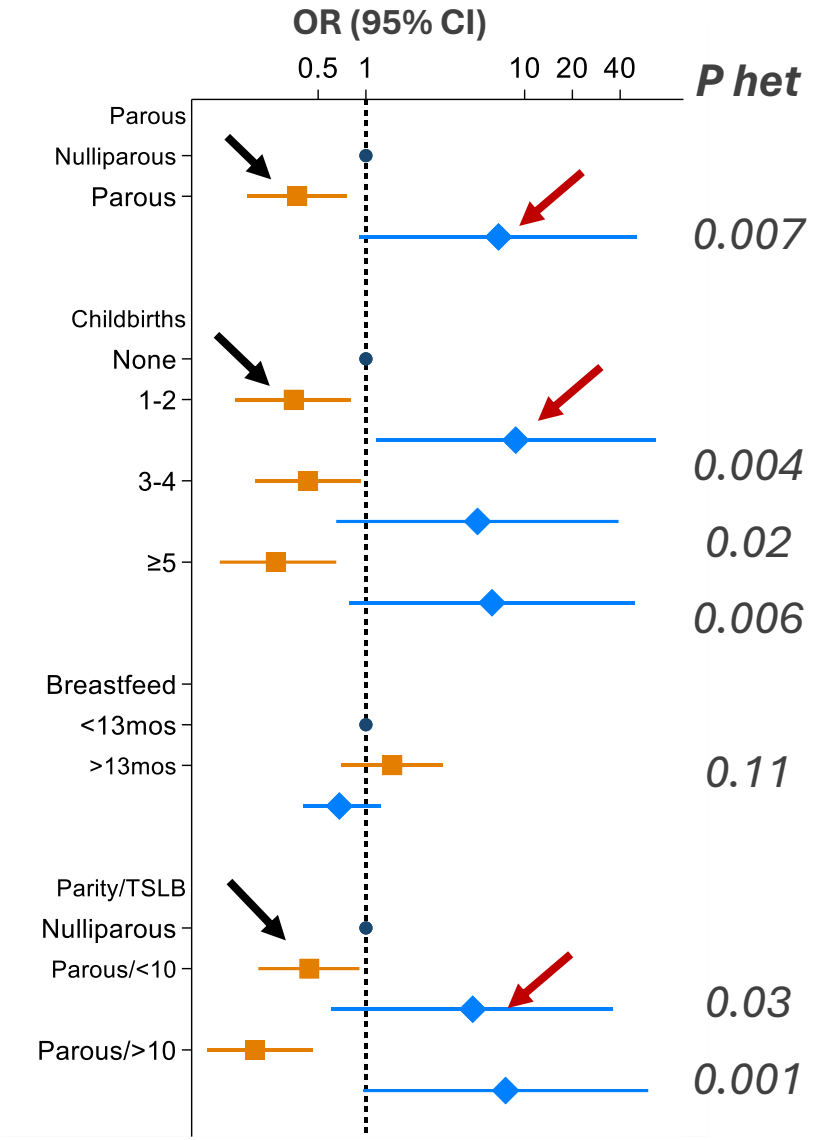


Persistence of parity-associated etiologic heterogeneity by inflammation-based subtypes of Triple Negative breast cancer

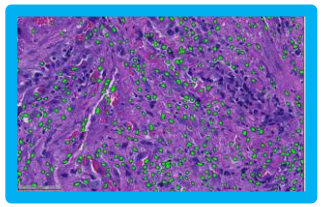
Reduced risk



Low-grade stromal inflammation (LGSI)



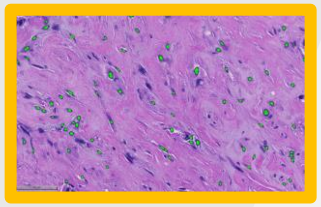
Increased risk



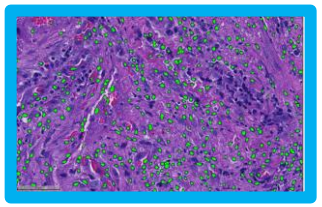
High-grade stromal inflammation (HGSI)

Results 2: Associations of parity-related factors with risk of inflammation-based breast cancer subtypes

- Among women ≤50 years
- By ER status

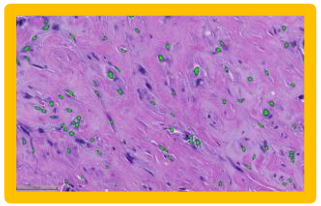


Low-grade stromal inflammation (LGSI)

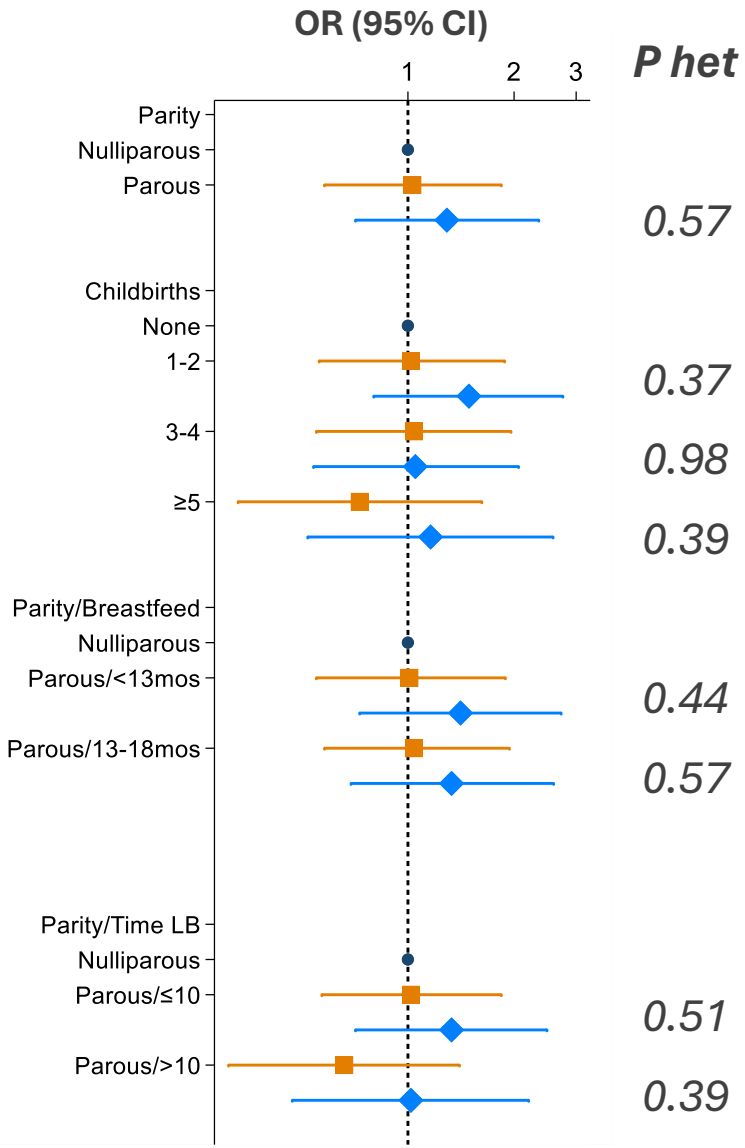


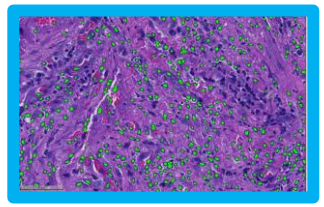
High-grade stromal inflammation (HGSI)

The protective effect of parity-related factors for low-grade stromal inflammation subtype was attenuated among women ≤50 years



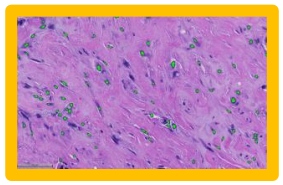
Low-grade stromal inflammation (LGSI)



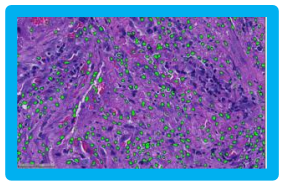


High-grade stromal inflammation (HGSI)

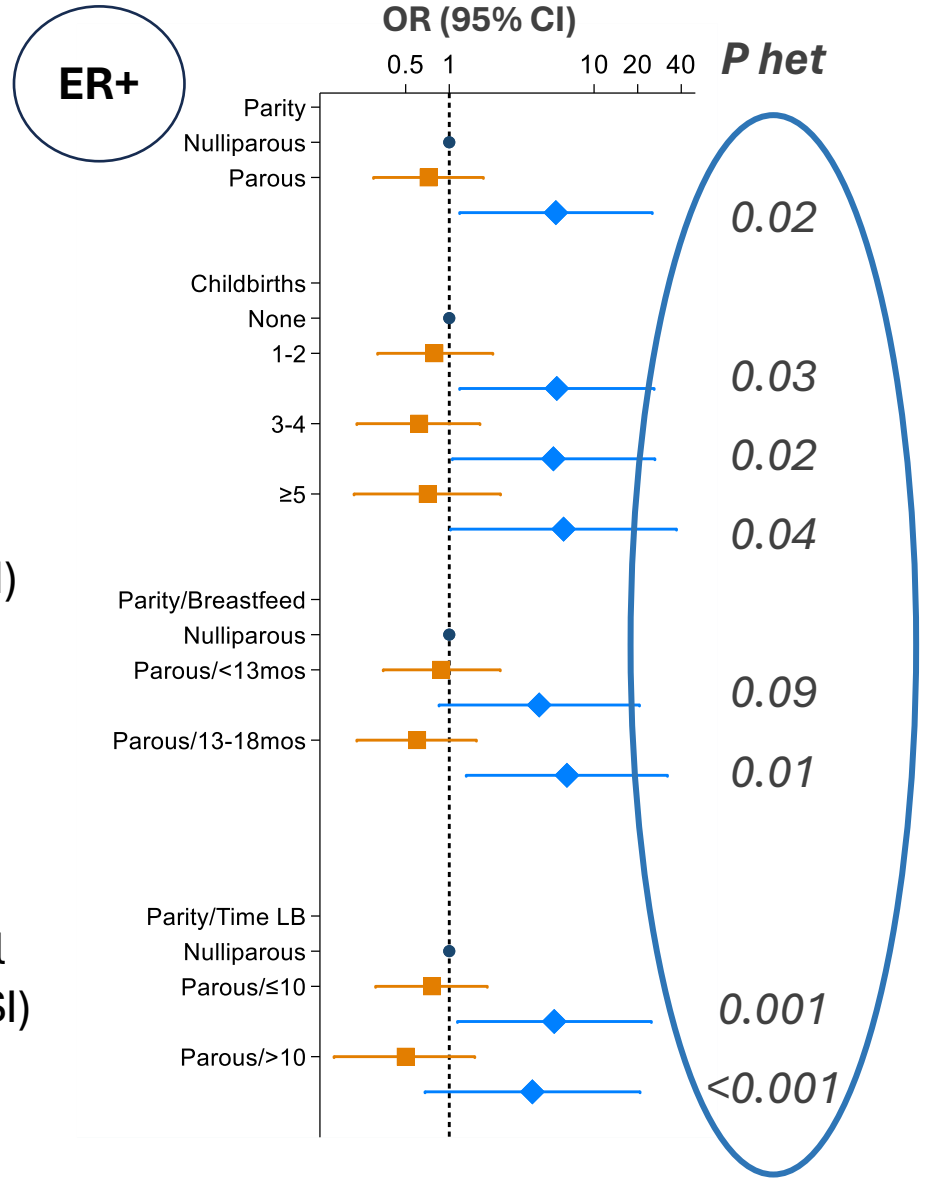
Etiologic heterogeneity of inflammation-based subtypes by parity status for ER+ but not ER- early onset tumors

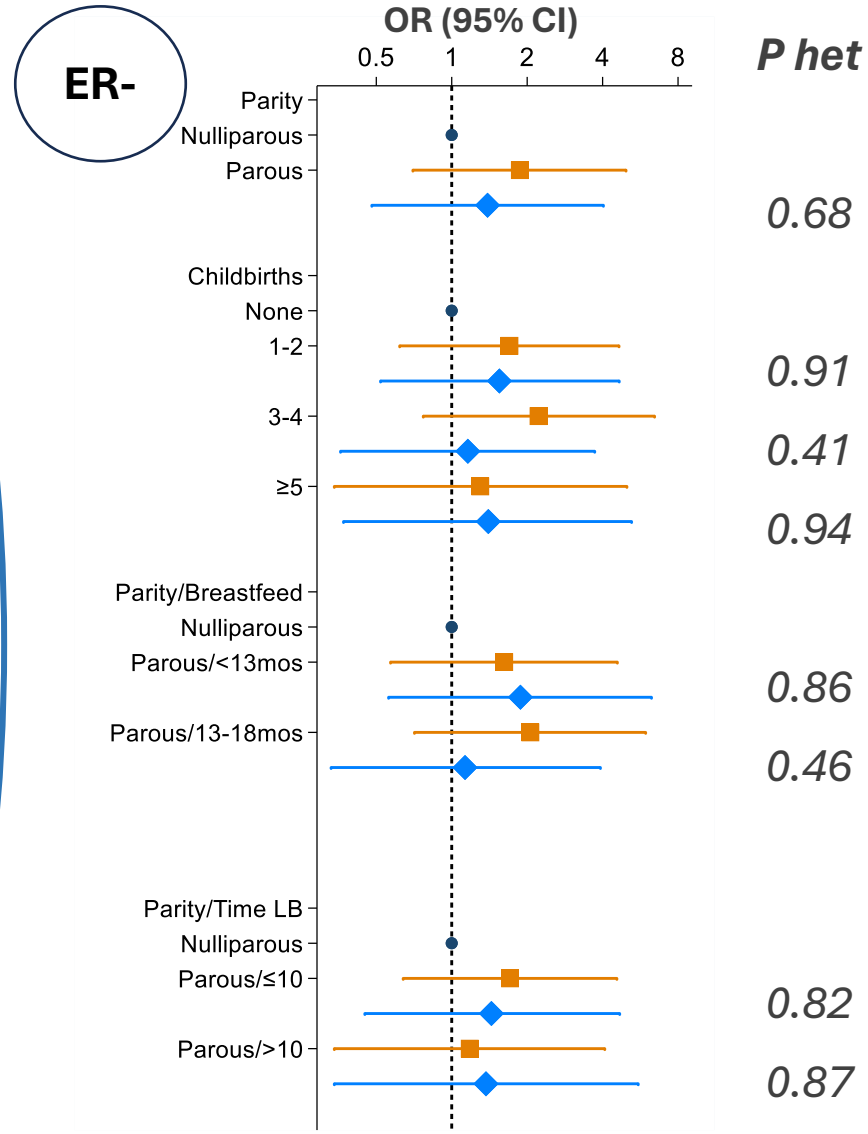


Low-grade stromal inflammation (LGSI)



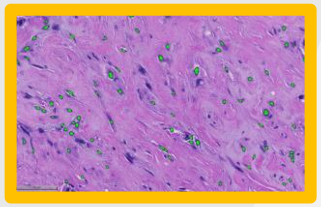
High-grade stromal inflammation (HGSI)



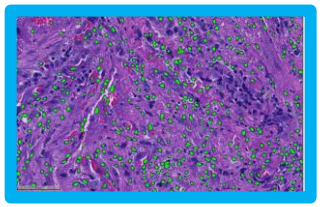


Results 3: Associations of parity-related factors with risk of inflammation-based breast cancer subtypes

- Among women >50 years
- By ER status



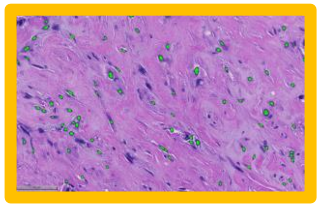
Low-grade stromal inflammation (LGSI)



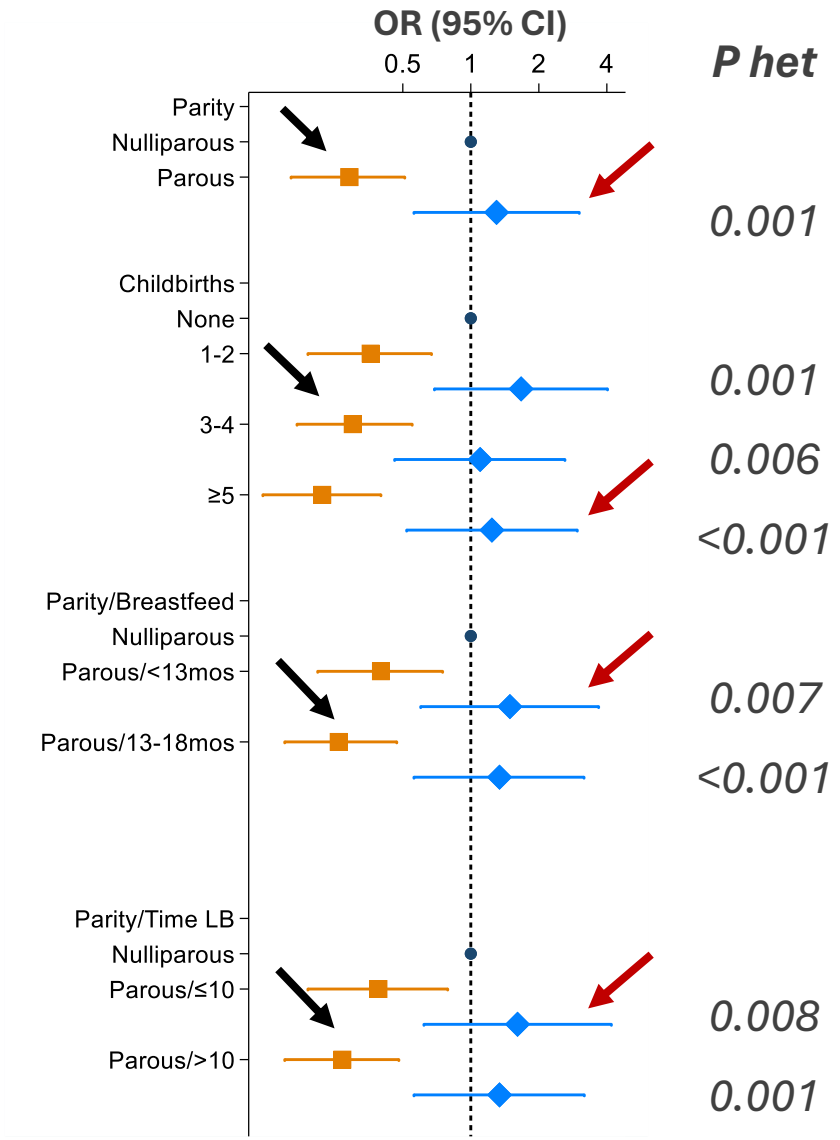
High-grade stromal inflammation (HGSI)

Parity-related factors and risk of inflammation-based subtypes among women >50 years of age

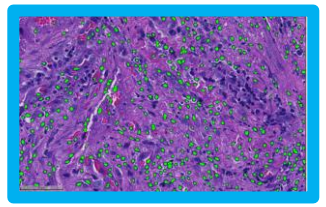
Reduced risk



Low-grade stromal inflammation (LGSI)

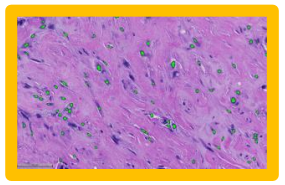


Increased risk

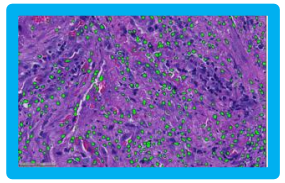


High-grade stromal inflammation (HGSI)

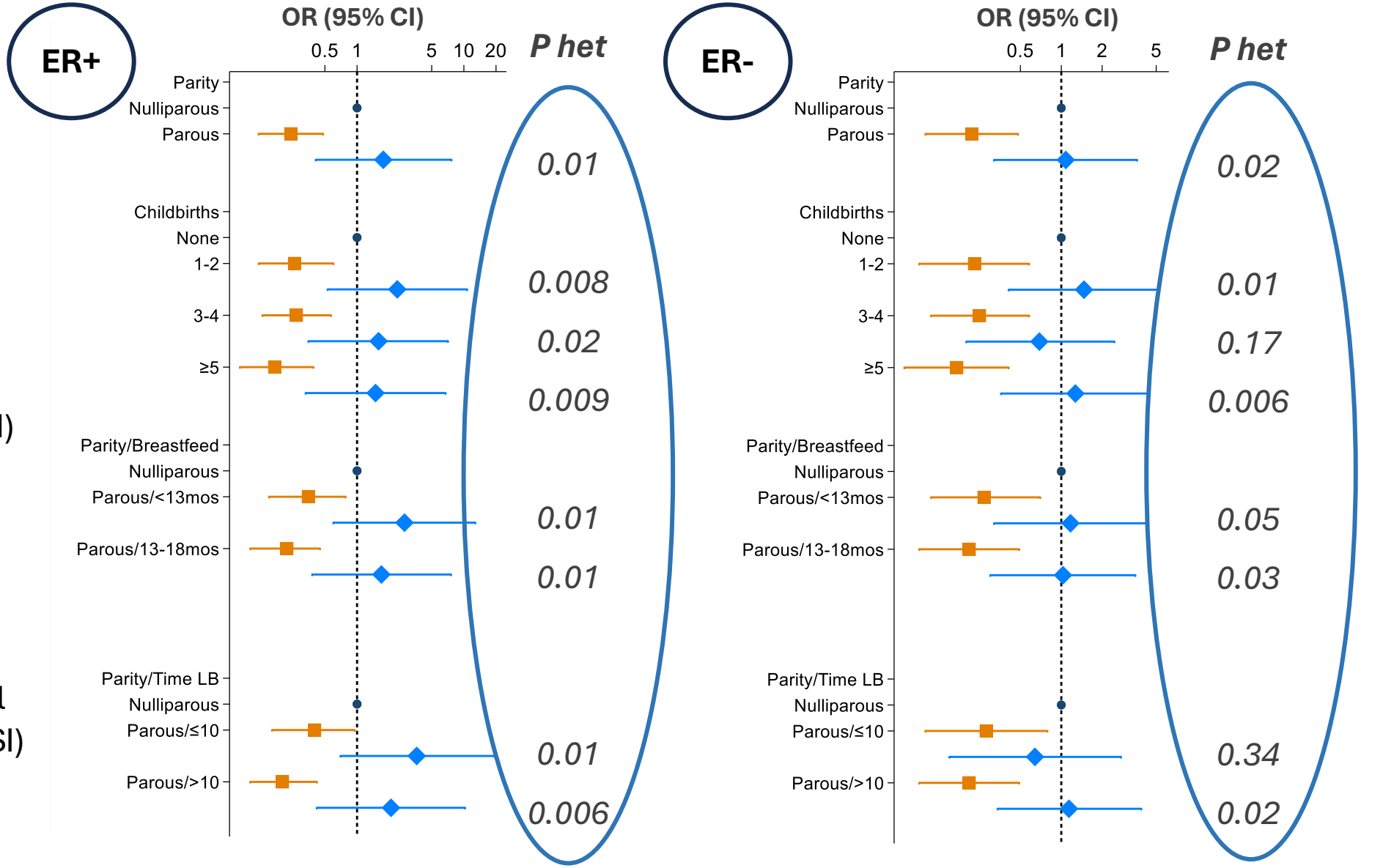
Etiologic heterogeneity of inflammation-based subtypes by parity status for late-onset tumors, irrespective of ER status



Low-grade stromal inflammation (LGSI)



High-grade stromal inflammation (HGSI)

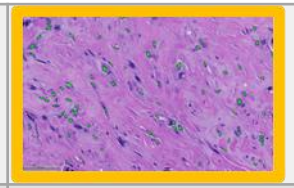
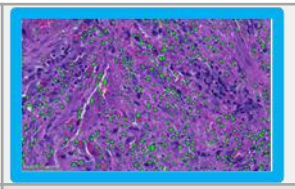


Summary

- The findings highlight the contribution of stromal inflammation to driving parity-related breast cancer etiologic heterogeneity

- Contrary to the sole focus on ER status with respect to parity-related breast cancer etiologic heterogeneity, the degree of stromal inflammation is additionally informative for understanding parity-related breast cancer risk

Conclusions: Implications for breast cancer precision-prevention among women in Sub-Saharan Africa

Strategy	 Low-grade Stromal Inflammation		 High-grade Stromal Inflammation	
	ER+	ER-	ER+	ER-
Antenatal education	✓	✓	✓	✓
Postpartum surveillance	✓	✓	✓	✓
Breastfeeding	✓	✓	—	—

SERMs: Selective estrogen receptor modulators

✓ Possible benefit — May not be beneficial

- Further studies are required to confirm findings

Acknowledgements

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Daniel Ansong

Baffour Awuah

Nicolas Titiloye

Joseph Oppong

Ernest Baawuah Osei-Bonsu

Peace and Love Hospital

Beatrice Addai Wiafe

Seth Wiafe

University of Ghana

Richard Britwum

Kofi Nyarko

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www.cancer.gov www.cancer.gov/espanol

Characterizing the Immune and Non-immune Landscape of Premalignant and Preinvasive Breast Lesions

Vagmi Luhar, B.S. 2025
Pre-Baccalaureate Research Fellow
Integrative Tumor Epidemiology Branch (ITEB)
Division of Cancer Epidemiology and Genetics (DCEG)

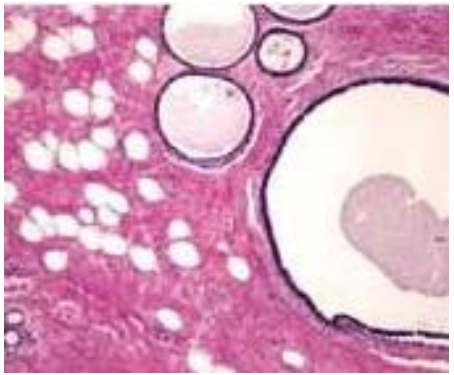
NIH NATIONAL CANCER INSTITUTE

Introduction

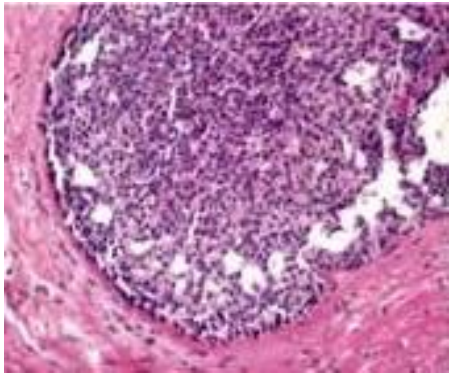
- The immune system plays a complex role in cancer development
- Cancer immunoediting hypothesis identifies these roles in three phases:
  - Elimination
  - Equilibrium
  - Escape

Schreiber, *et al. Science* 2011

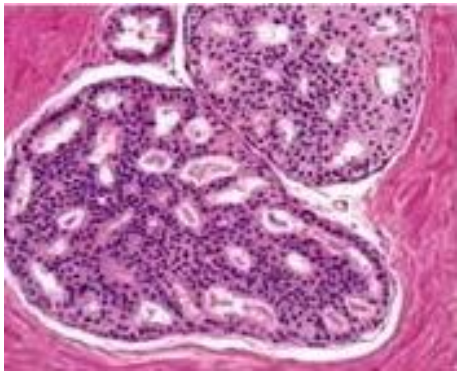
Immune System and Breast Carcinogenesis



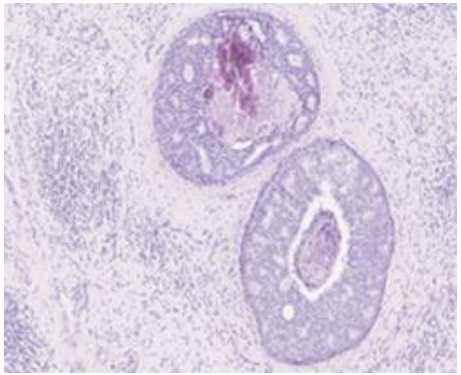
Non-Proliferative Disease (NPD)



Proliferative Disease without atypia (PDWA)



Atypical Hyperplasia (AH)



Ductal Carcinoma In Situ (DCIS)

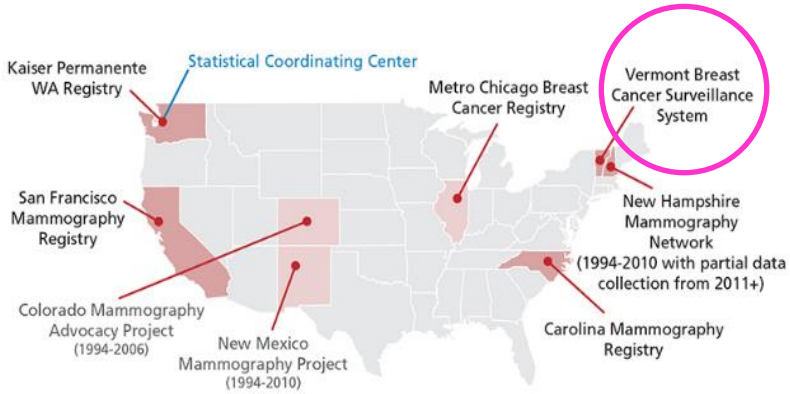
- Current understanding of progression of benign lesions is predicated on proliferative epithelial changes.
- The role of the immune and stromal landscape within these pre-invasive stages is not well known.

Lynn, C. H., et al. N. England J. M 2005

Hypothesis and Aims

- Immune landscape of premalignant and preinvasive tissues may reflect distinct pathways of breast cancer development.
- Mechanisms may reflect either primarily epithelial or primarily stromal changes.
- Aim:
  - Characterize the immune landscape of premalignant tissues which showcase disparate degrees of epithelial and stromal changes.

The Breast Radiology Evaluation And Study of Tissues (BREAST) Stamp Project



Breast Cancer Surveillance Consortium

Enroll Women referred to diagnostic image-guided breast biopsy due to abnormal mammogram (n=1,227)

Collect Risk factor data, biologic specimens (blood, buccal cells, breast tissues)

Stamp Act Fund

Consent for 10-year follow up: Registry linkage 2022

Gierach GL, et al. *Cancer Prev Res* 2015

Analytic Population / Demographics

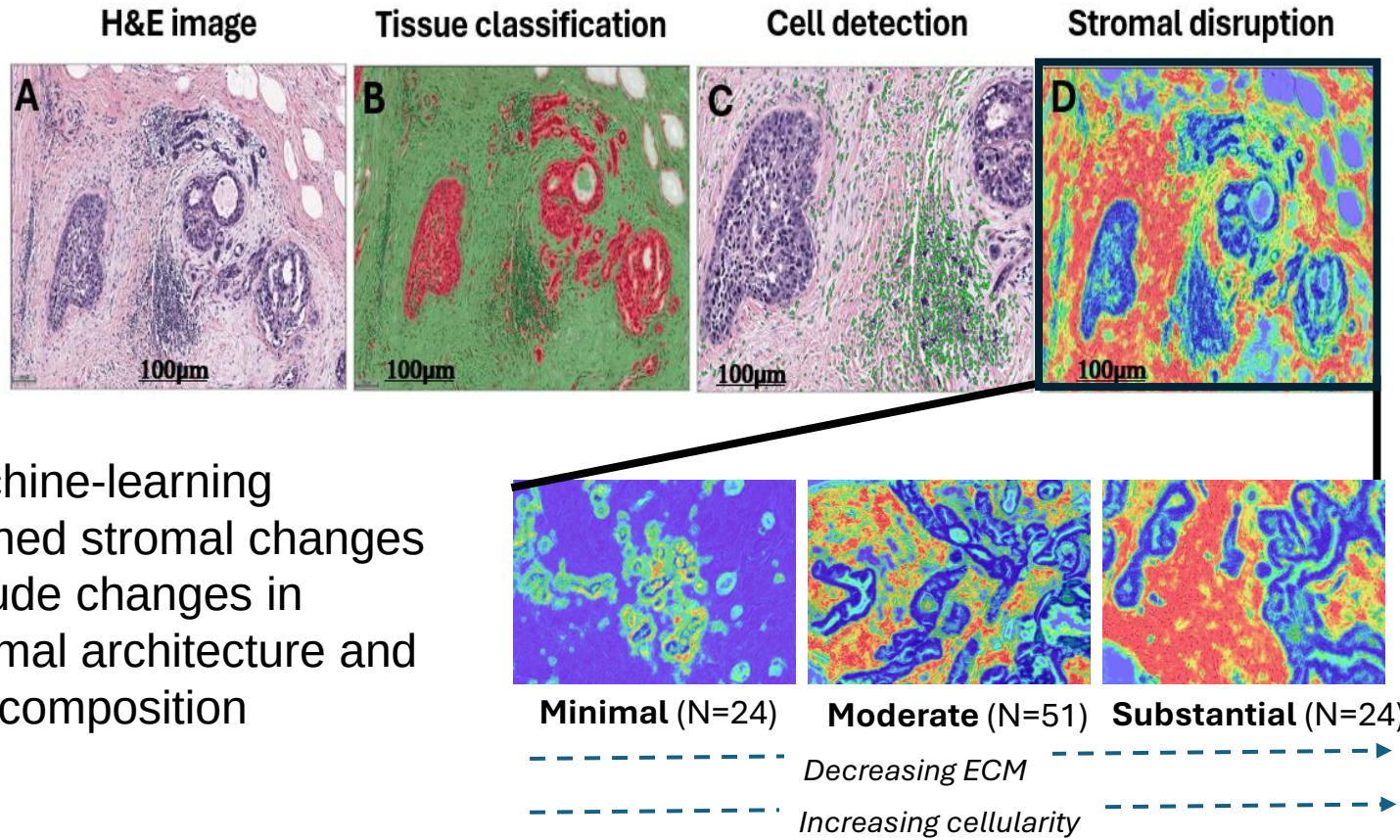
- We characterized breast biopsy tissues from 99 women participating in the BREAST Stamp Project

Age (years)	**Analytic Population** (N = 99)
Mean	50.80
Race	***N(%)***
White, non Hispanic	96 (97)
Other	3 (3)
BMI	
<= 25	68 (69)
> 25	31 (31)

Methodology: Classification of Epithelial Changes

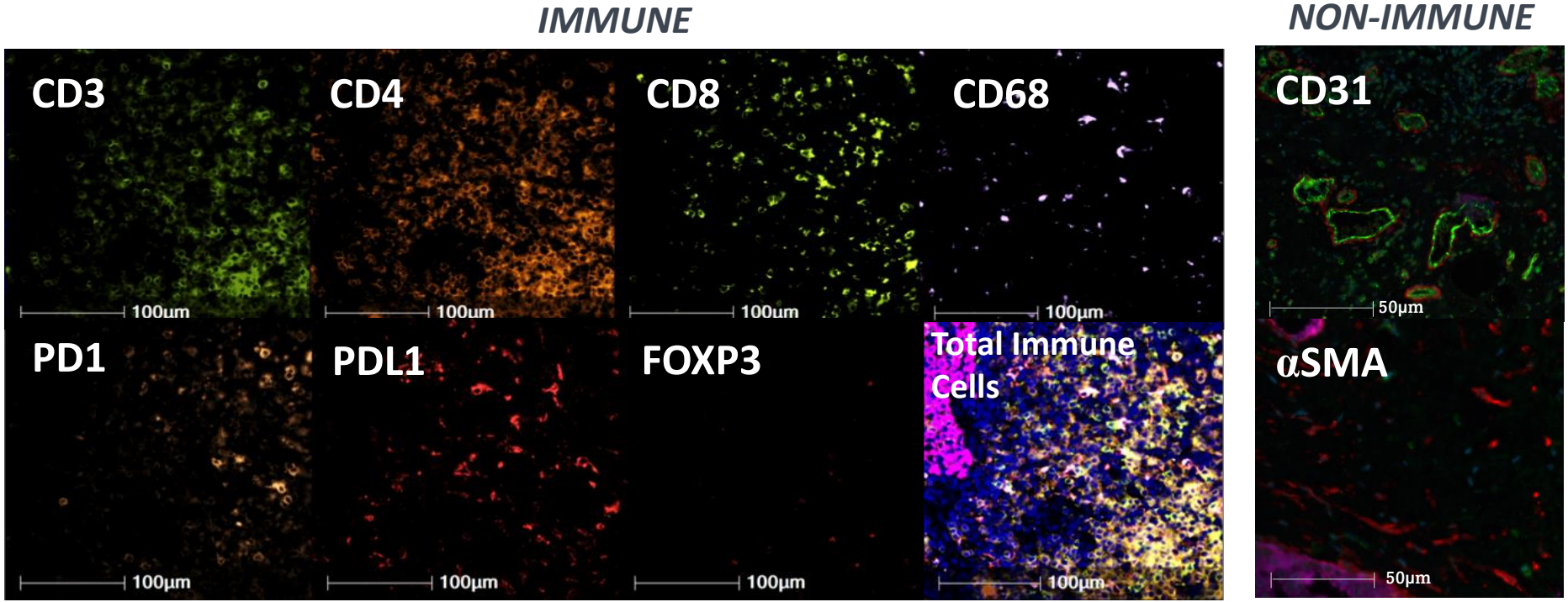
- Pathologists defined histologic subtypes of epithelial changes as follows:
  - Non-proliferative disease (NPD, N=24)
  - Proliferative disease without atypia (PDWA, N=25)
  - Atypical Hyperplasia (AH, N=26)
  - Ductal Carcinoma In Situ (DCIS, N=24)

Methodology: Machine-learning classification of stromal changes



- Machine-learning defined stromal changes include changes in stromal architecture and cell composition

Methodology: 10 plex immunofluorescence staining of biomarkers

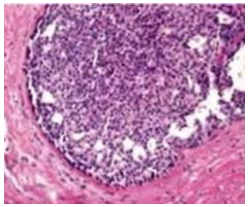


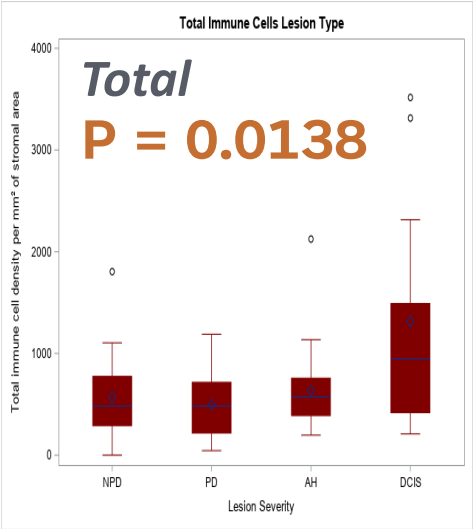
Results

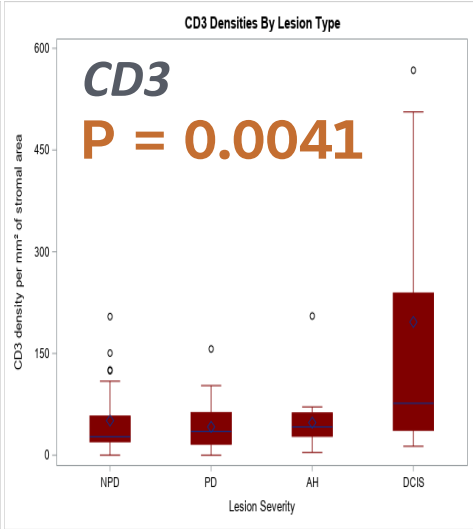
Epithelial Pathway

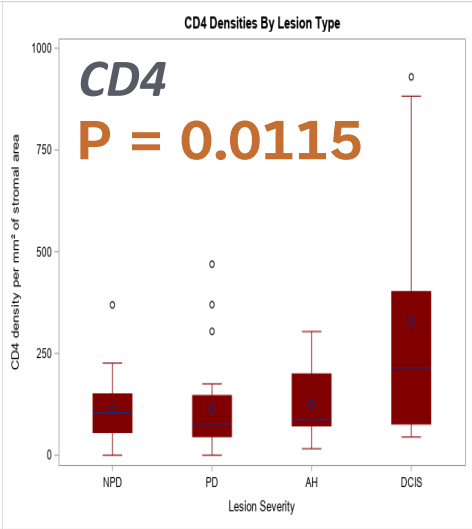
Biomarker densities by BBD lesion severity

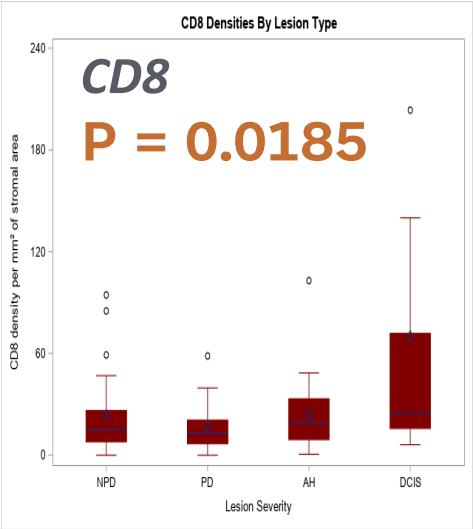
Varying biomarker densities observed by epithelial lesion severity for adaptive immune cell markers

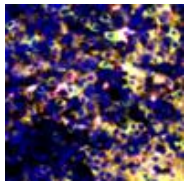


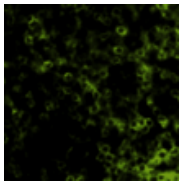


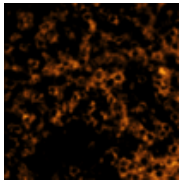


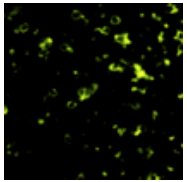




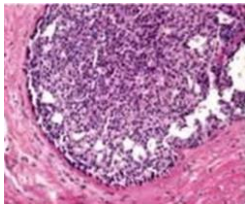




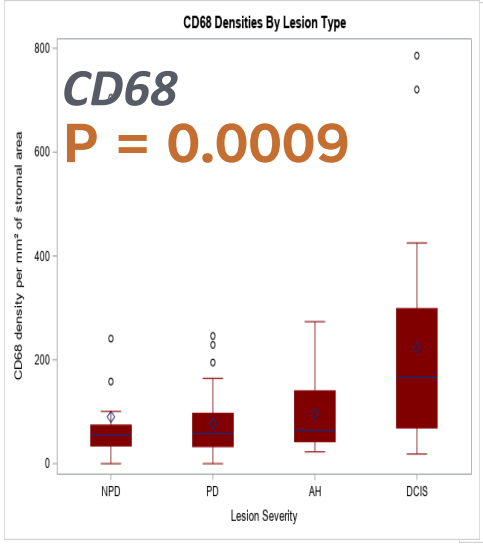




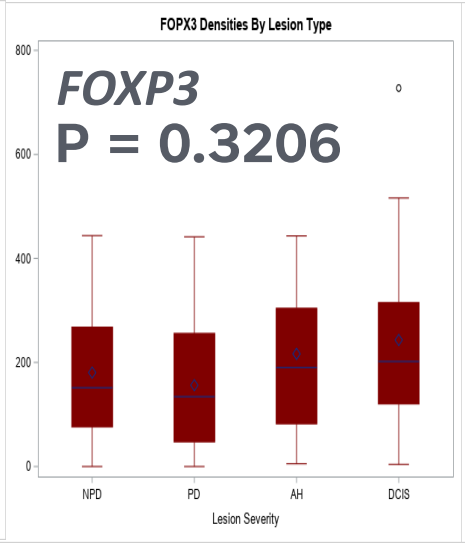
Variation in biomarker densities observed among epithelial lesions for CD68 and PDL1, but not PD1 and FOXP3



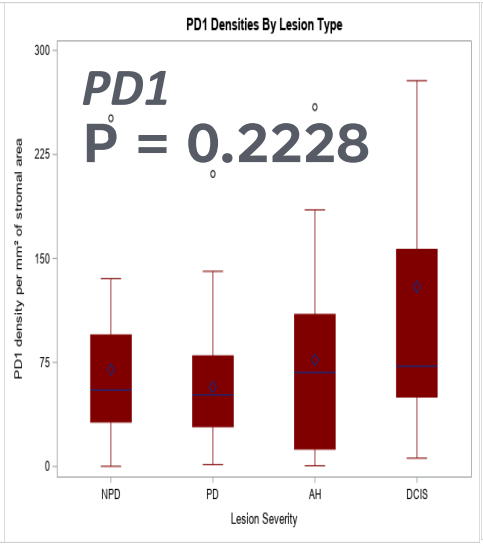
Innate

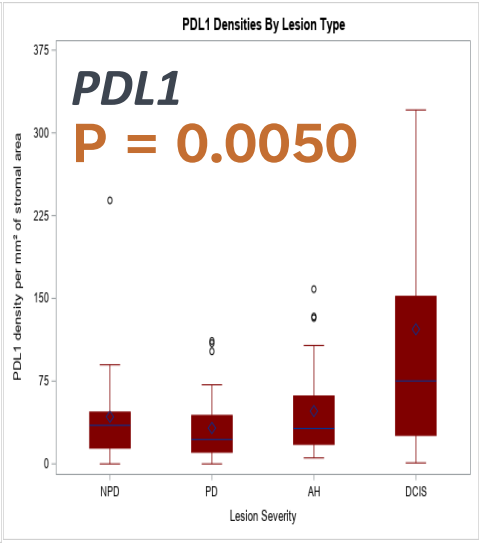


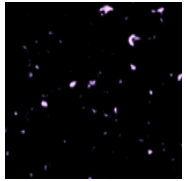
Immunoregulatory

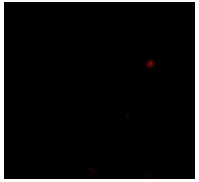


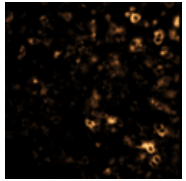
Immune Escape

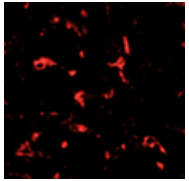




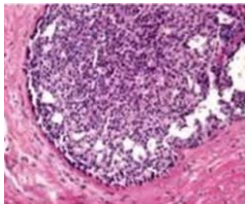


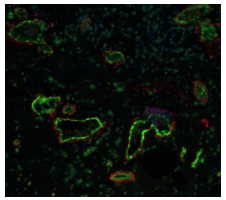


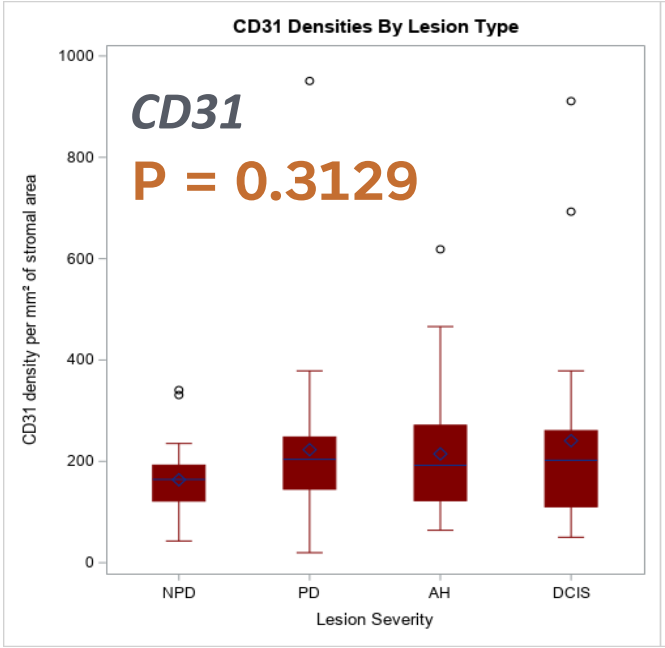


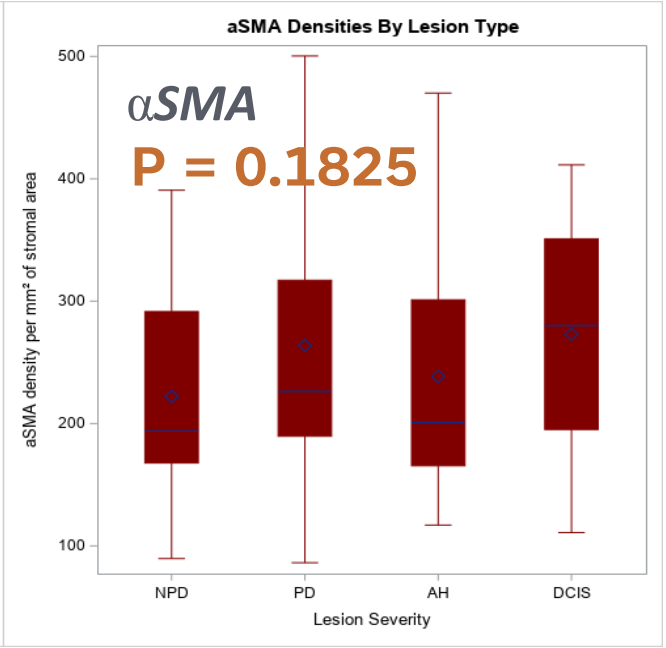


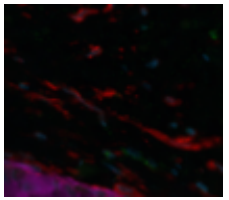
No clear patterns of biomarker densities by lesion severity for non-immune markers, CD31 and αSMA









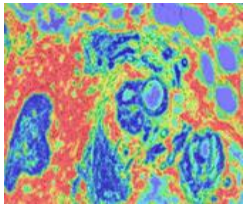


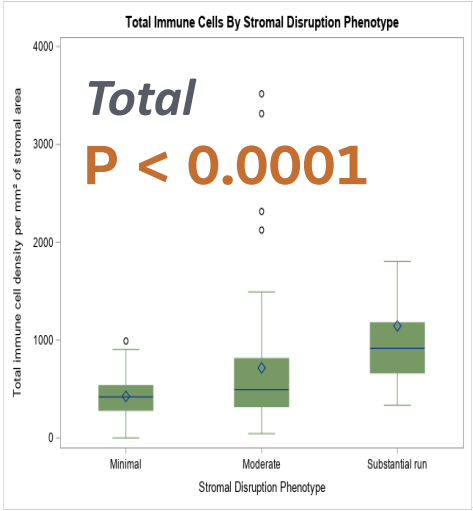
Results

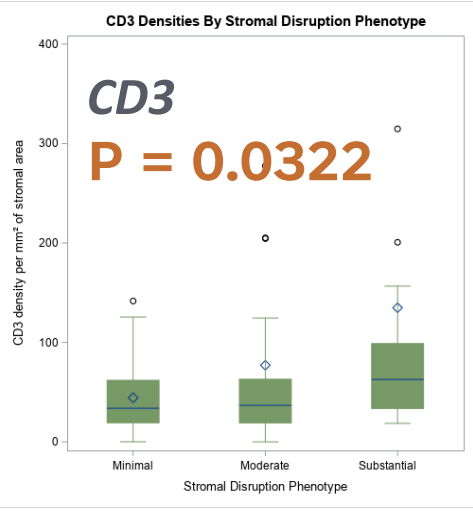
Stromal Pathway

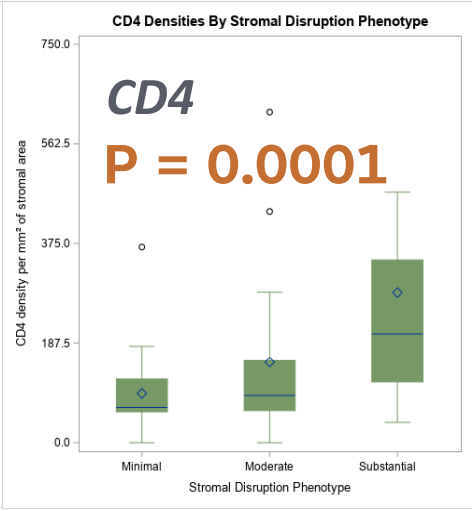
Biomarker densities by stromal disruption phenotypes

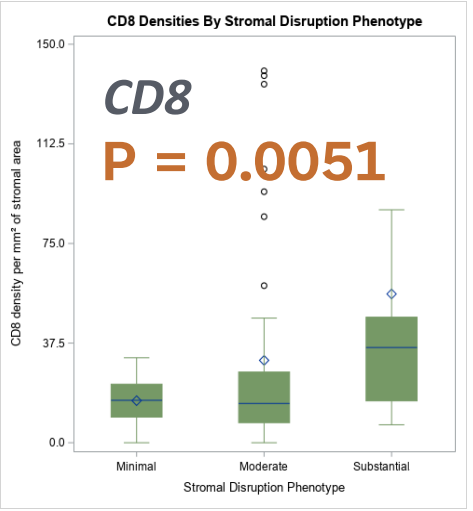
Significant differences observed in adaptive immune cell biomarker expression within stromal disruption phenotypes

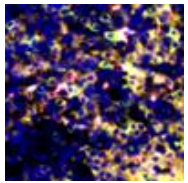


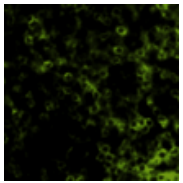


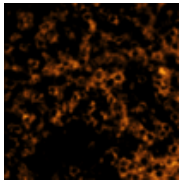


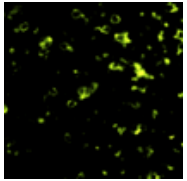




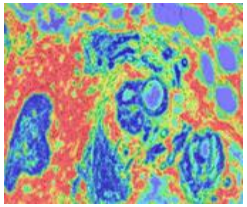




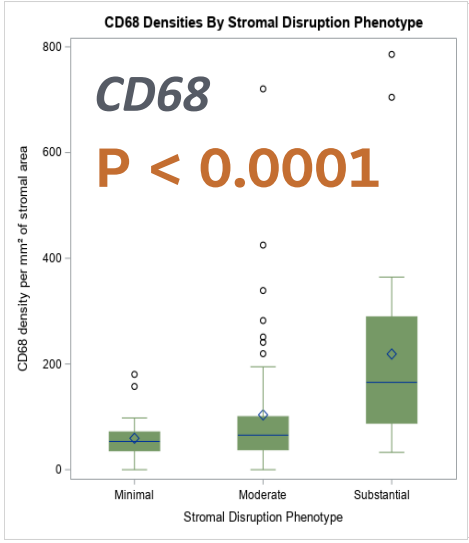




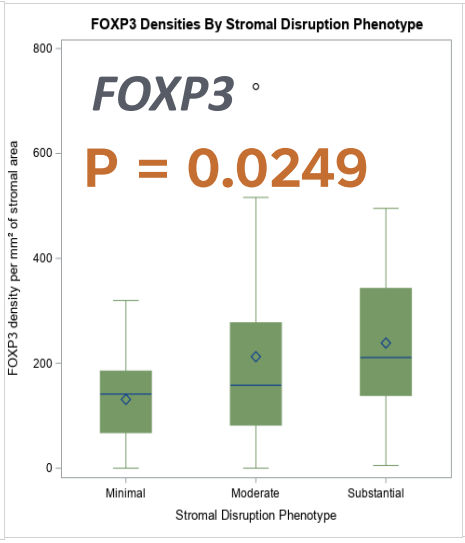
Significant differences observed in biomarker densities among stromal disruption phenotypes for innate immune markers CD68, FOXP3, and PDL1 but not for PD1



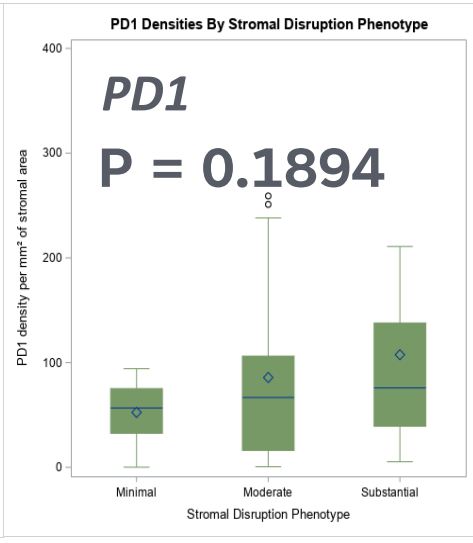
Innate

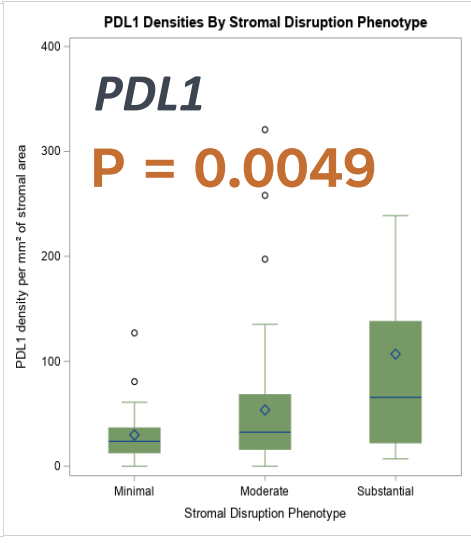


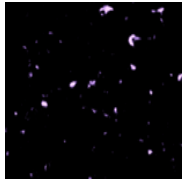
Immunoregulatory

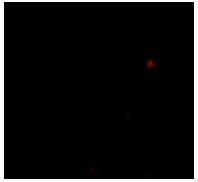


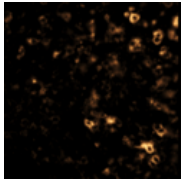
Immune Escape

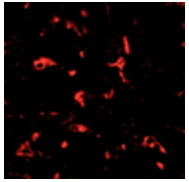




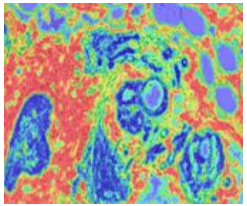


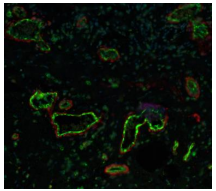


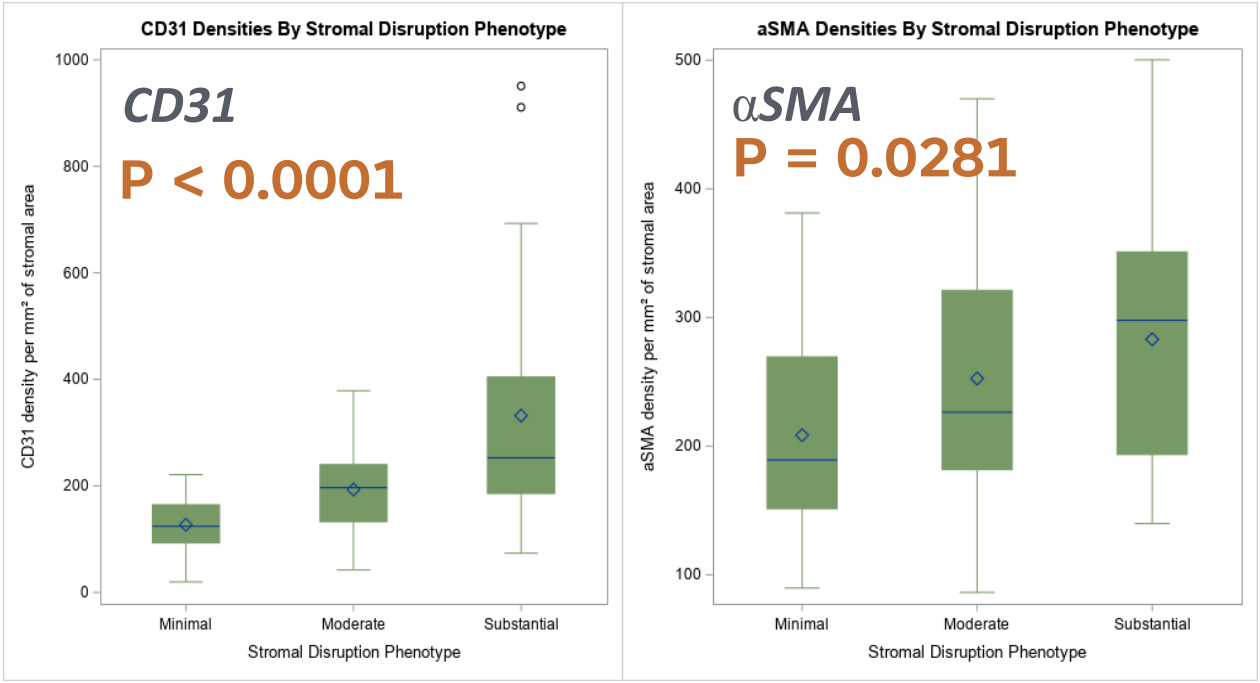


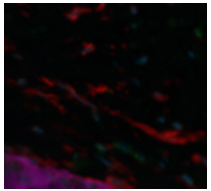


Significant differences observed in non-immune biomarker densities within stromal disruption phenotypes





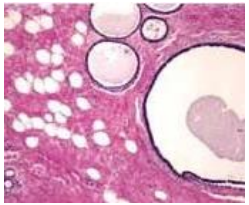




Results

1. *Epithelial pathway regression model*
2. *Stromal disruption regression model*

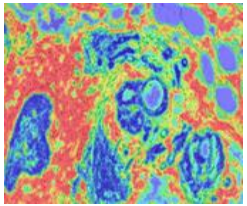
DCIS is associated with increased immune infiltration compared to NPD



	Epithelial lesion severity (predictors)						
	PDWA vs NPD		AH vs NPD		DCIS vs NPD		
	β (95% CI)	*P value*	β (95% CI)	*P value*	β (95% CI)	*P value*	*P trend*
Marker *(outcome)*							
CD3	-1.262 (-4.10, 1.58)	0.38	-0.224 (-2.98, 2.53)	0.87	4.728 (1.90, 7.56)	0.00	0.001
CD4	-2.190 (-5.32, 0.94)	0.17	0.031 (-3.01, 3.07)	0.98	5.160 (2.04, 8.28)	0.00	0.000
CD8	-1.121 (-2.85, 0.61)	0.20	-0.287 (-1.97, 1.40)	0.74	2.050 (0.33, 3.77)	0.02	0.004
CD68	-1.815 (-4.30, 0.67)	0.15	0.523 (-1.89, 2.94)	0.67	4.686 (2.21, 7.16)	0.00	<0.0001
PD1	-0.588 (-2.87, 1.70)	0.61	-0.411 (-2.63, 1.81)	0.71	1.776 (-0.50, 4.05)	0.13	0.051
PDL1	-1.65 (-3.82, 0.52)	0.13	-0.239 (-2.35, 1.87)	0.82	2.896 (0.734, 5.058)	0.01	0.001
FOXP3	-1.942 (-5.23, 1.35)	0.24	0.140 (-3.06, 3.34)	0.93	1.327 (-1.95, 4.61)	0.42	0.115
Total Immune Cells	-4.092 (-9.72, 1.53)	0.15	-0.084 (-5.55, 5.38)	0.98	8.418 (2.81, 14.02)	0.00	0.000
CD31	0.408 (-1.96, 2.78)	0.73	0.683 (-1.62, 2.98)	0.56	0.868 (1.49, 3.23)	0.47	0.113
αSMA	0.750 (-1.06, 2.56)	0.41	0.232 (-1.53, 1.99)	0.79	1.375 (-0.43, 3.18)	0.13	0.104

* Adjusted for age, BMI, and biopsy type

Increasing stromal disruption is associated with increasing immune infiltration for all markers



	Stromal disruption (predictors)				
	Moderate vs Minimal		Substantial vs Minimal		
	β (95% CI)	*P value*	β (95% CI)	*P value*	*P trend*
Marker *(outcome)*					
CD3	1.630 (-0.80, 4.06)	0.19	3.218 (0.37, 6.07)	0.03	0.03
CD4	2.292 (-0.39, 4.97)	0.09	5.706 (2.56, 8.85)	0.00	0.00
CD8	1.224 (-0.26, 2.70)	0.10	2.672 (0.93, 4.41)	0.00	0.00
CD68	2.307 (0.18, 4.43)	0.03	5.930 (3.44, 8.42)	<0.0001	<0.0001
PD1	1.842 (-0.11, 3.80)	0.06	3.331 (1.04, 5.63)	0.00	0.00
PDL1	1.862 (0.01, 3.72)	0.05	4.124 (1.95, 6.30)	0.00	0.00
FOXP3	3.212 (0.40, 6.02)	0.03	4.90 (1.59, 8.20)	0.00	0.00
Total Immune Cells	6.05 (1.24, 10.86)	0.01	12.21 (6.56, 17.85)	<0.0001	<0.0001
CD31	2.428 (0.40, 4.45)	0.02	6.033 (3.66, 8.41)	<0.0001	<0.0001
αSMA	1.417 (-0.13, 2.97)	0.07	2.106 (0.28, 3.93)	0.02	0.02

* Adjusted for age, BMI, biopsy type, and lesion severity

Conclusion / Implications

- Results suggest that diverse immune and non-immune related mechanisms ‘might’ be operative in premalignant/preinvasive tissues
- The degree of epithelial and stromal changes on premalignant breast biopsies did correlate with disparate immune and non-immune cell infiltration phenotypes.
- If confirmed, the findings could have implications for the way we approach breast cancer prevention strategies
- Further, larger longitudinal studies are required to understand how these distinct (epithelial or stromal) immune mechanisms may have potentially different implications for BC risk and tumor biology.

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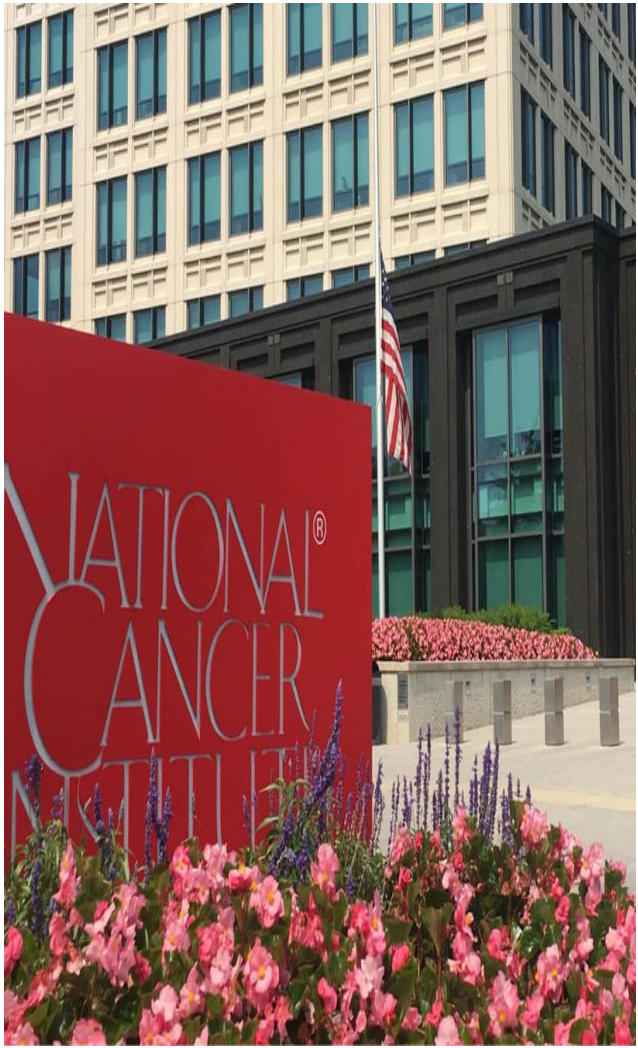

Thank You

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Risk Assessment for Digital Breast Tomosynthesis to Identify Women Who Need Additional Care

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Department of Public Health and Primary Care, University of Cambridge
November 2, 2024, RiseUp

Disclosures

Patent on "system and method for assesing breast cancer risk using imagery" with a licence to iCAD medical, Nashua, NH, U.S.

Patent on "compositions and methods for monitoring the treatment of breast disorders" with a licence to Atossa Therapeutics, Seattle, WA, U.S.

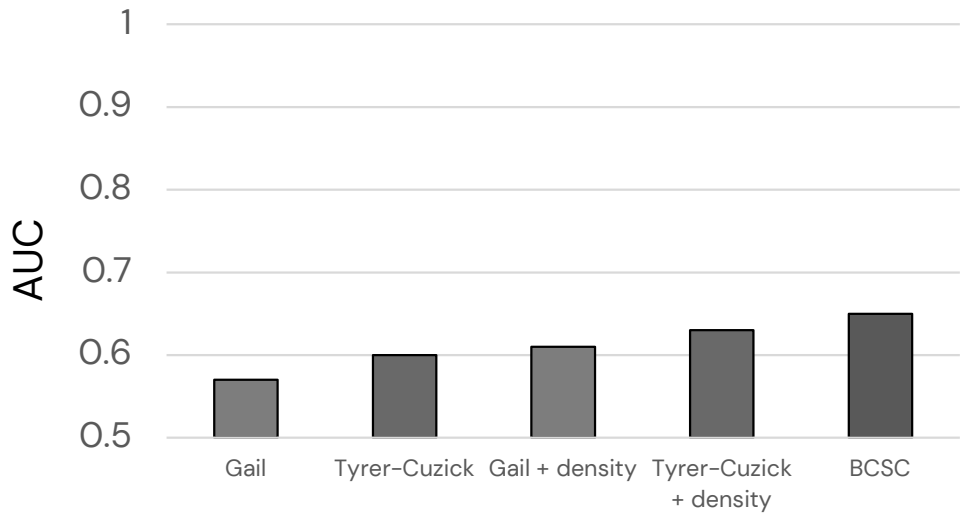
Several clinical uses of breast cancer risk assessment

- Identify women who could benefit from additional care to improve screening outcomes
  - Identify women at high risk in the short-term. 1-5-year risk assessment
  - Women diagnosed with a more aggressive tumor (e.g. symptomatic cancer, late-stage cancer)
  - Women may benefit from supplemental screening after being identified in an actionable time-window

- Identify women who could benefit from risk reducing intervention to prevent breast cancer
- Identify women who do not benefit from regularly attending breast cancer screening

Clinically available risk models and reported discriminatory performances

Women at general risk of breast cancer in a Swedish screening population (5-year risk)

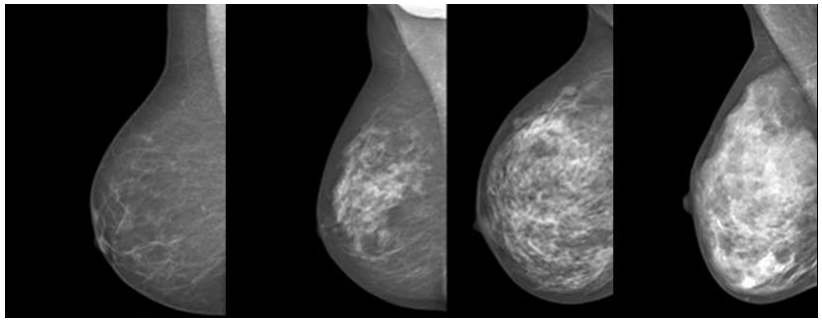


Could image data be used for risk assessment?

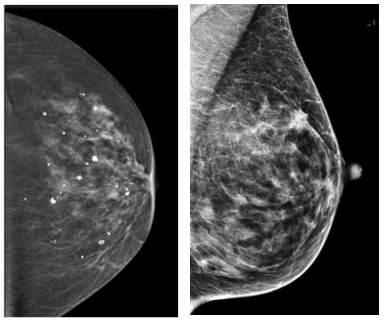
- Mammographic density is a well-known risk factor that has been studied over several decades
- Mammographic density has been added to risk models such as Gail, Tyrer-Cuzick, BCSC, and CanRisk (BOADICEA)
- More mammographic features beyond density could also be associated with risk of breast cancer
- By combining multiple mammographic features, an image-based risk model could be created
- Replication of predictive performance of a model across different population can assure the clinical value of the model
- For short-term risk models, a recent systematic review showed that 20 image-derived AI risk models now have been developed and evaluated (Hussain et al, 2024)

Risk models have been developed using mammographic features that includes density and features beyond density

Mammographic density, left-right breast asymmetry, age

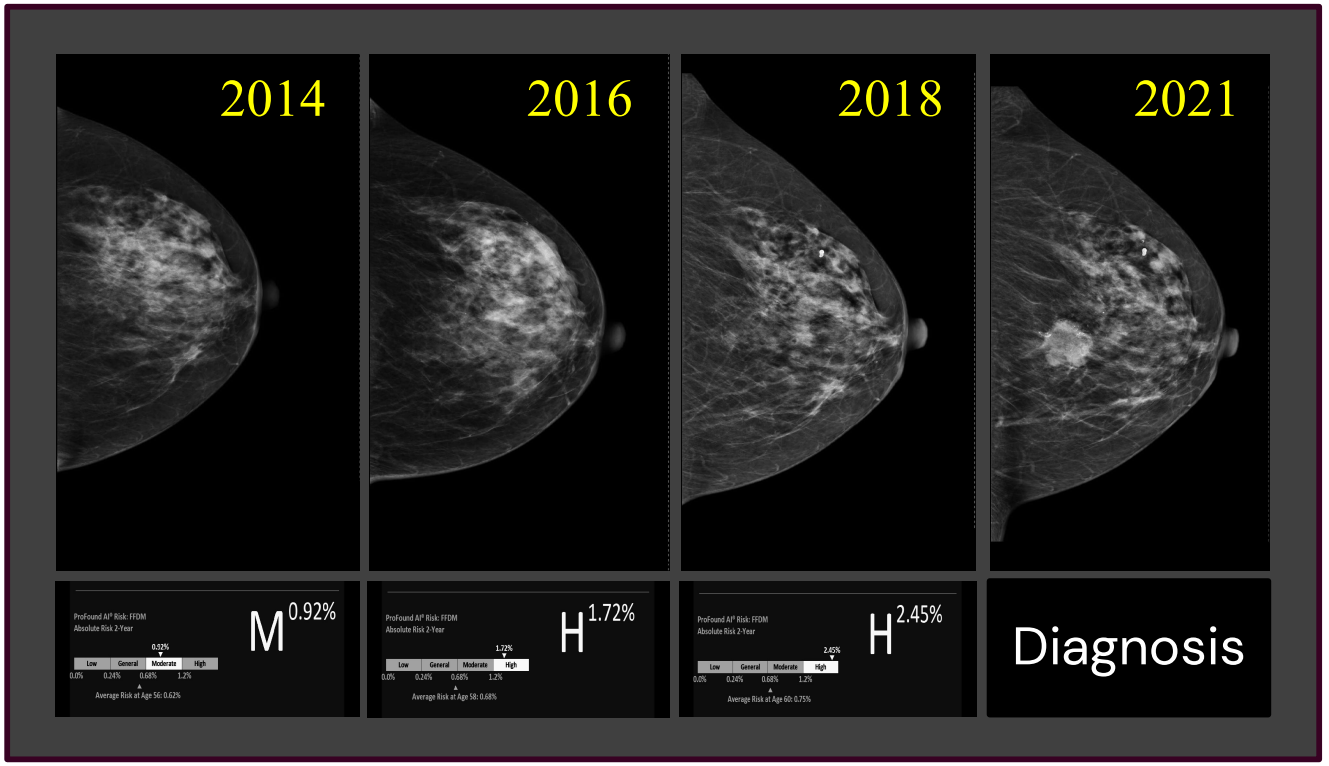


Calcifications / masses,
left-right breast asymmetry



OPTIONAL: BMI, menopausal status, family history of breast cancer, hormone replacement therapy, alcohol, tobacco, polygenic risk score (313 SNPs)

Use of short-term risk assessment in the clinic



63-year old woman diagnosed in 2021

Courtesy Axel Gräwingholt, radiologist, Germany

A risk model for DBT for use in screening in the U.S.

- Approximately 80% of screening units in the U.S. use digital breast tomosynthesis (DBT)

- *We developed and evaluated an image-based risk model for DBT that assesses the short-term risk of breast cancer*

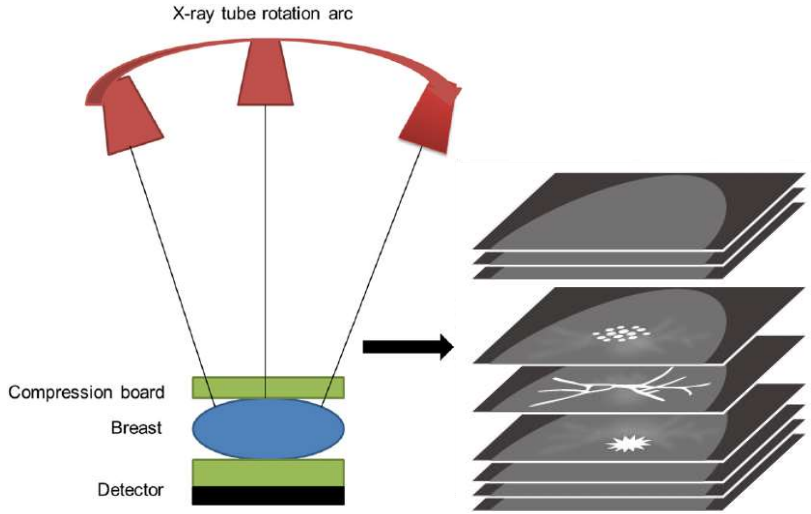
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

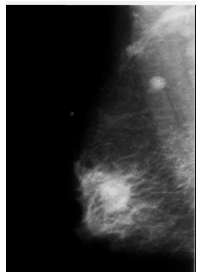
A risk model for digital breast tomosynthesis to predict breast cancer and guide clinical care

Mikael Eriksson[1]*, Stamatia Destounis[2], Kamila Czene[1], Andrew Zeiberg[3], Robert Day[4], Emily F. Conant[5], Kathy Schilling[6], Per Hall[1,7]

Digital Breast Tomosynthesis generates an image stack of 200-300 images in millimeter-thick slices of the breast

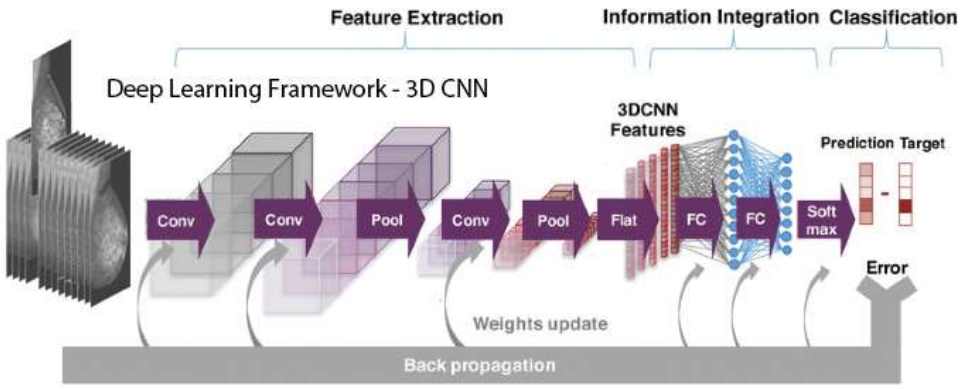


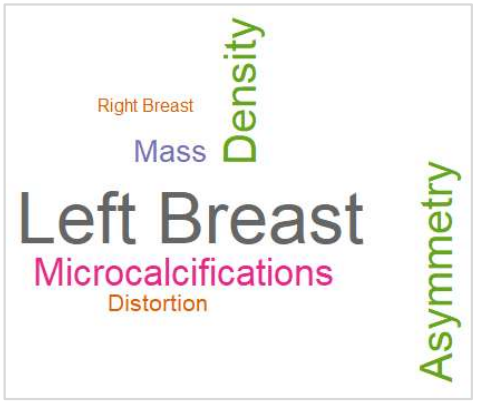
In comparison, digital mammography only 4 images



AI extracts image features from negative mammograms

A deep learning algorithm based on the convolutional neural networks. Transfer learning techniques and regularization is also used during model training.





The DBT AI risk model was developed in the U.S. screening setting

In total, 154,200 women were screened from 2014-2019 at the four U.S. screening sites using DBT. We performed a nested case-control study including:

Characteristic	Healthy, n = 5,173	Cases, n = 805
Age at mammography	57.88 (9.93)	61.11 (9.12)
Age >50 (postmenopausal)	3,809 / 5,173 (74%)	672 / 805 (83%)
Age at breast cancer diagnosis	-	61.93 (8.86)
Screen detected cancers	-	677 / 805 (84%)
Site		
Boca Raton	523 / 5,173 (10%)	81 / 805 (10%)
Elizabeth Wende Breast Care	452 / 5,173 (8.7%)	420 / 805 (52%)
Larchmont	1,153 / 5,173 (22%)	227 / 805 (28%)
Zwanger-Pesiri	3,045 / 5,173 (59%)	77 / 805 (9.6%)

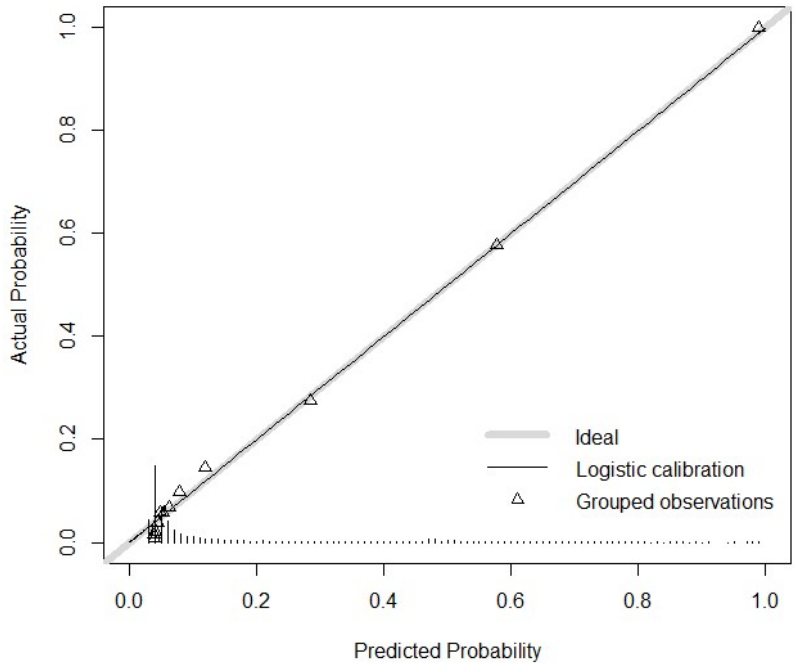
Methods – Absolute risk model and final risk evaluation

- An absolute risk model was developed based on the extracted AI mammographic features, age, breast cancer incidence rates, and competing mortality rates
- Risk model validation was performed in a separate test set
- Discriminatory performance to assess the ability separate future cases from controls
- Model calibration to assess the ability to corresponding number of events as was observed in the cohort
- Risk classification using clinical guidelines to identify women who could be offered supplemental screening

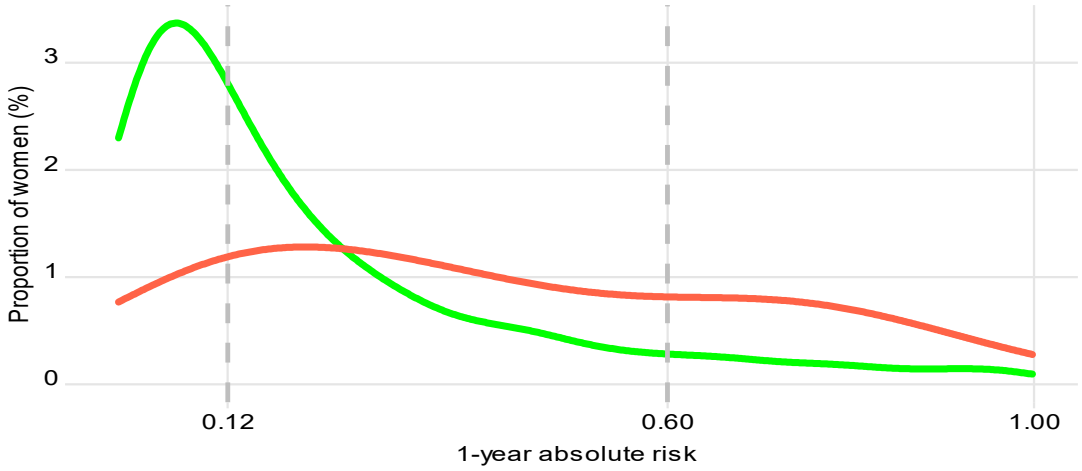
Results on discriminatory performance of DBT AI risk

Subgroups of women by DBT vendor	All women		Premenopausal (age≤50)		Postmenopausal (age>50)	
Validation set (n=1,792)	AUC	95% CI	AUC	95% CI	AUC	95% CI
Vendors combined	0.82	0.79 - 0.85	0.88	0.83 - 0.92	0.80	0.77 - 0.84
Hologic	0.88	0.85 - 0.91	0.93	0.89 - 0.96	0.86	0.82 - 0.89
Siemens	0.76	0.69 - 0.82	0.77	0.64 - 0.88	0.74	0.66 - 0.81
GE	0.77	0.66 - 0.86	0.70	0.42 - 0.92	0.78	0.66 - 0.88

Model calibration of DBT AI risk – a comparison between predicted risks and observed proportions of breast cancers



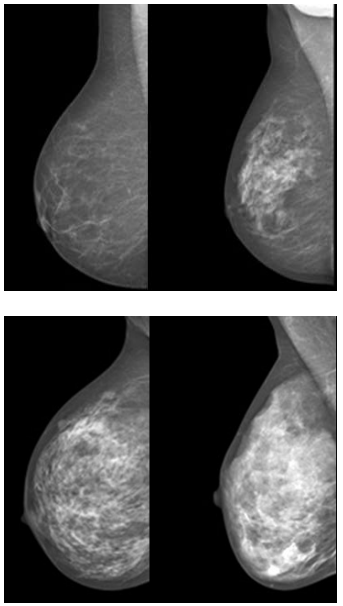
Risk classification of women into five categories from low to very high risk of breast cancer in 1 year using USPSTF guidelines



Risk group (risk-cutoff)	Women at risk, %	Absolute 1-year risk, %	Risk ratio
Low (<0.12)	45	0.05	1.0 (ref.)
General (0.12-<0.34)	31	0.20	3.9
Moderate (0.34-<0.6)	11	0.45	8.7
High (0.6-<1.2)	8.6	0.84	16.2
Very high (≥1.2)	5.4	1.30	25.1

Interestingly, similar risk stratification performances were seen for women with dense and non-dense breasts

USPSTF risk group (risk-cutoff)	Women at risk, %	Absolute 1-year risk, %	Risk ratio
Low mammographic density			
Low (<0.12)	46	0.05	1.0 (ref.)
General (0.12-<0.34)	30	0.20	3.9
Moderate (0.34-<0.6)	10	0.46	8.8
High (0.6-<1.2)	9.9	0.85	16.3
Very high (≥1.2)	4.3	1.29	24.8
High mammographic density			
Low (<0.12)	43	0.05	1.0 (ref.)
General (0.12-<0.34)	32	0.21	4.0
Moderate (0.34-<0.6)	11	0.45	8.7
High (0.6-<1.2)	7.3	0.83	16.0
Very high (≥1.2)	6.5	1.31	25.3



DBT AI risk stratification results for overall breast cancer and by breast cancer subtypes

Women at risk, %	Cancers combined % (95% CI)	Invasiveness % (95% CI)		Stage % (95% CI)		
		In-situ	Invasive	0	I	II or later
USPSTF risk categories (cumulative %)						
Very high (5.4)	36 (33-39)	33 (27-40)	37 (33-41)	33 (27-40)	35 (31-39)	53 (41-64)
High (14)	59 (56-62)	59 (52-65)	59 (55-63)	59 (52-65)	58 (53-62)	76 (65-85)
Moderate (25)	73 (70-76)	74 (67-80)	73 (69-76)	74 (67-80)	72 (68-75)	88 (78-94)
General (56)	89 (87-91)	90 (84-93)	89 (86-91)	90 (84-93)	89 (86-91)	97 (90-99)
Low (100)	100	100	100	100	100	100

Conclusion

- The 1-year DBT AI risk model had a good ability to identify women at high risk of breast cancer in screening
  - AUC=0.82 with good calibration
  - After one year, 58% of stage 1 and 76% of the stage II+ cancers were diagnosed in the 14% of women at high-risk at baseline (high-risk defined using USPSTF guidelines).
  - Similar risk stratification performances were observed in women with mammographic dense and non-dense tissue.
  - In addition, 45% of the women had low risk of breast cancer (4 times lower than general risk)
- DBT AI risk has the potential to inform clinical decision on women at high risk of breast cancer who may need follow-up after a negative screening exam

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MAMMOGRAPHY
risk assessment


KAROLINSKA INSTITUTET
ANNO 1810
Karolinska
Institutet

RISE UP for BC Session 4

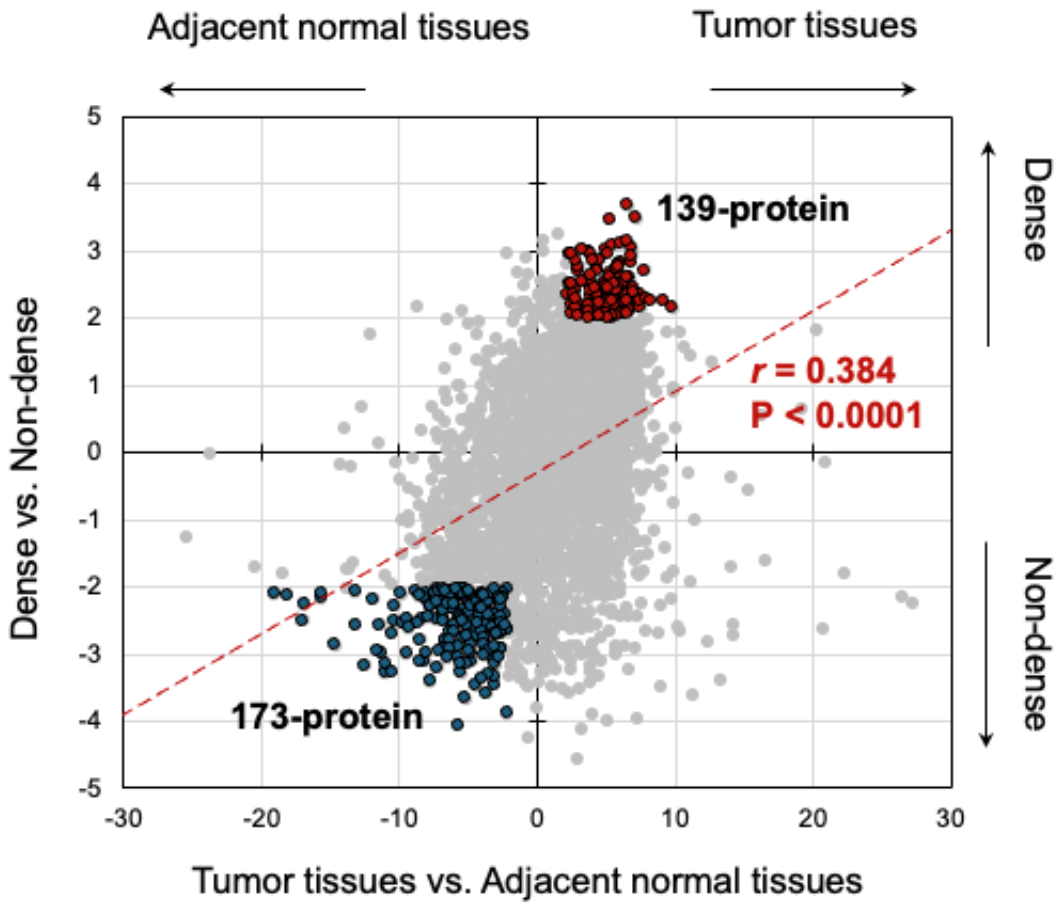
Risk Prediction and Biomarkers for Prevention Trials

‘Omics’ Approaches to Identify Pathways for Prevention

- Adetunji T. Toriola: Identifying New Targetable Pathways for Breast Cancer Prevention in Premenopausal Women

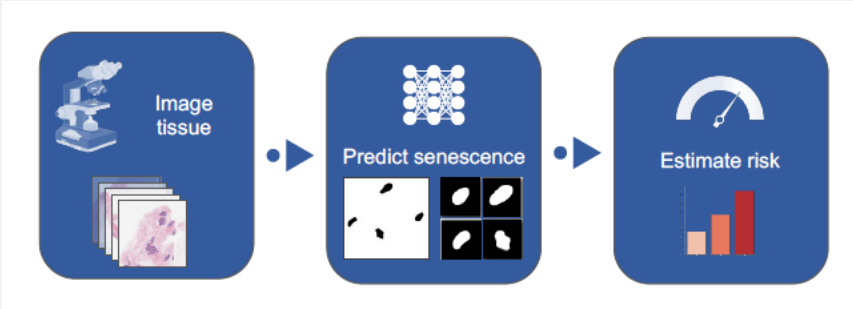
Common pathways linking early life adiposity, dense breast tissue and breast cancer tissue

Goal: cheap, effective, and specific drugs that can be used for prevention

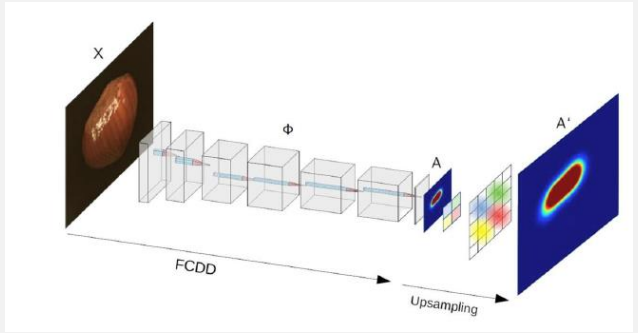


AI image analysis for BC risk prediction

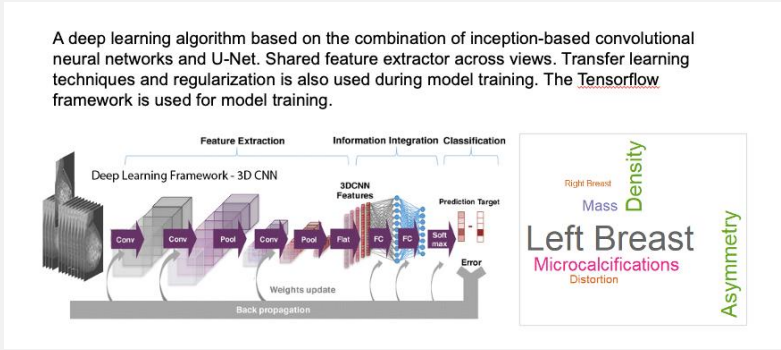
- Mark Powell: Senescence-Based Deep Learning Predicts Breast Cancer Risk Using H&E Core Biopsy Images From Healthy Women.



- Suleeporn (Yui) Sujichantararat: Predicting Risk of Future Breast Cancer Based on Screening MRI Features.

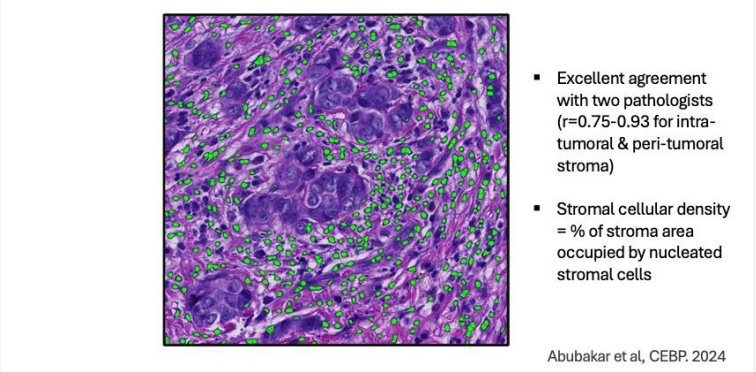


- Mikael Eriksson: Using Digital Breast Thomosynthesis Images for Short Term (1-5 year) Risk Prediction.

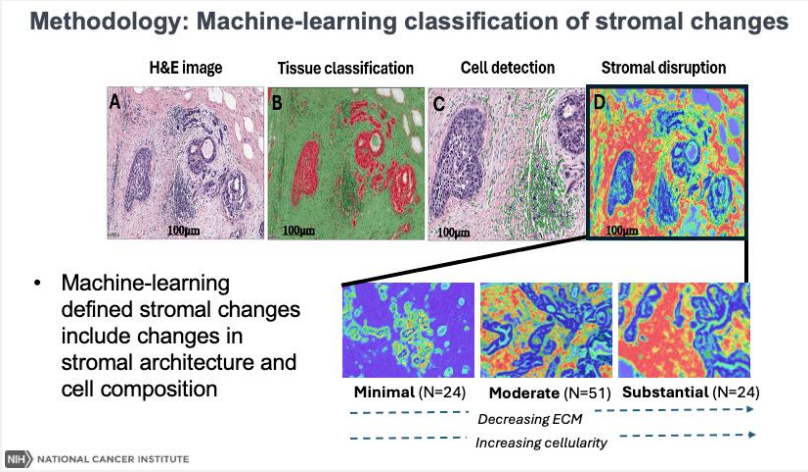


AI Imaging Analysis for Understanding Pre-Malignant Tissue and Immune Features Associated with BC Risk

- Mustapha Abubakar: Stromal Inflammation (AI on H&E images) as a Driver of Parity-related Breast Cancer Etiologic Heterogeneity



- Vagmi Luhar: Correlation between epithelial and stromal changes (AI-on H&E images) in premalignant tissue and immune and non-immune cell infiltration phenotypes



The New Era of Risk Prediction

- Traditional risk factor-based models provide relatively limited prediction.
- Polygenic risk scores are improving but AUC is still <0.7.
- AI is transforming how we solve classification problems: AI image interpretation models are hitting AUC >0.8.
- Potential for combining PRS with AI-image based and EHR data for risk prediction.

Important Considerations

- AI has larger amounts of data from NHW individuals. This can affect accuracy of prediction in other groups.
- Think about the implementation of AI based risk prediction based on image data, EHR and PRS in low resource settings (US and abroad) where this type of data is limited or patchy.
- Patients' acceptance of the use of AI for their care decision making.