Parity, Breast Cancer & Postpartum Breast Cancer

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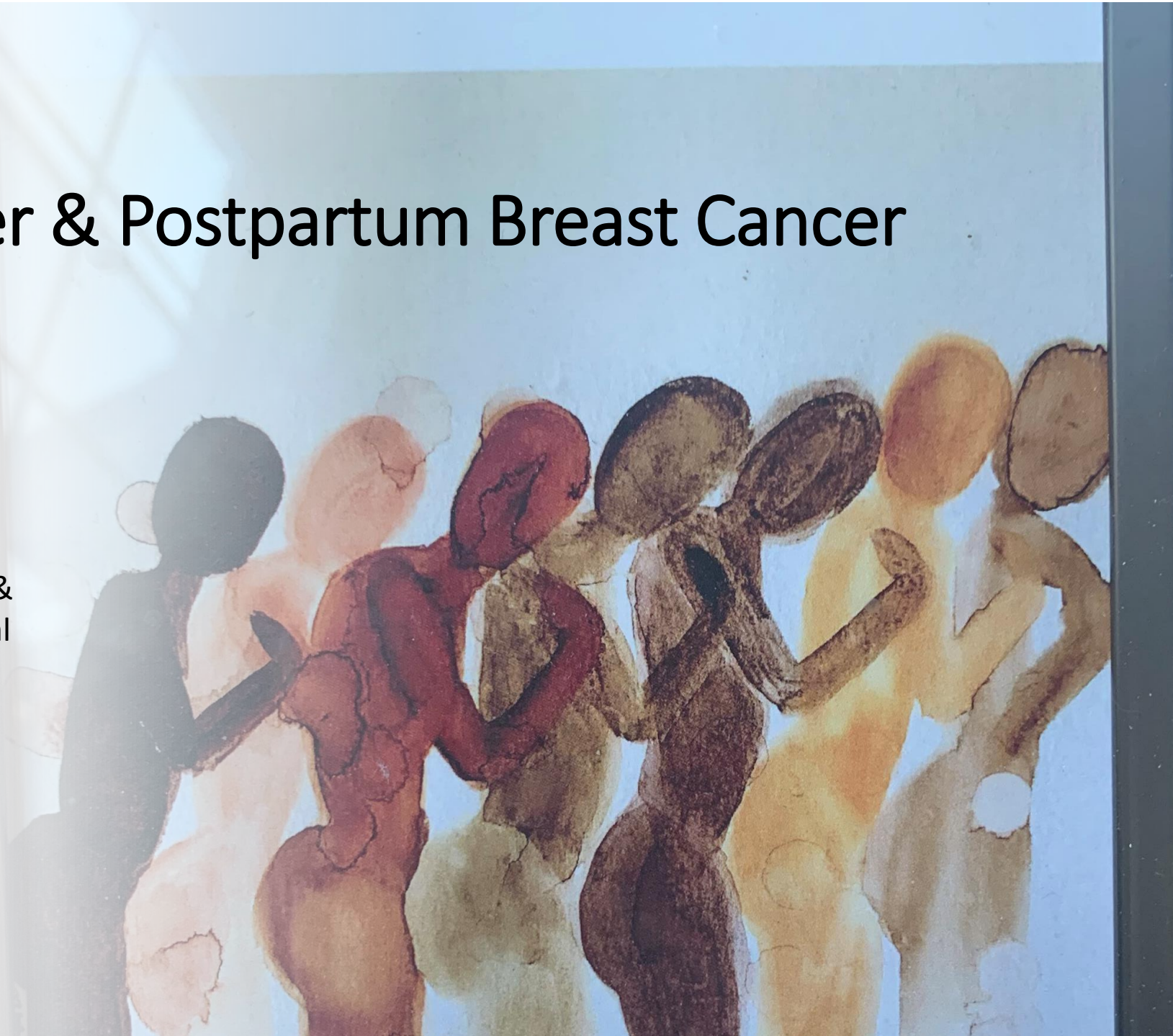
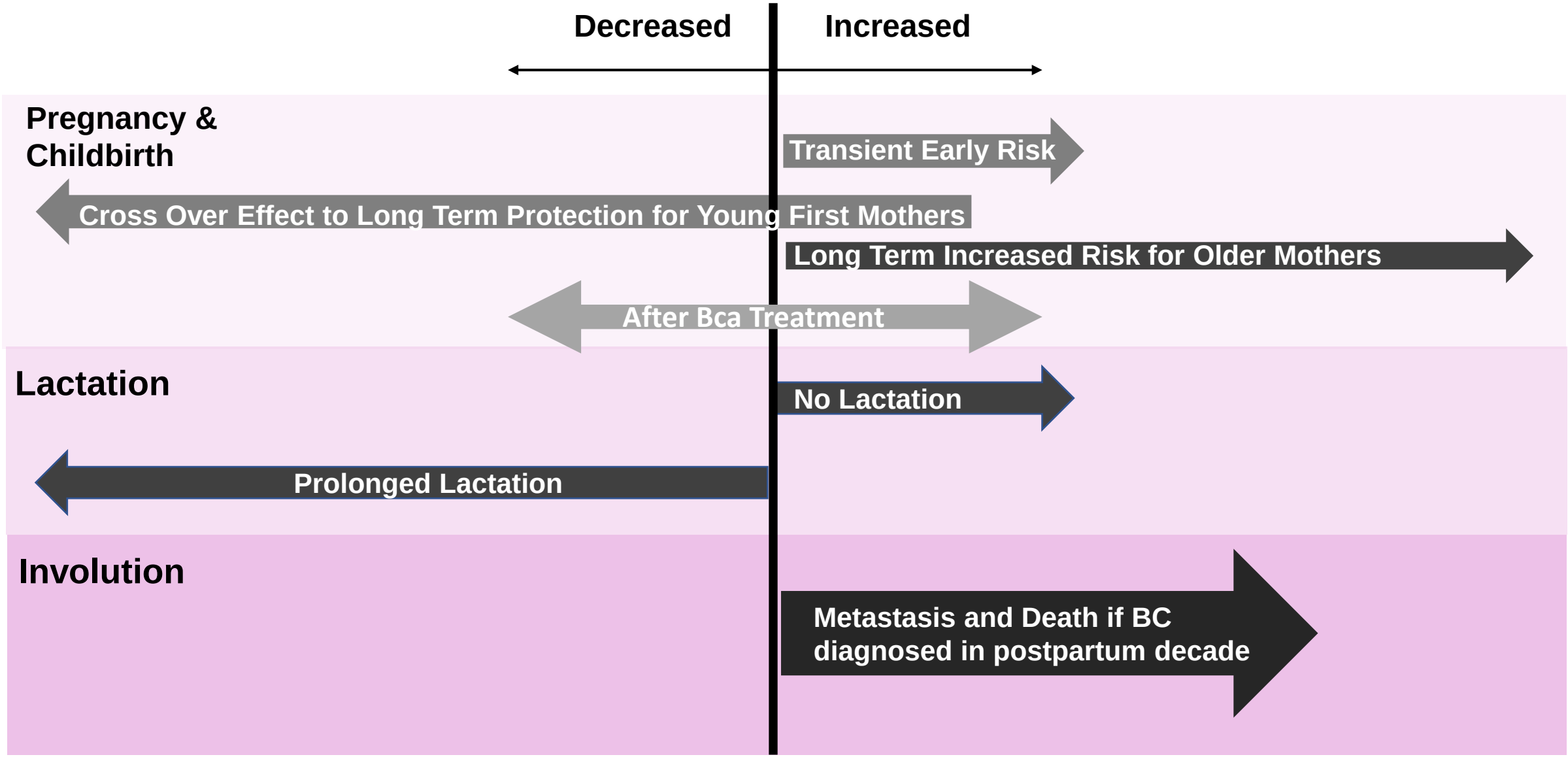
University of Colorado
Cancer Center
Young Women's Breast Cancer
Translational Program

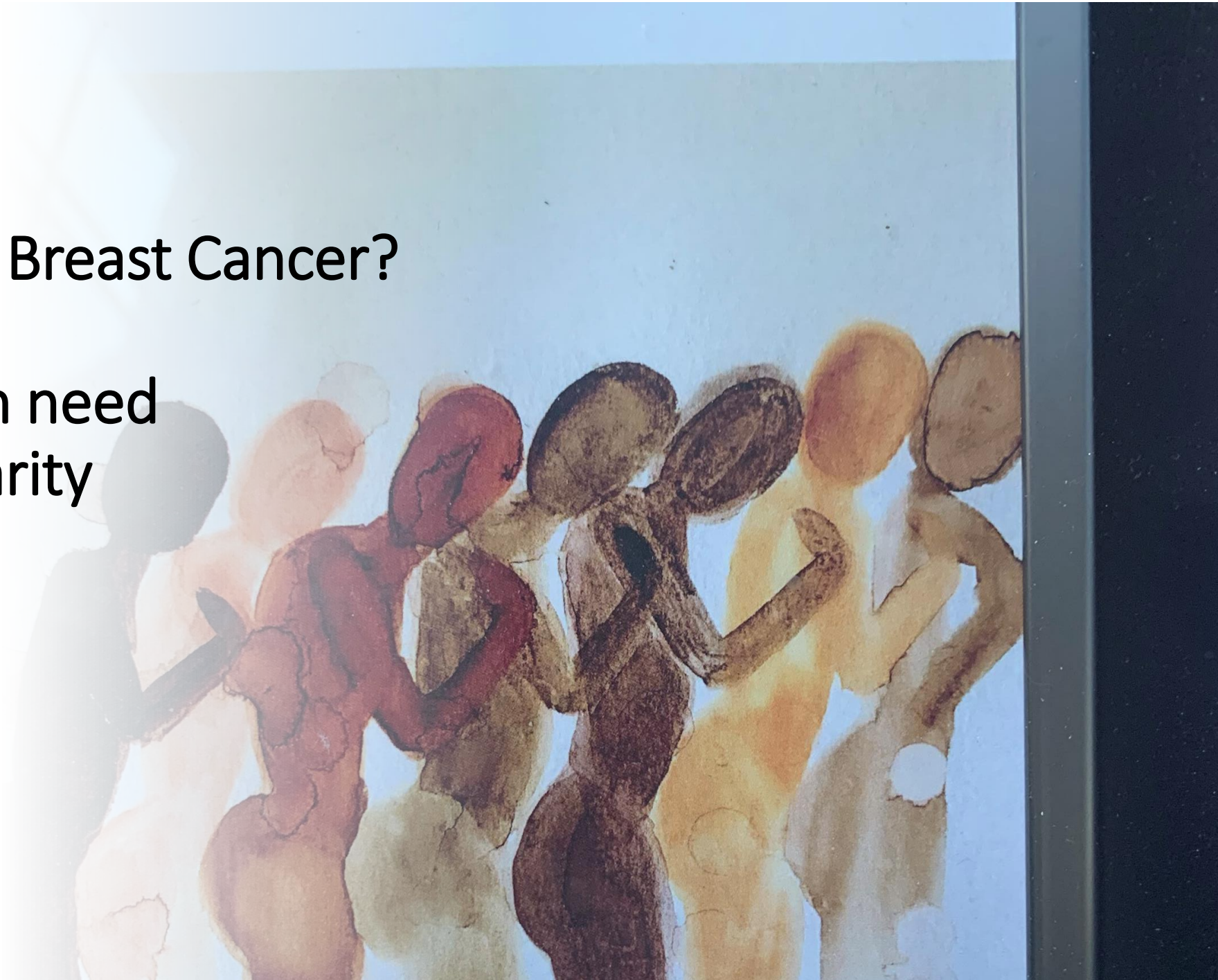


Breast Cancer Risk Over Time



What is Postpartum Breast Cancer?

Global unmet health need
Cancer of high disparity



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What is Postpartum Breast Cancer?

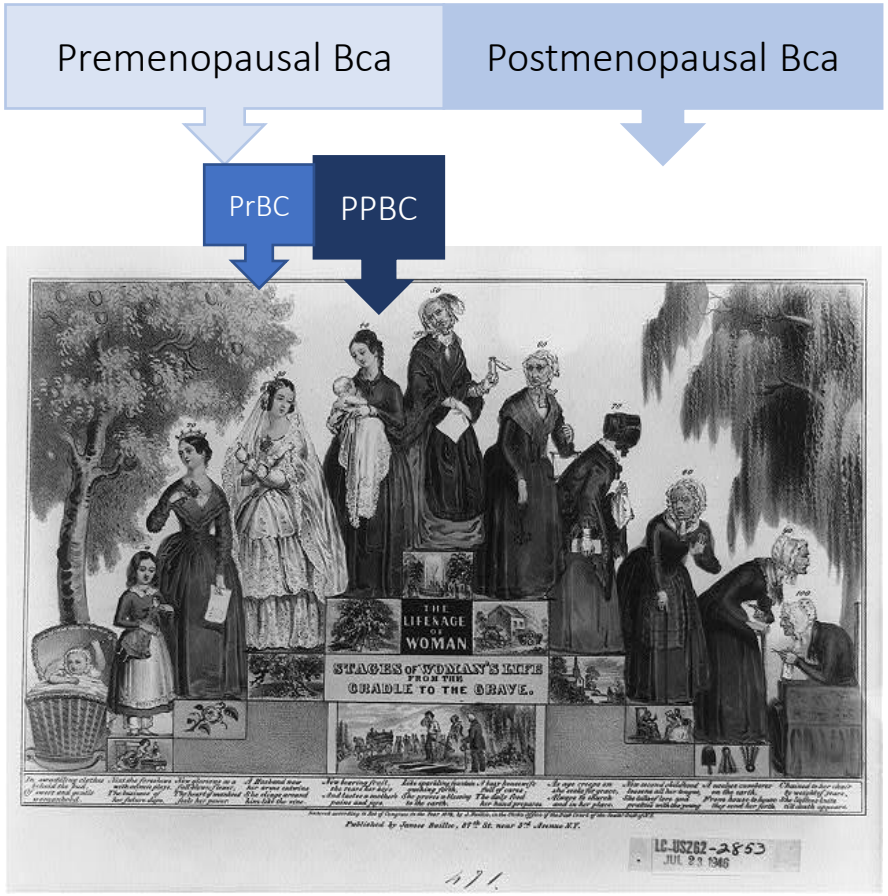
* Women diagnosed within 10 years of last childbirth
  estimation of 150,000 women/year, Globally
  32,000 women ≤45, 18,000 are PPBC/year in the US

* Higher likelihood for metastatic recurrence and death

*The cancers themselves are more aggressive and have less response to current treatments

* The incidence is increasing worldwide

Life windows of BCA Risk



Childbirth is a Risk Factor for Young Women's Breast Cancer

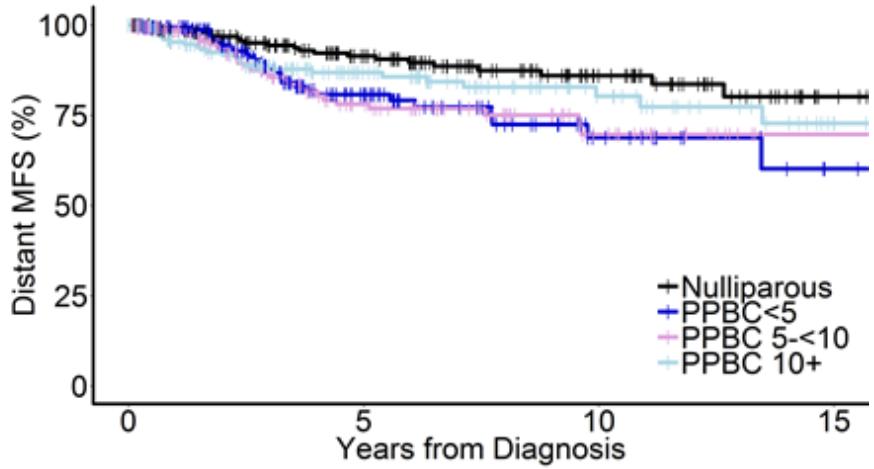
Diagnosis during early motherhood is a postpartum breast cancer

Studying breast cancer by the menopause divide dilutes YWBC/PPBC data

We treat our women under 45 based on results from pivotal trials where they are often ~10% representation.

Postpartum Diagnosis of Breast Cancer Independently Predicts for Poor Metastasis Free and Overall Survival

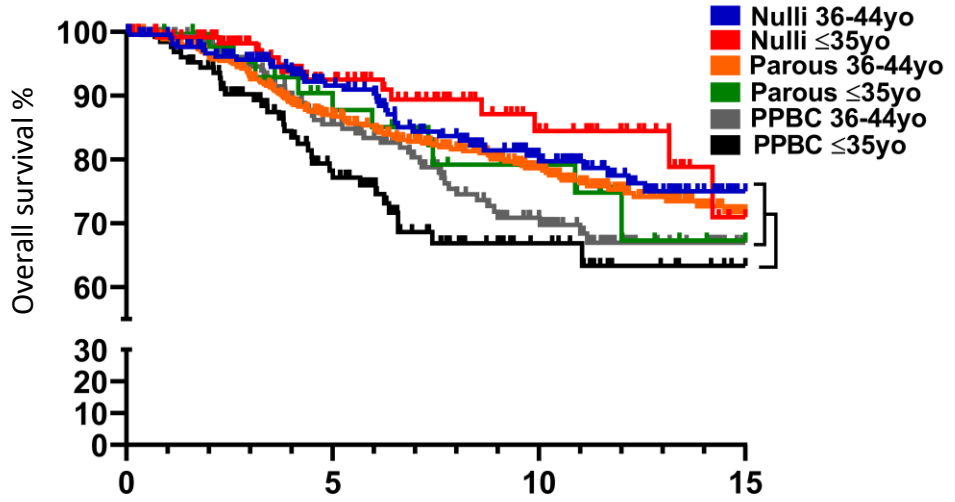
Colorado Young Women's Breast Cancer Cohort



Number at risk

Nulliparous	217	110	45	6
PPBC<5	175	58	17	4
PPBC 5-<10	153	64	23	1
PPBC 10+	156	75	31	9

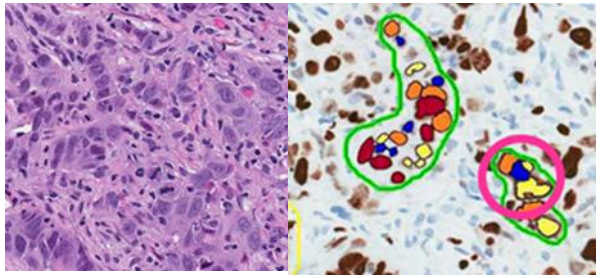
Colorado & Breast Cancer Health Disparities Study

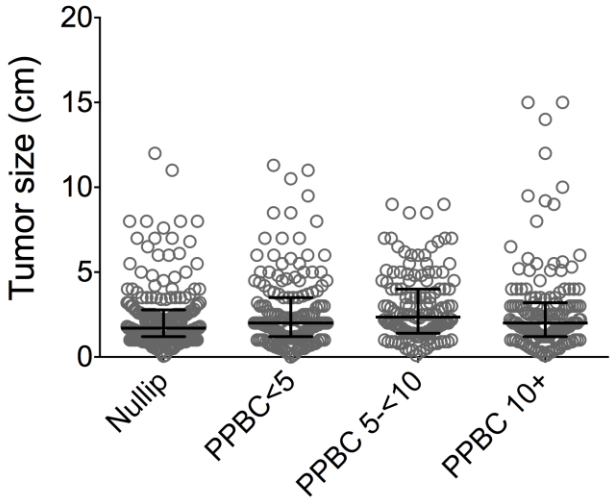


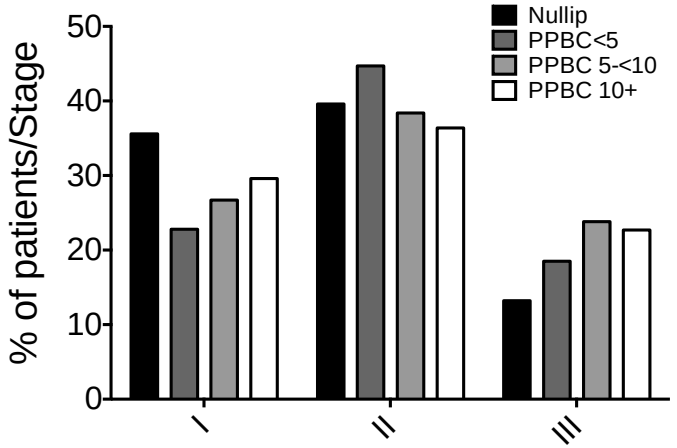
Nulli 36-44yo	217	149	92	23
Nulli ≤35yo	123	72	31	6
Parous 36-44yo	455	322	217	53
Parous ≤35yo	45	34	23	5
PPBC 36-44yo	205	124	64	18
PPBC≤35yo	128	71	22	4

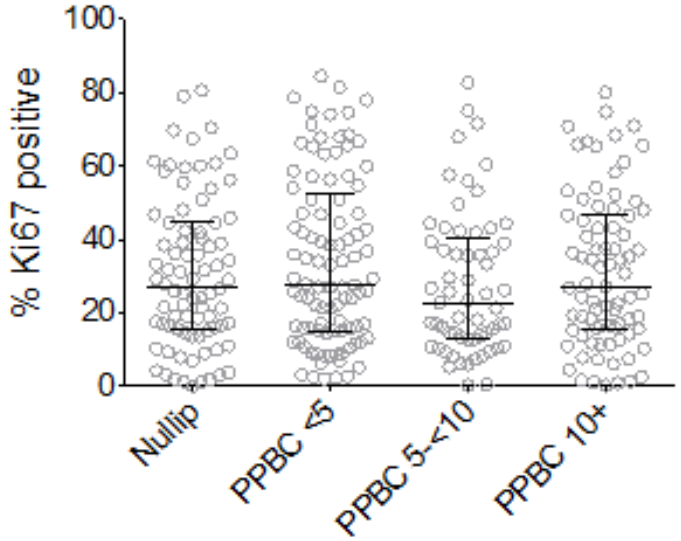
Goddard, JAMA Network, 2019 and Shagisultanova, Eur J Can, 2022

The poor prognosis of postpartum breast cancer was NOT associated with increased stage, tumor size or proliferation

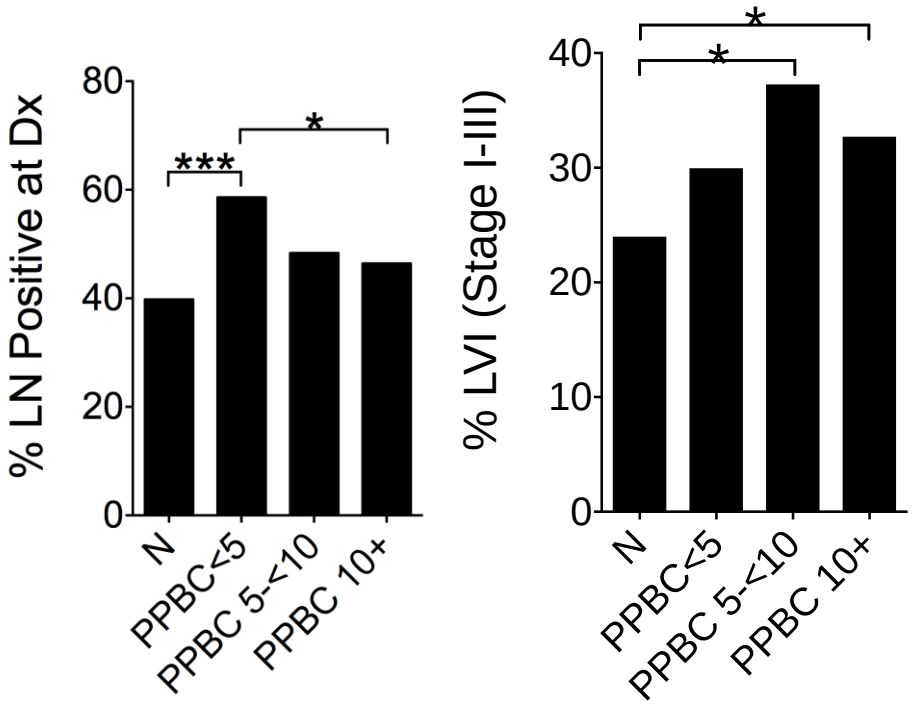


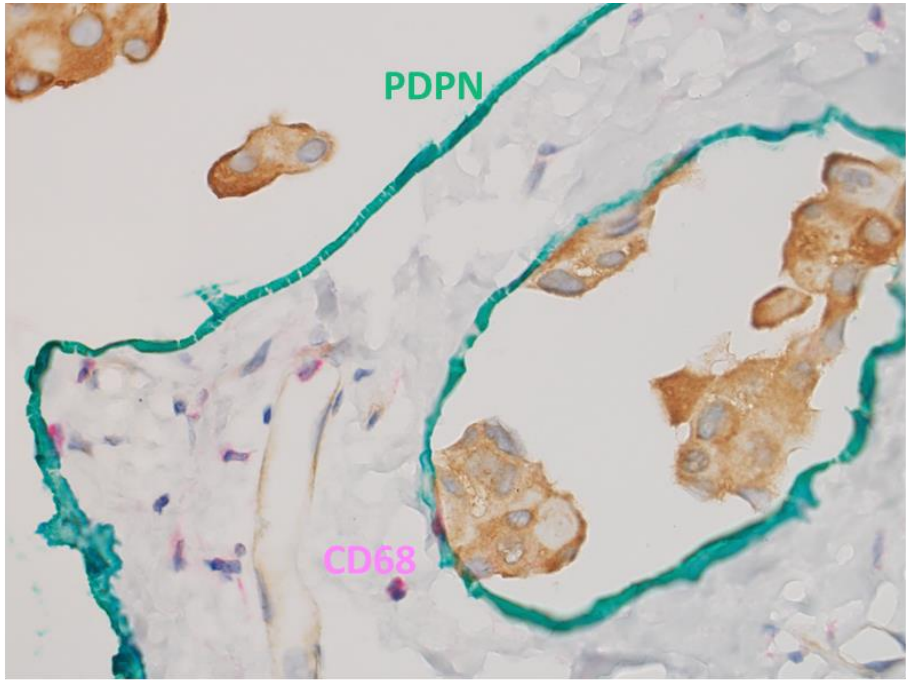






Goddard, et al JAMA Network 2019





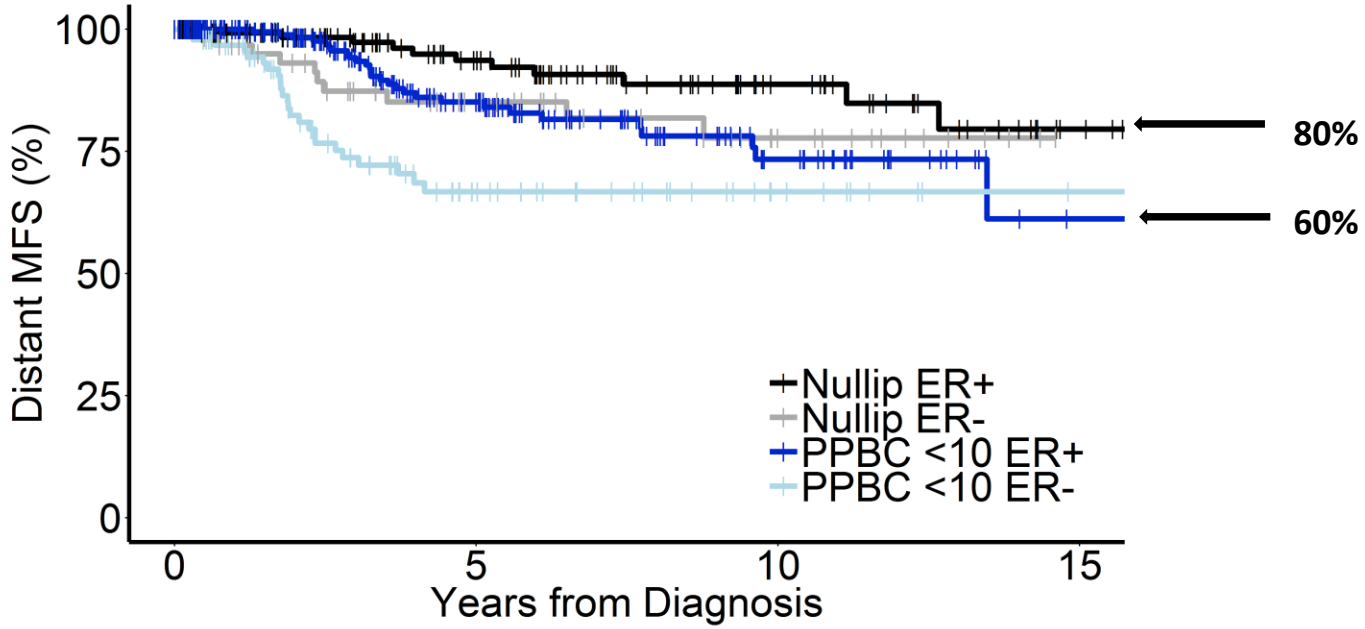
PPBC Patient: 36 years old, 1 month after birth of second child (G2P2), LN+, Luminal B

PPBC associated with increased LVI, LVD, LN involvement

JAMA Network Open Original Investigation Oncology January 11, 2019

Association Between Postpartum Breast Cancer Diagnosis and Metastasis and the Clinical Features Underlying Risk

Erica T. Goddard, PhD; Solange Bassale, MS; Troy Schedin, BS; Sonali Jindal, MD; Jeremy Johnston, BS; Ethan Cabral, BS; Emile Latour, MS; Traci R. Lyons, PhD; Motomi Mori, PhD; Pepper J. Schedin, PhD; Virginia F. **Borges**, MD, MMSc

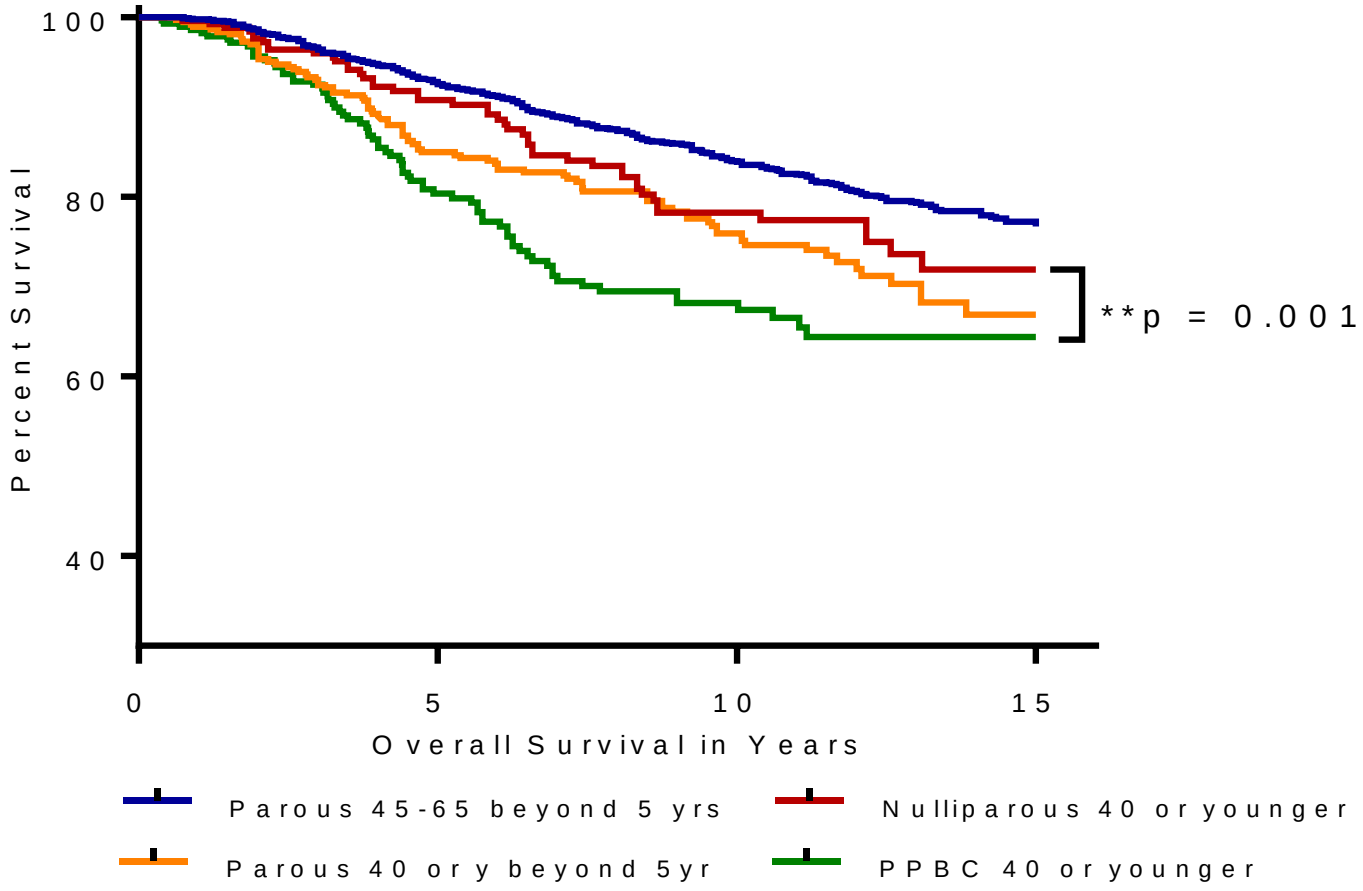


Number at risk

Nullip ER+	142	70	28	5
Nullip ER-	62	33	12	0
PPBC <10 ER+	218	82	28	3
PPBC <10 ER-	93	29	9	1

Colorado Young Women's Breast Cancer Cohort N=701 Years 1981-2014

Postpartum Breast Cancer *Drives* the Risk of Young Woman's Breast Cancer



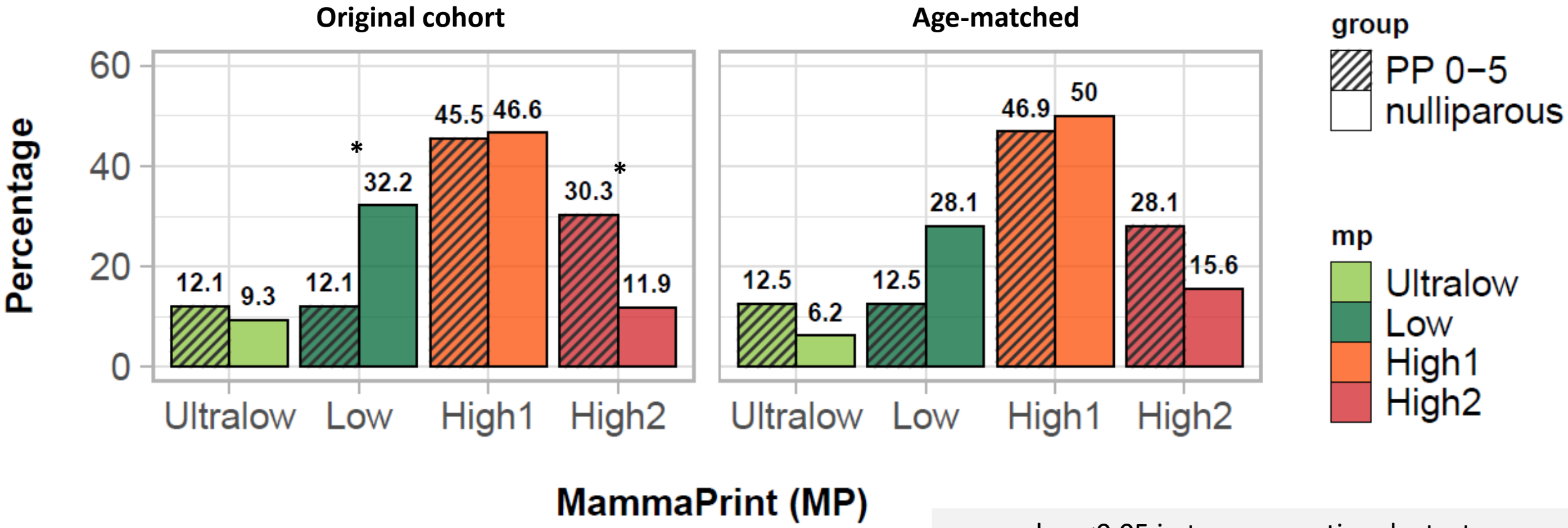
N=4262

Shagisultanova, Eur J Can, 2022

AGENDIA FLEX study: PPBC Collaborative study
Clinical data

	0-5 (N=33)	6-10 (N=51)	0-10 (N=84)	>10 (N=175)	nulliparous (N=118)	0-5 pval	6-10 pval	0-10 pval	>10 pval
Age years									
Median	38	44	41	47	43	< 0.001	0.338	0.25	< 0.001
Range	28.00 - 47.00	28.00 - 50.00	28.00 - 50.00	33.00 - 50.00	27.00 - 50.00				
T stage									
T1	13 (48.1%)	23 (62.2%)	36 (56.2%)	85 (66.4%)	43 (53.8%)	0.66	0.446	0.972	0.247
T2	13 (48.1%)	9 (24.3%)	22 (34.4%)	36 (28.1%)	30 (37.5%)				
T3	1 (3.7%)	3 (8.1%)	4 (6.2%)	6 (4.7%)	5 (6.2%)				
T4	0 (0.0%)	2 (5.4%)	2 (3.1%)	1 (0.8%)	2 (2.5%)				
Grade									
G1	5 (15.6%)	12 (24.0%)	17 (20.7%)	52 (30.4%)	26 (22.8%)	0.236	0.946	0.772	0.353
G2	16 (50.0%)	29 (58.0%)	45 (54.9%)	86 (50.3%)	65 (57.0%)				
G3	11 (34.4%)	9 (18.0%)	20 (24.4%)	33 (19.3%)	23 (20.2%)				
N stage									
N0	21 (80.8%)	29 (82.9%)	50 (82.0%)	101 (82.8%)	66 (84.6%)	0.76	0.788	0.819	0.846
N1	5 (19.2%)	6 (17.1%)	11 (18.0%)	21 (17.2%)	12 (15.4%)				
Histology									
IDC	31 (93.9%)	40 (81.6%)	71 (86.6%)	151 (87.8%)	106 (90.6%)	0.866	0.183	0.62	0.763
ILC	1 (3.0%)	7 (14.3%)	8 (9.8%)	14 (8.1%)	8 (6.8%)				
Mixed IDC&ILC	1 (3.0%)	2 (4.1%)	3 (3.7%)	7 (4.1%)	3 (2.6%)				
Menopausal									
Pre-/Peri-	31 (93.9%)	46 (92.0%)	77 (92.8%)	129 (75.9%)	96 (84.2%)	0.247	0.219	0.08	0.102
Post-	2 (6.1%)	4 (8.0%)	6 (7.2%)	41 (24.1%)	18 (15.8%)				

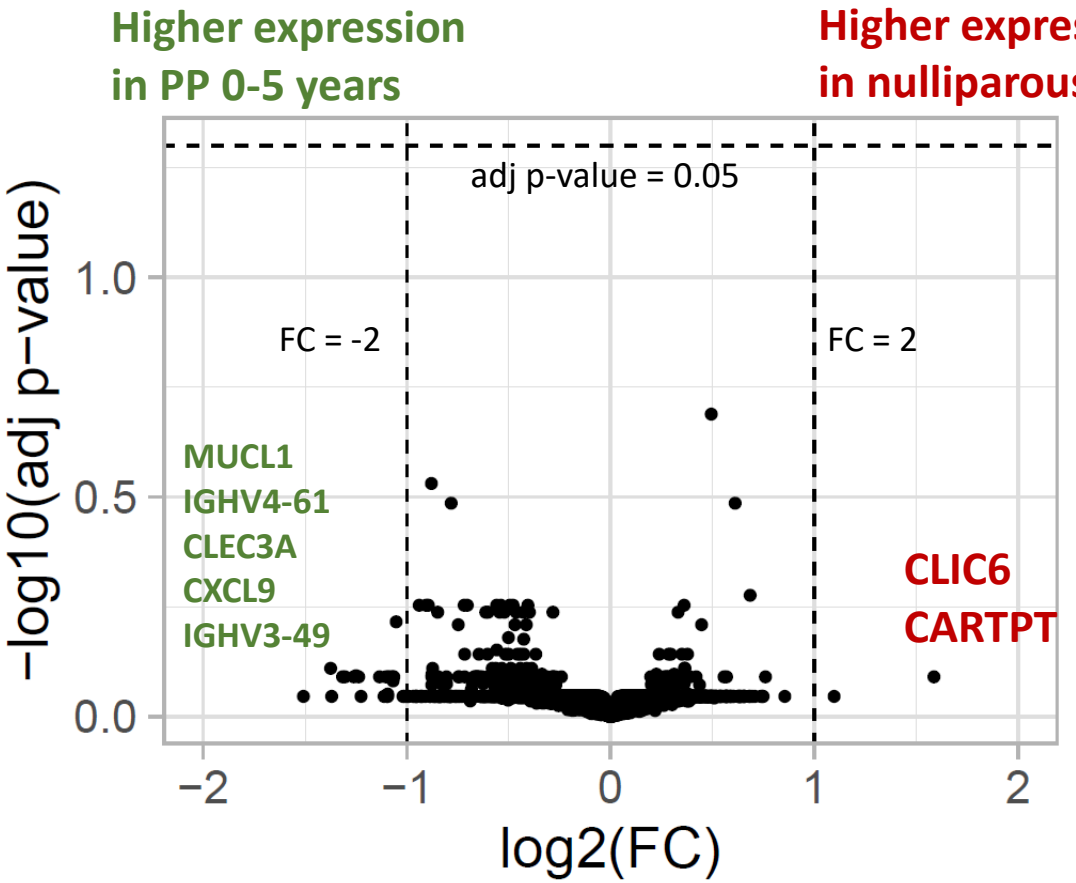
MammaPrint risk groups from original and age-matched groups from PP 0-5 years and nulliparous



- p-value <0.05 in two proportional z-test
- We see similar pattern of % differences in age-matched group, does not reach statistical significance – potentially due to low numbers, n less than 10 in most groups

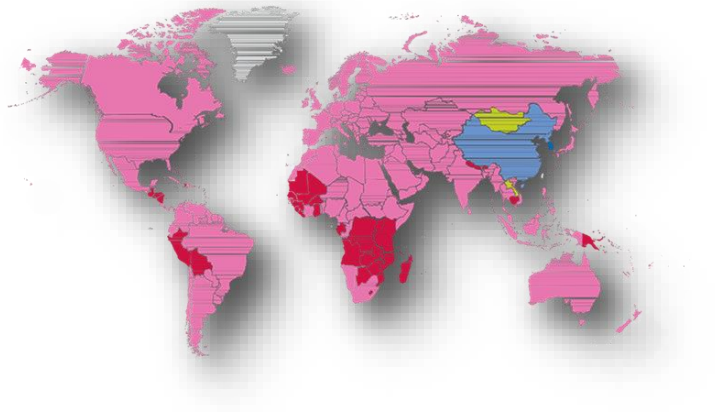
Borges, et al, ESMP Breast 2024

Whole transcriptome comparison in age-matched group – PP 0-5 years vs nulliparous



- No genes with significant difference adj pvalue < 0.05
- 2 genes have higher expression (FC >2) in nulliparous,
- 25 genes have higher expression (FC>2) in PP 0-5 years
  - Top 5 genes listed on the left

Borges, et al, ESMP Breast 2024



PrBC and PPBC are a global problem with disparity

- In 2020, there were 684,996 breast cancer deaths worldwide, with a disproportionally higher percentage affecting YWBC.
- The global mortality of breast cancer in women under age 50 is increasing fastest in parts of the world that have the least access to detection and treatment, East Asia & Pacific, Latin America & Caribbean, and all the African global regions.
- Notably, countries with the highest birth rates per 1000 people are also the same countries with the highest BC mortality < 50.
- PPBC is likely to increase and most so in countries where mortality is the highest
- Concurrent with this data and since 2021 alone, reports of higher risk for postpartum breast cancer have been reported.
  - Mexico, Northern Europe and Canada, Japan, Sub-Sahara African, Korea, Southern India and Singapore.

Thus, PPBC has gained international recognition as
a ***poor-prognostic subset of breast cancer of high unmet need***.

Amant et al, Lancet Oncology, 2021 and ESMO guidelines 2023!

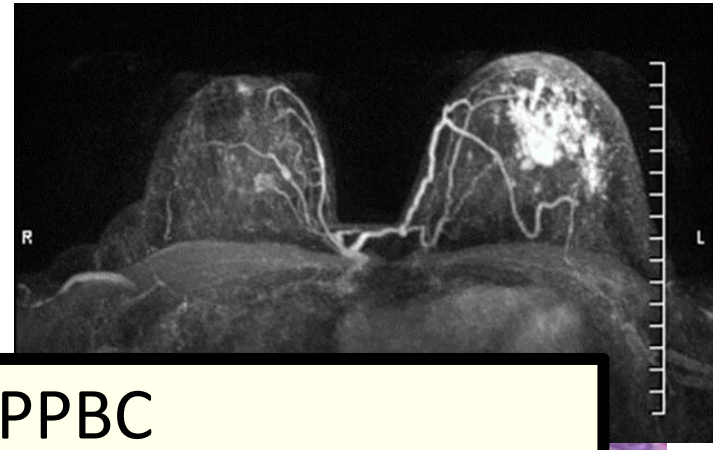
Parity and Breast Cancer Epidemiology

YWBC at diagnosis

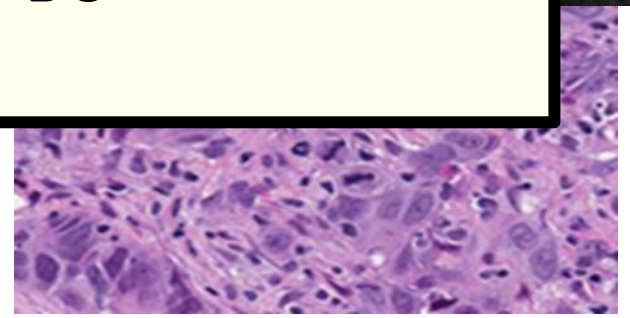
Nulliparous	Pregnant	Postpartum	Later Parous
Never pregnant or prior Incomplete pregnancy	Treatment initiated during pregnancy Trimester separation	Up to 5-10 years	>10 year post childbirth

Parity and Breast Cancer Epidemiology

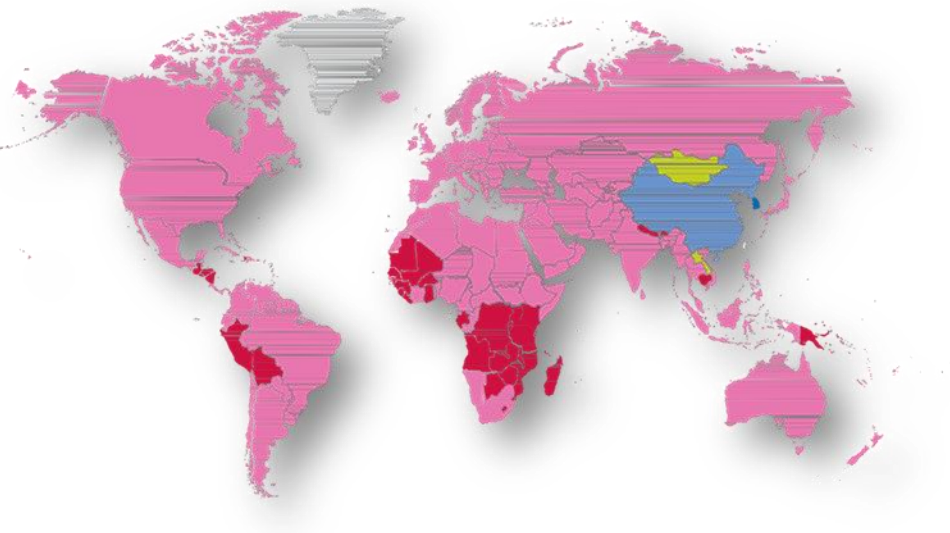
Goals of the Strategy



Reduce the mortality of YWBC/PPBC
Reduce the incidence of PPBC



Feasibility, Safety and Biomarker Clinical Study for the Prevention of Postpartum Breast Cancer



The next prevention drug?

Feasible
Cost-effective
Global applicability
Safety - No breast milk excretion
Acceptability
Efficacious

Young Women's Breast Cancer Translational Program

Virginia F. Borges, Director

Traci Lyons, Program Senior Scientist

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Elena Shagisultanova
Hannah Parrish
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CU: Jill Slansky, PhD; Jennifer Richer, PhD; Diana Cittelly, PhD, Heide Ford, PhD; Matt Sikora, PhD; Sarah Tevis, MD; Marie Wood, MD

CDMRP

Donors: Connor Family, Ghrone Family, Glass Family, Carpenter Family, Bolin Family & others

Studies of postpartum breast cancer inform novel treatment options

Traci R Lyons, PhD

Associate Professor

University of Colorado Anschutz Medical Campus

Medical Oncology

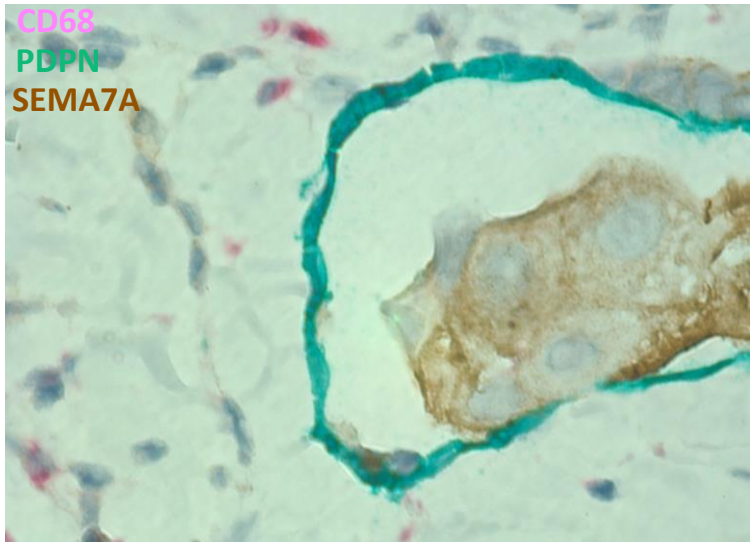
Young Women's Breast Cancer Translational Program

Disclosures

- Traci R Lyons, PhD: Co-founder and CSO of Pearl Scientific and on the scientific advisory board for Global Cancer Technology.

- The speaker(s) plans to discuss off-label use of a product during this discussion: alpelisib

Lyons Lab (est. 2015)



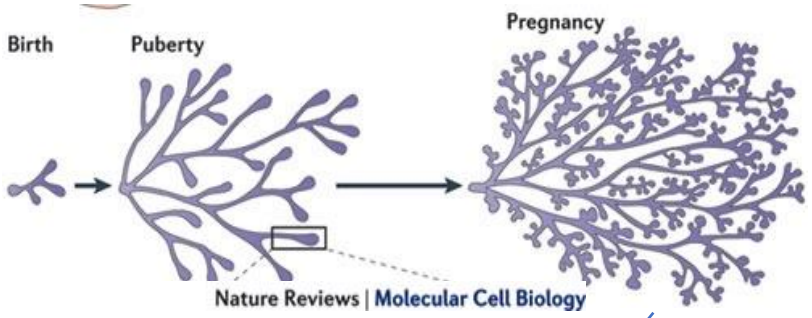
PPBC Patient (WOO16): 36 years old, 1 month after birth of 2nd child (G2P2), LN+, Luminal B

Images from USA Today, New York Times, 5280 Magazine

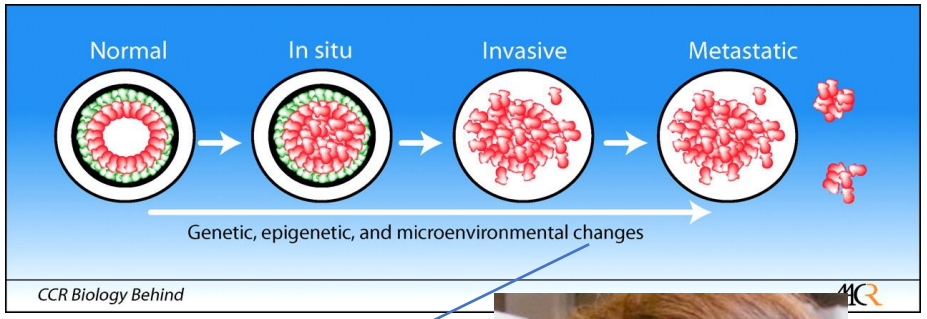
University of Colorado Cancer Center Young Women's Breast Cancer Translational Program (YWBCTP)

Lyons Lab

Studies of normal mammary development



Pre-clinical studies of tumor progression



Involution

Lactation

Young Women's Tissue Bank

Virginia Borges, MD

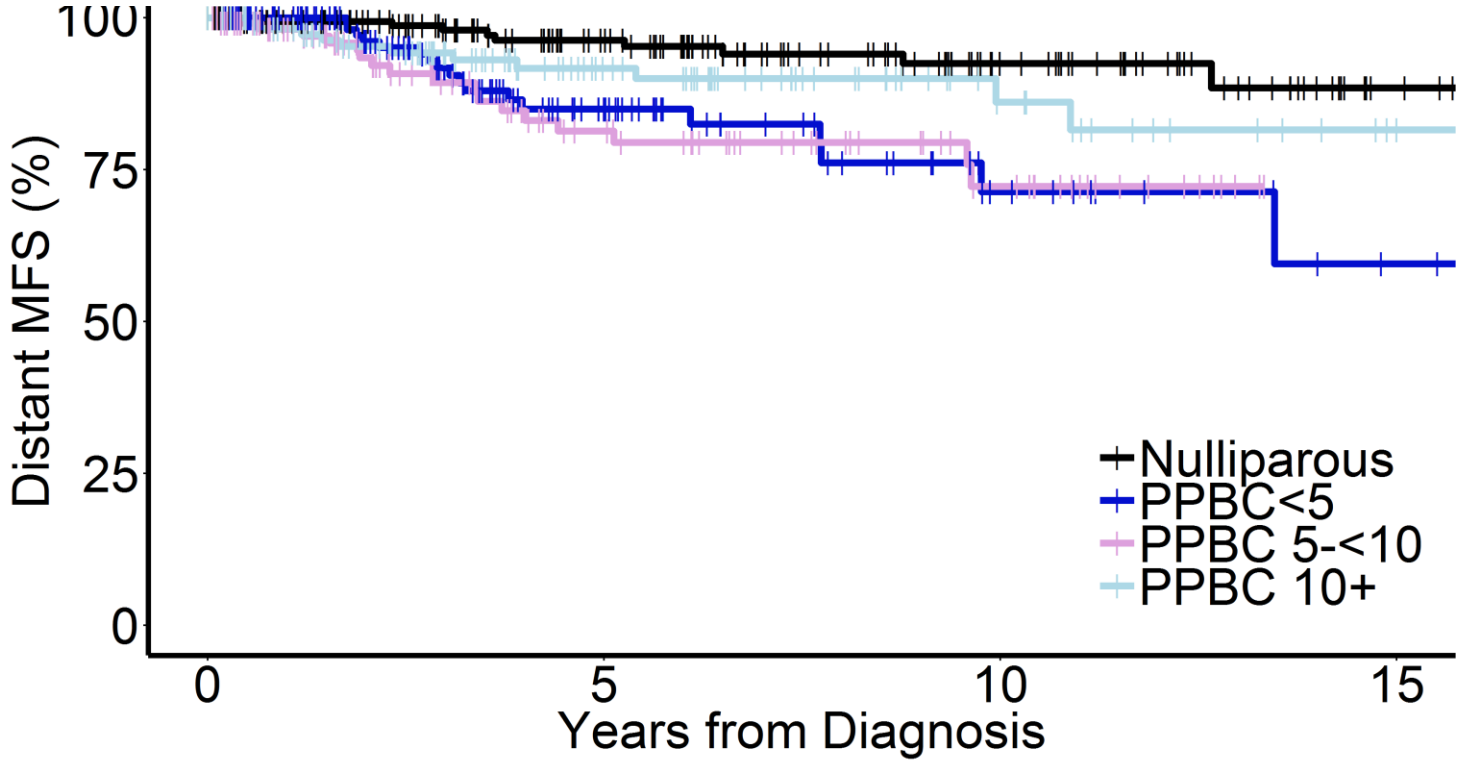
Targeted therapies

Original Investigation | Oncology

Association Between Postpartum Breast Cancer Diagnosis and Metastasis and the Clinical Features Underlying Risk

University of Colorado Young Women's Cohort

Erica T. Goddard, PhD; Solange Bassale, MS; Troy Schedin, BS; Sonali Jindal, MD; Jeremy Johnston, BS; Ethan Cabral, BS; Emile Latour, MS; Traci R. Lyons, PhD; Motomi Mori, PhD; Pepper J. Schedin, PhD; Virginia F. Borges, MD, MMSc



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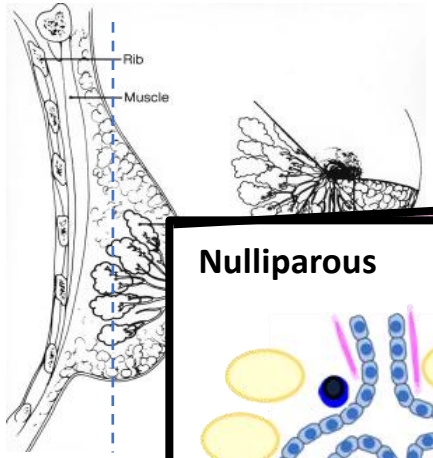
PPBC 10+	116	56	21	7

(*JAMAnetwork 2019)*

Hypothesis: Long-term changes to normal mammary tissue, induced by pregnancy, lactation, and involution may be driving aggressive/treatment refractory tumors in postpartum women.

Normal breast tissues from UC Young Women's cohort

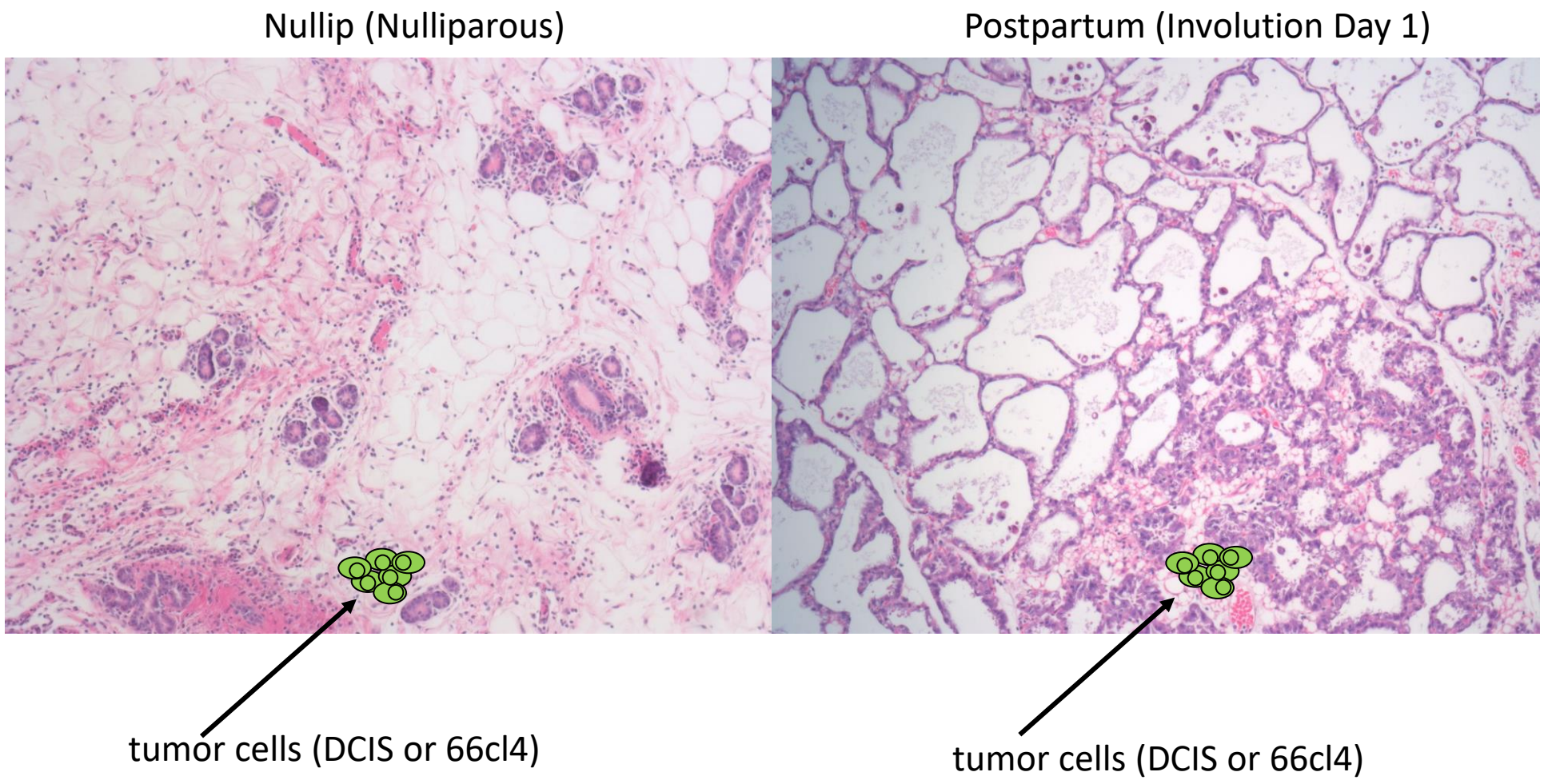


Regr

Lyons, Schedin, and Borges *JMGBN* 2009

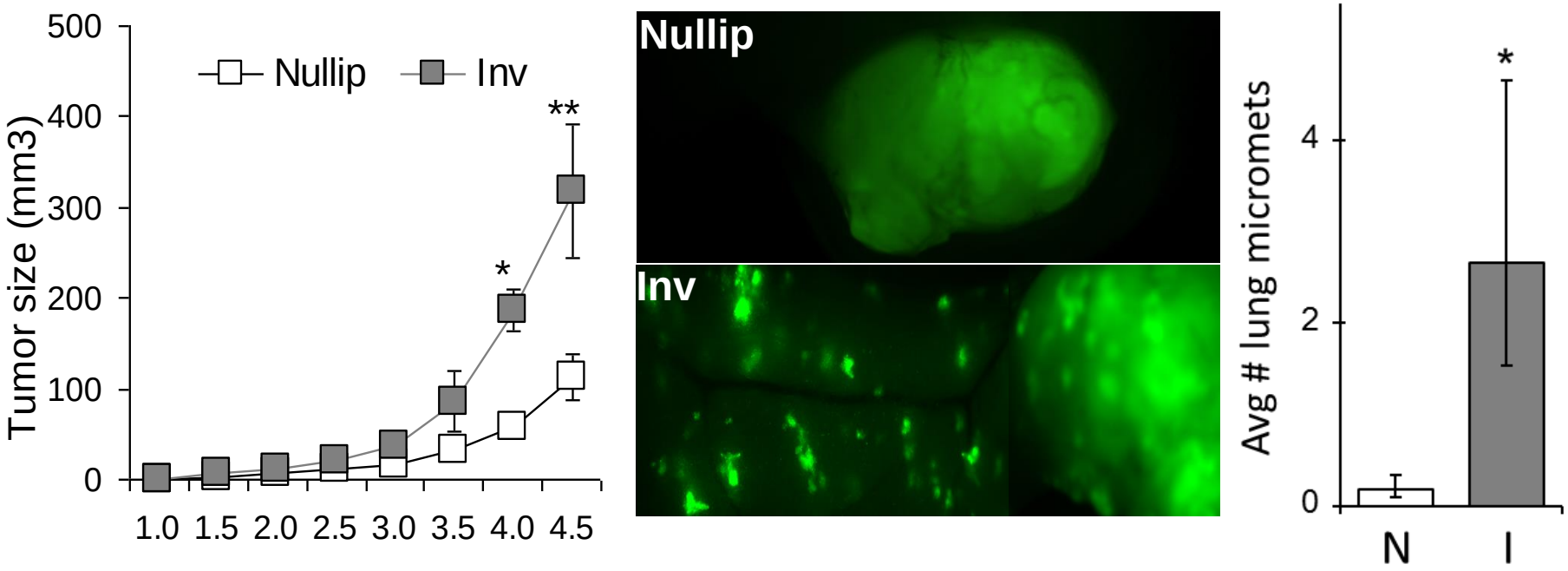
Fornetti et al, *JMGBN* 2014

Involution Hypothesis: Postpartum mammary involution facilitates breast tumor metastasis



Schedin, Nat Rev Cancer 2006; Lyons, Schedin, and Borges JMGBN 2009

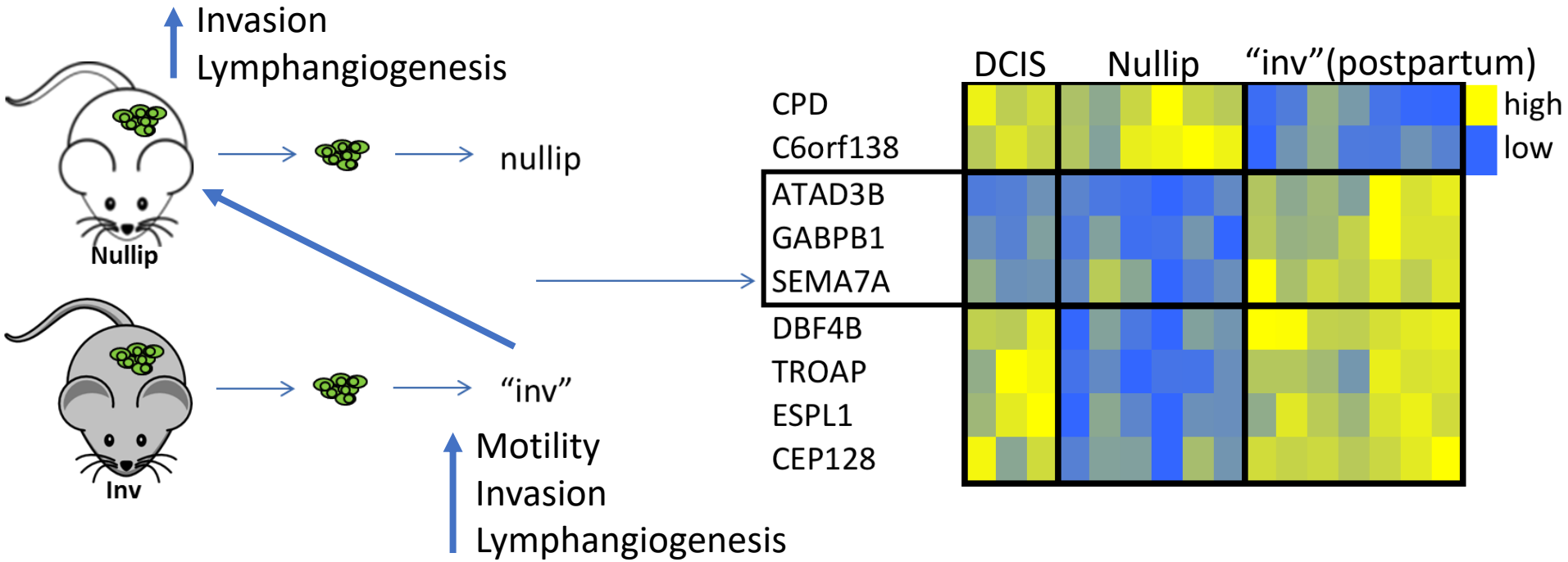
Involution drives tumor progression in pre-clinical models



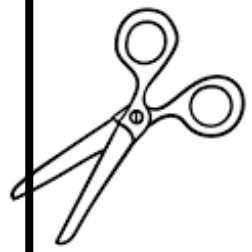
What are the mechanisms by which postpartum involution drives metastasis?

Lyons et al, *Nature Medicine*, 2011

Ex vivo analyses of postpartum tumor cells reveals “imprinting” of tumor cells



Representative immune semaphorins



Angiogenesis, Tumorigenesis Angiogenesis Morphogenesis

n of
y cells
of the
tract

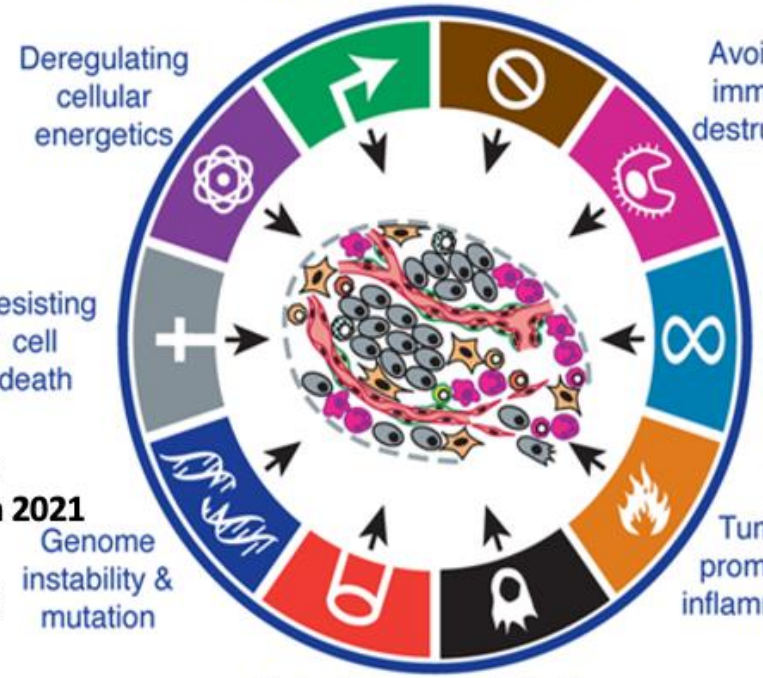
[Cellular & Molecular Immunology](#) (2010)

Lyons et al Nature Medicine 2011
Black et al Oncogene 2016
Elder er al Cancer Research 2018
Tarullo et al Oncogene 2020
Crump et al Cancer Research 2021

- Increases proliferation in multiple cell lines

- Promotes drug resistance

Tarullo et al Oncogene 2020
Rutherford et al
Cell Death and Disease 2021



- Associated with PD1/PDL1 expression

Tamburini et al Frontiers in Immunology 2019

- Associated with decreased caspase activity in multiple breast cancer cell lines

Tarullo et al Oncogene 2020
Crump et al Cancer Research 2021
Rutherford et al
Cell Death and Disease 2021

- Pro-tumorigenic effect on monocytes
- Regulated by pro-inflammatory enzyme, COX2.

Lyons et al Nature Medicine 2011
Black et al Oncogene 2016

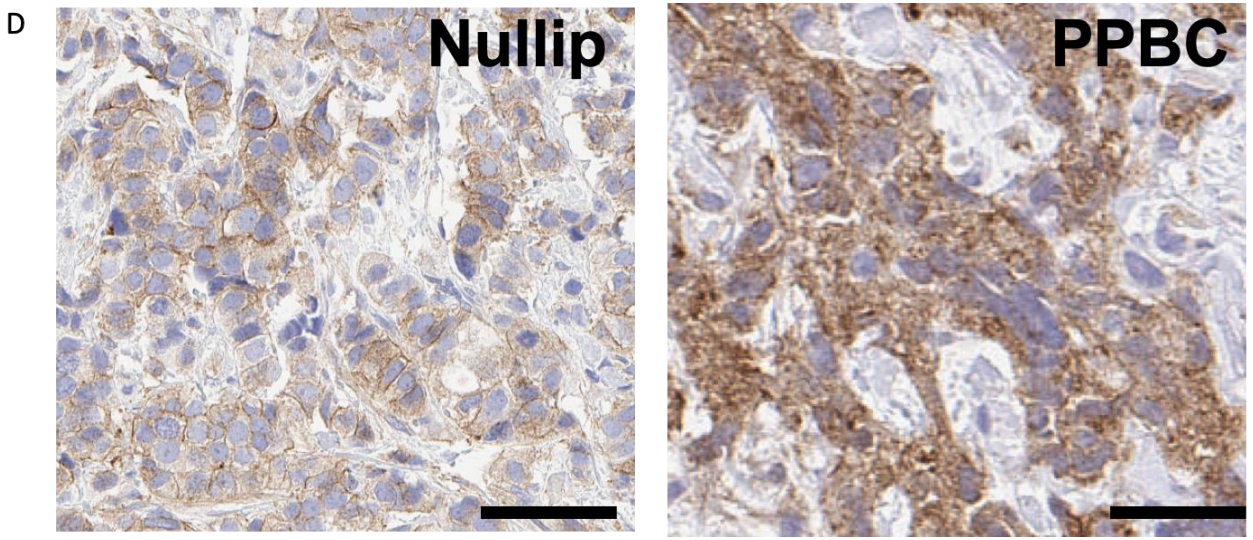
- Lymphatic remodeling
- VEGFA/VEGFR2-mediated angiogenesis

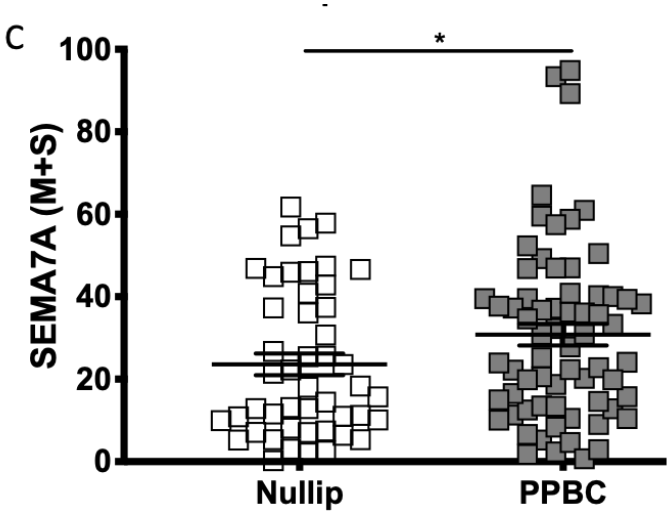
- Invasion on collagen
- Promotes metastasis in multiple models

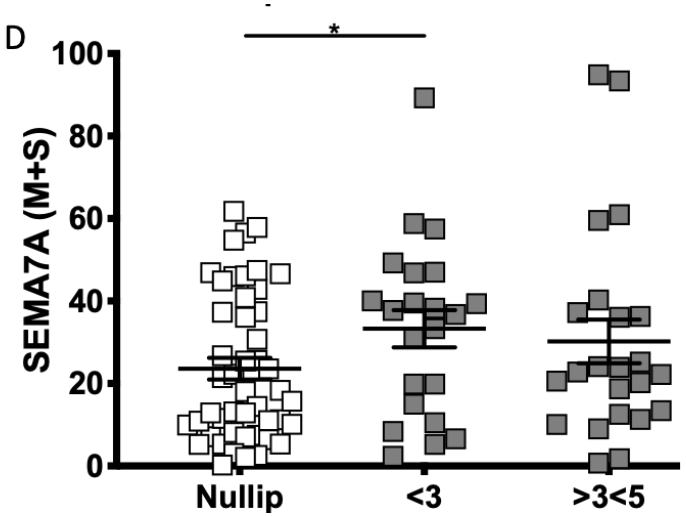
Tarullo et al Oncogene 2020
Crump et al Cancer Research 2021

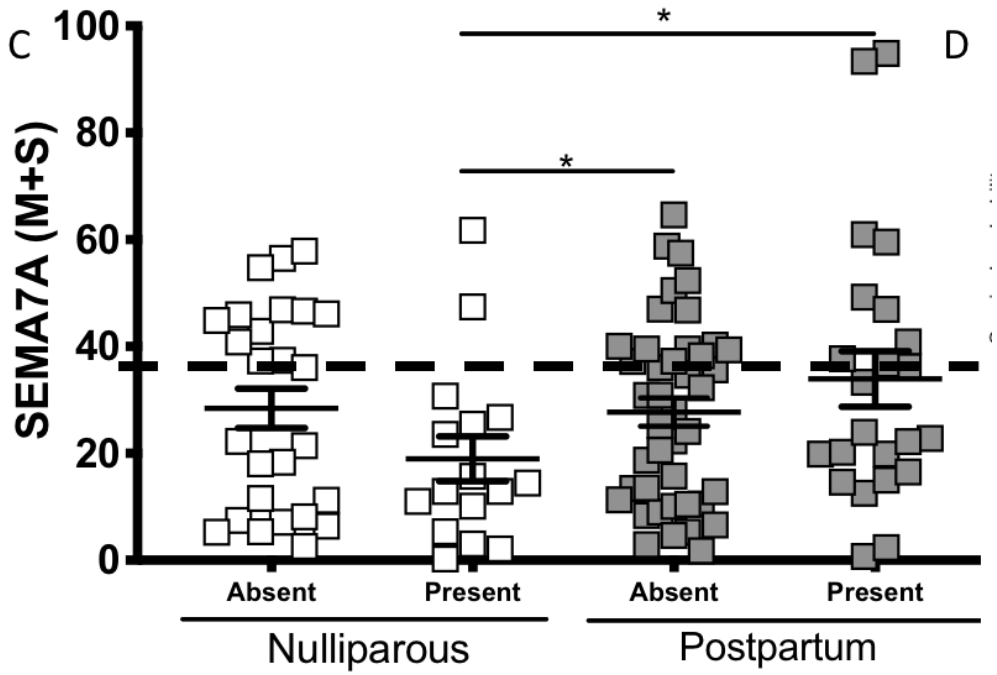
Elder et al Cancer Research 2018
Garcia-Areas et al Frontiers in Physiology 2014

SEMA7A in UC Young Women's BC cohort









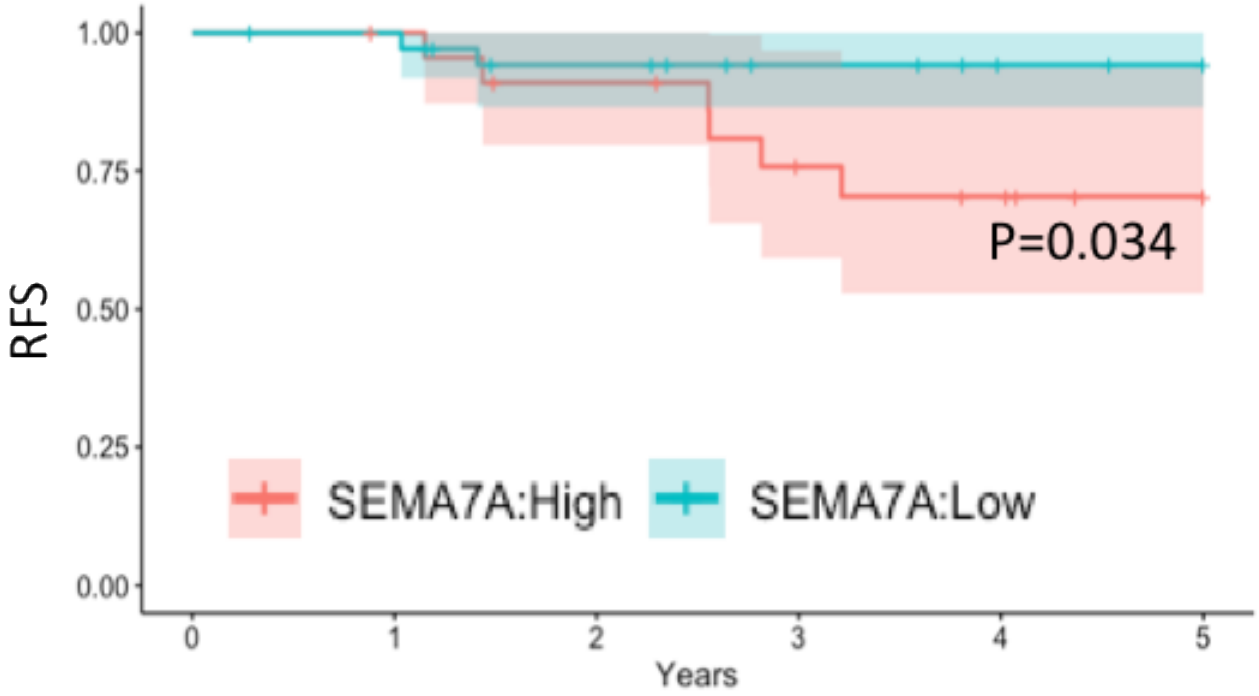
Veronica Wessells (PRA)

CASE REPORT OPEN

Check for updates

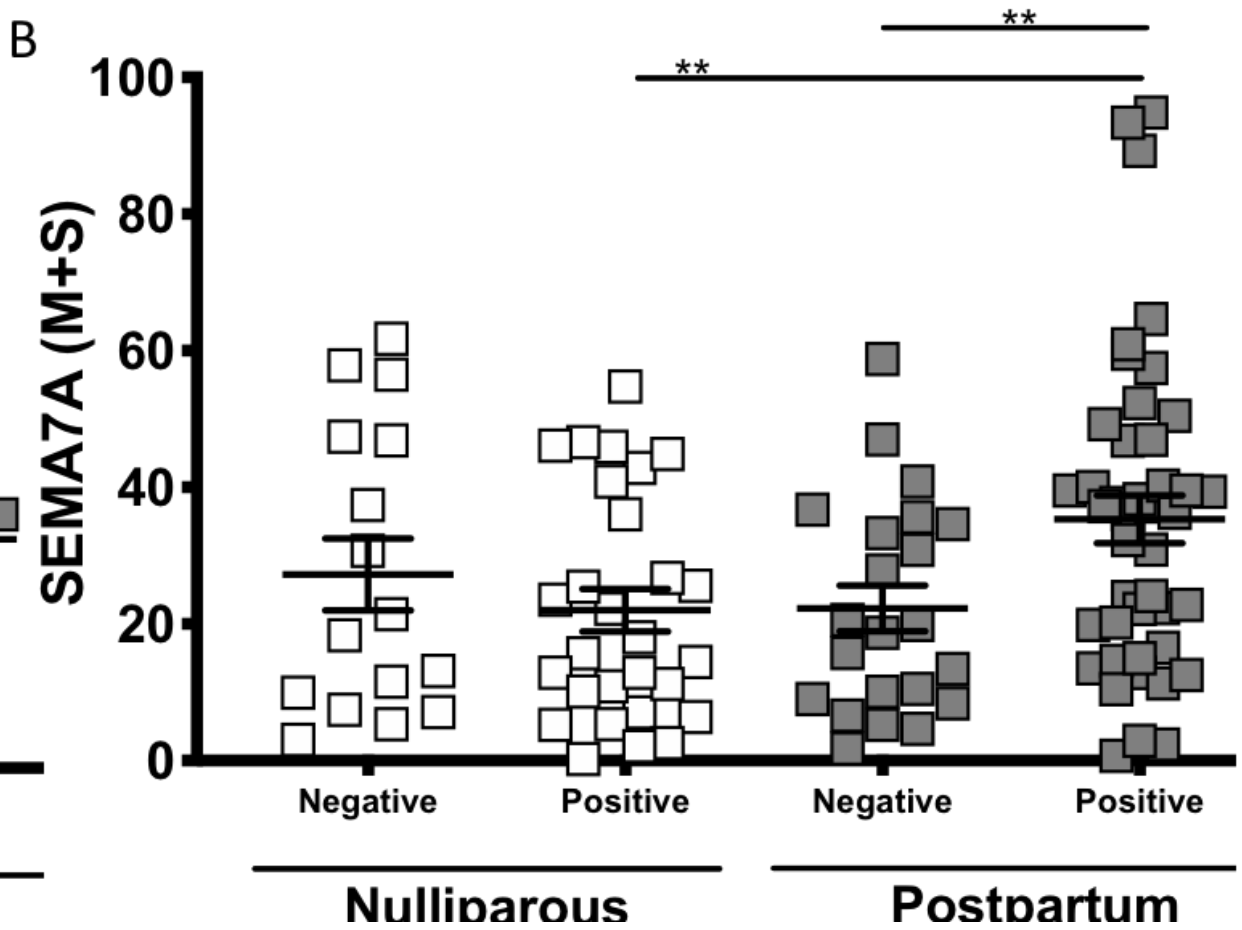
Semaphorin 7a is a biomarker for recurrence in postpartum breast cancer

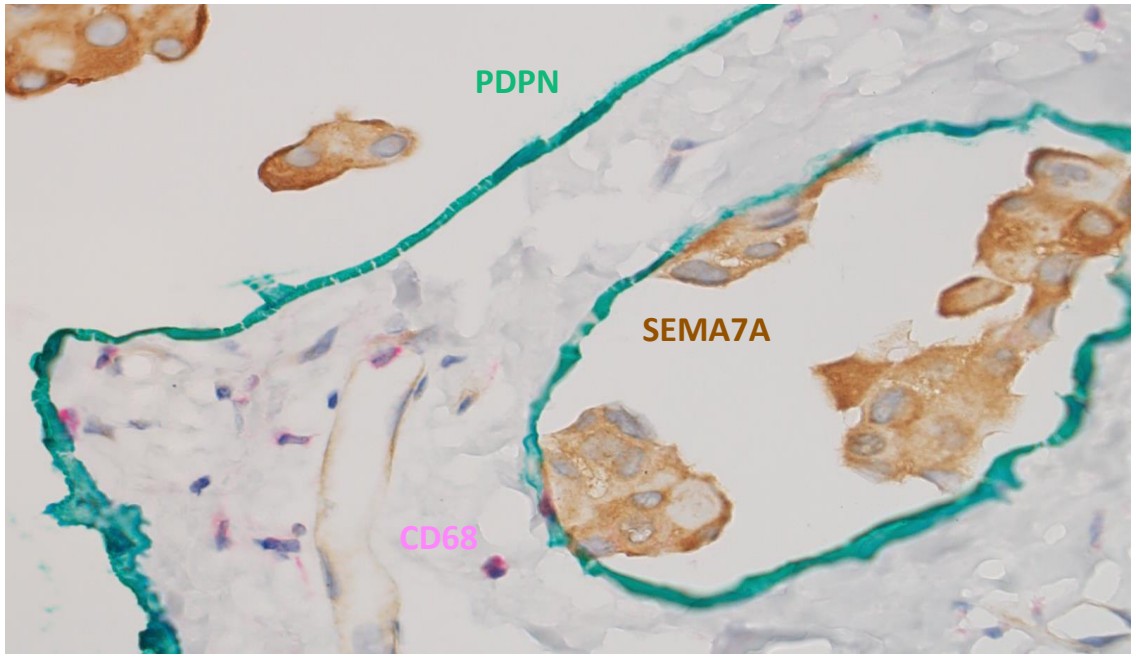
Virginia F. Borges[1,2]✉, Junxiao Hu[3], Chloe Young[2], Jaron Maggard[2], Hannah J. Parris[1,4], Dexiang Gao[3] and Traci R. Lyons[1,2]✉



npjBreast Cancer, 2020

SEMA7A promotes lymph node metastasis



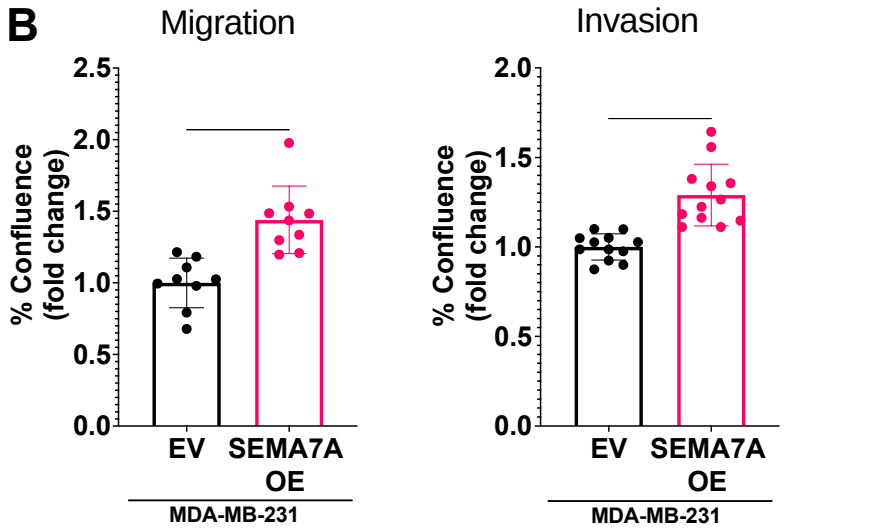


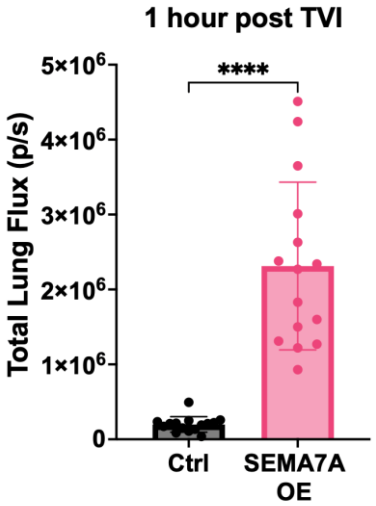
PPBC Patient: 36 years old, 1 month after birth of 2nd child (G2P2), LN+, Luminal B

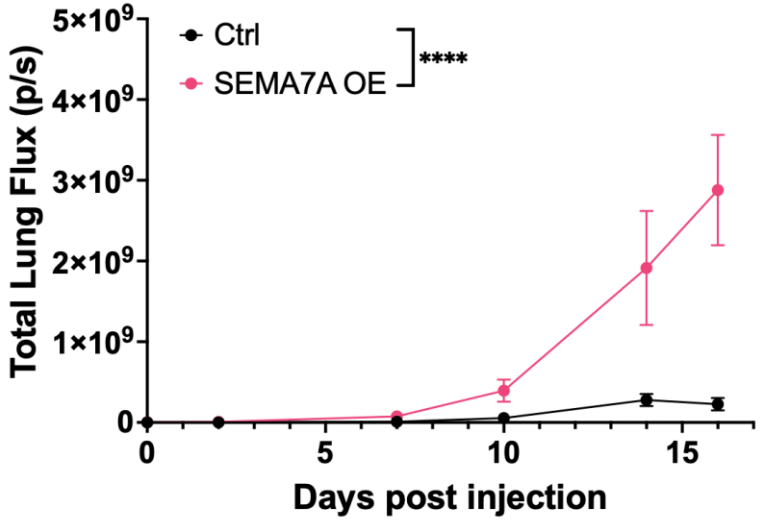
Veronica Wessells (PRA)

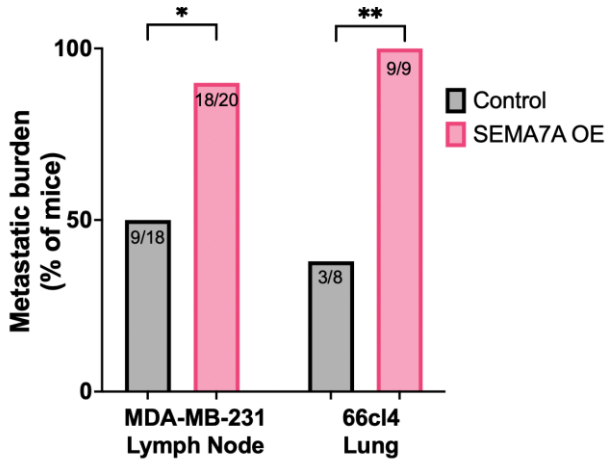
Elder *Cancer Research* November 2018
Goddard *Jama Network* November 2016

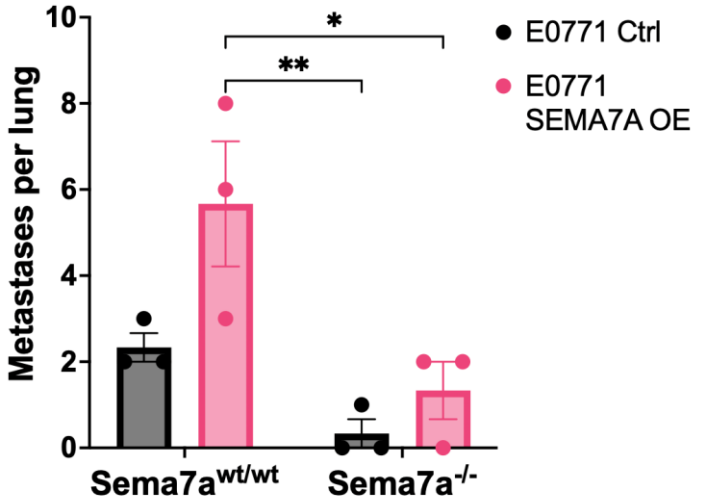
SEMA7A promotes metastasis





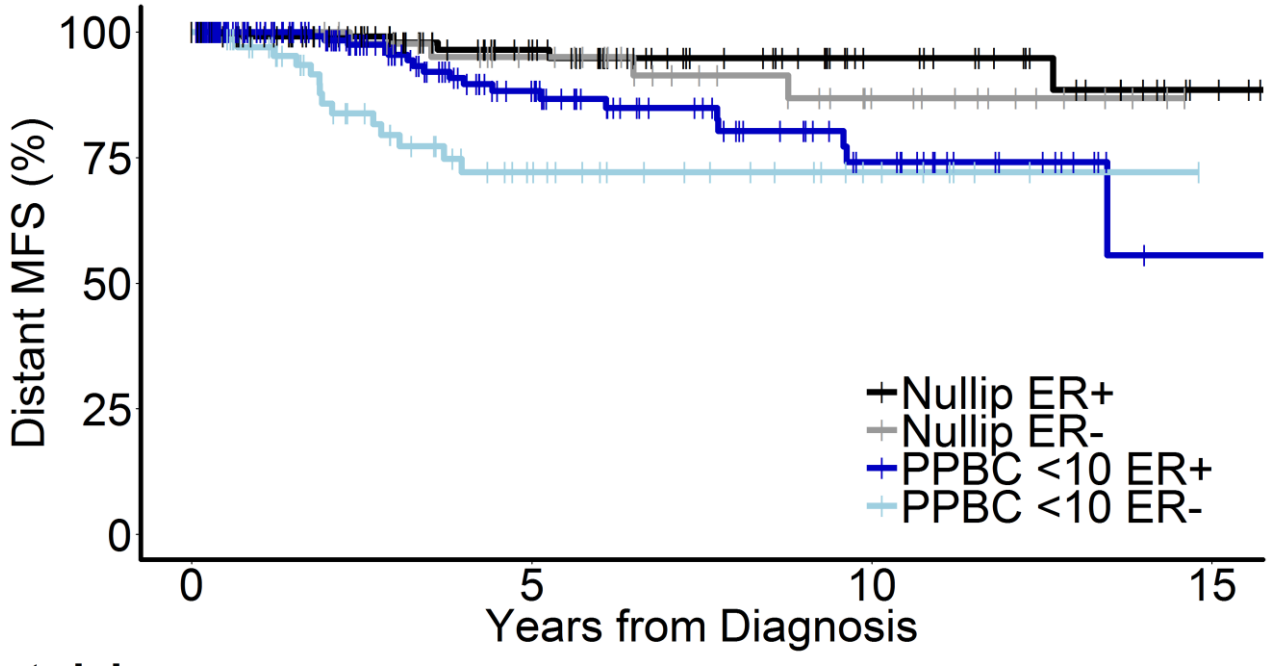


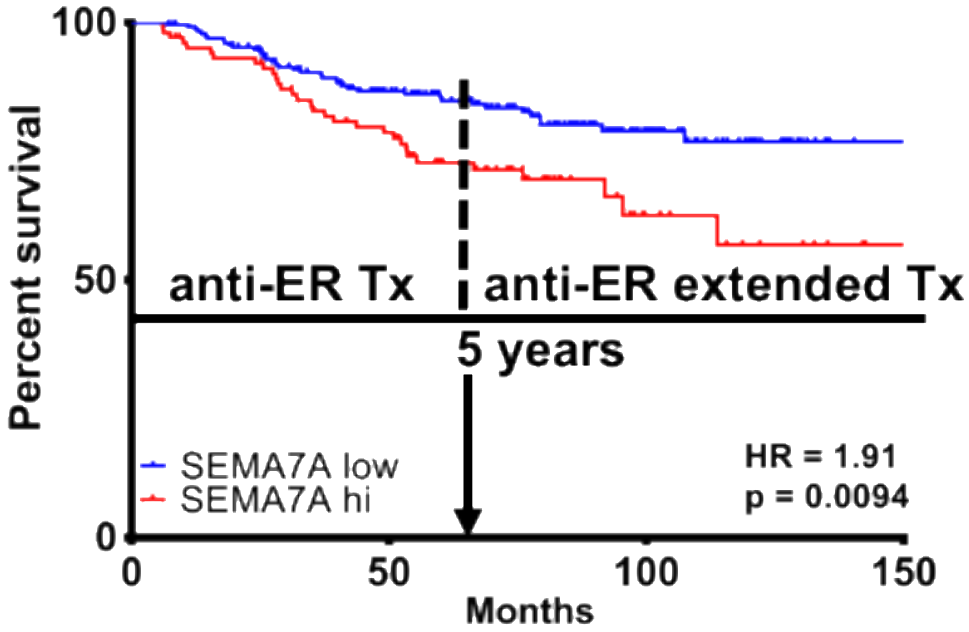




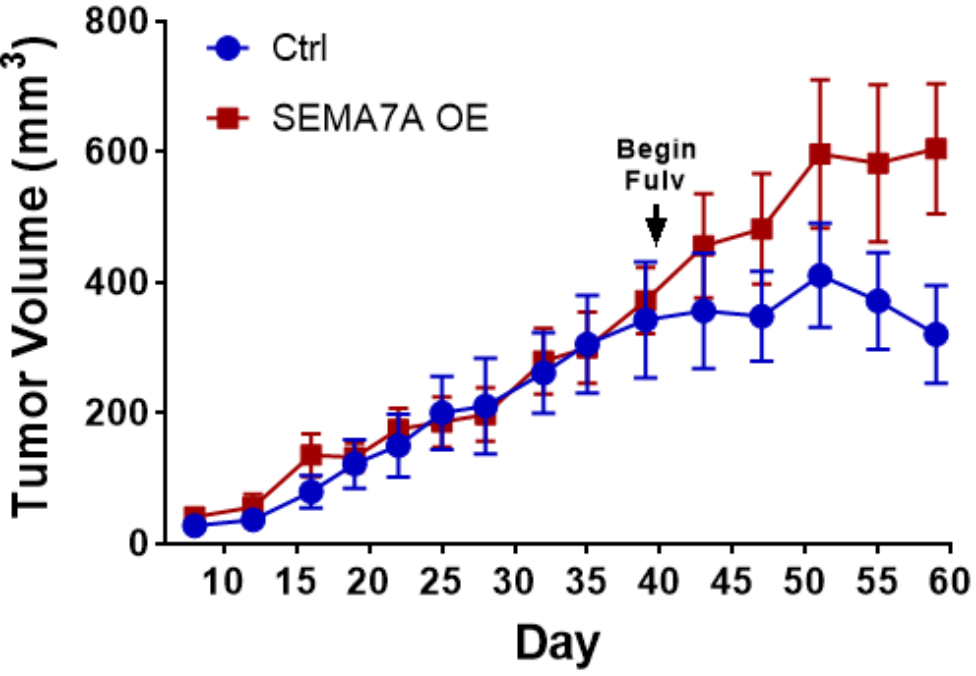
Kelsey Kines (CANB/MSTP)

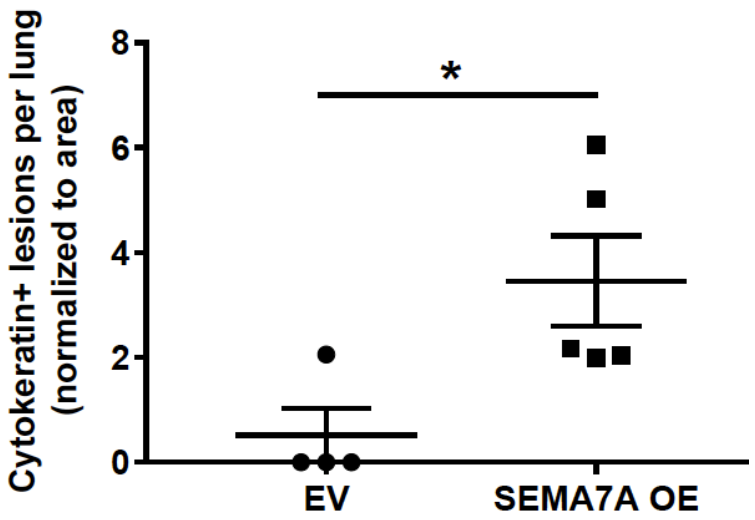
PPBCs and SEMA7A+ BC are resistant to endocrine therapy

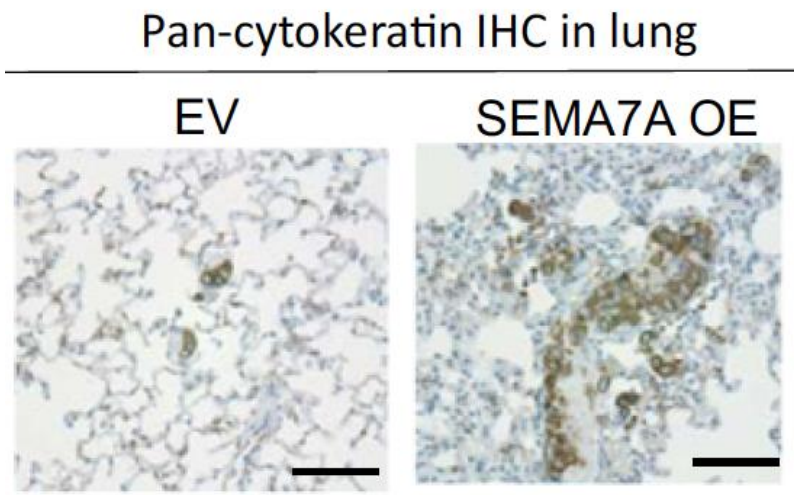




SEMA7A+ER+BC are resistant to endocrine therapy

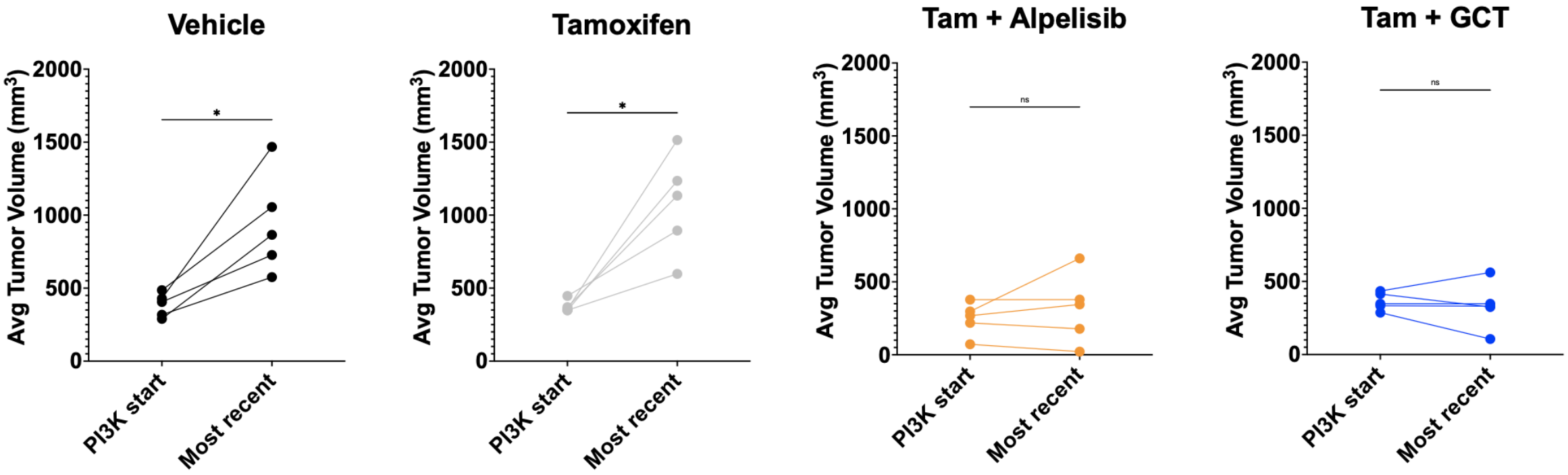






Lyndsey Crump, MS, PhD, Cancer Research 2020

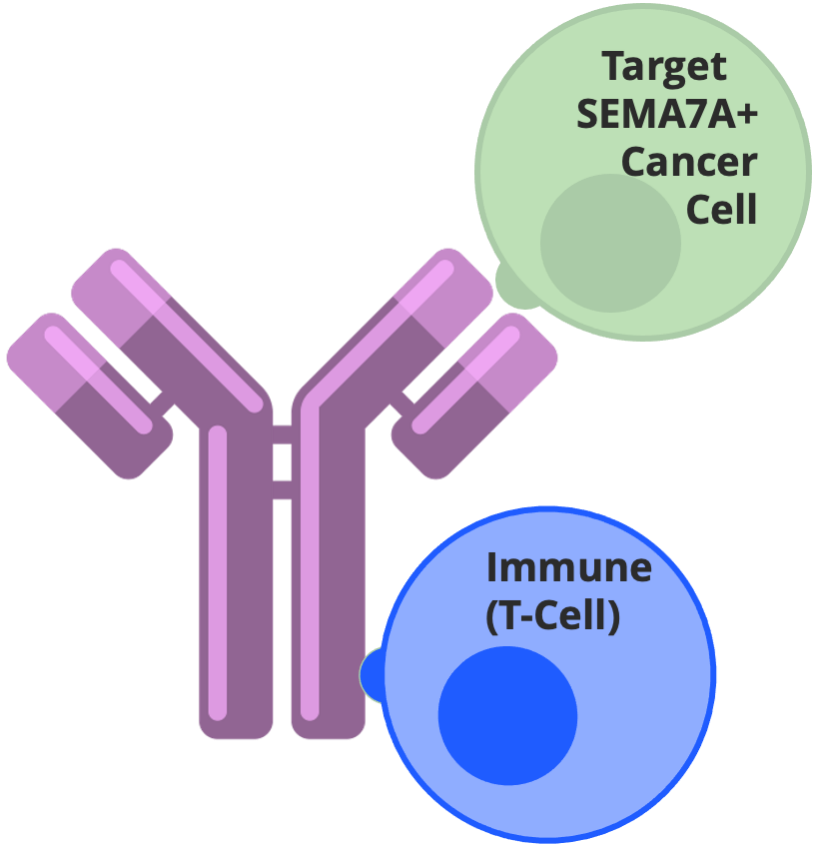
ER+SEMA7A+BC are sensitive to inhibitors of PI3K



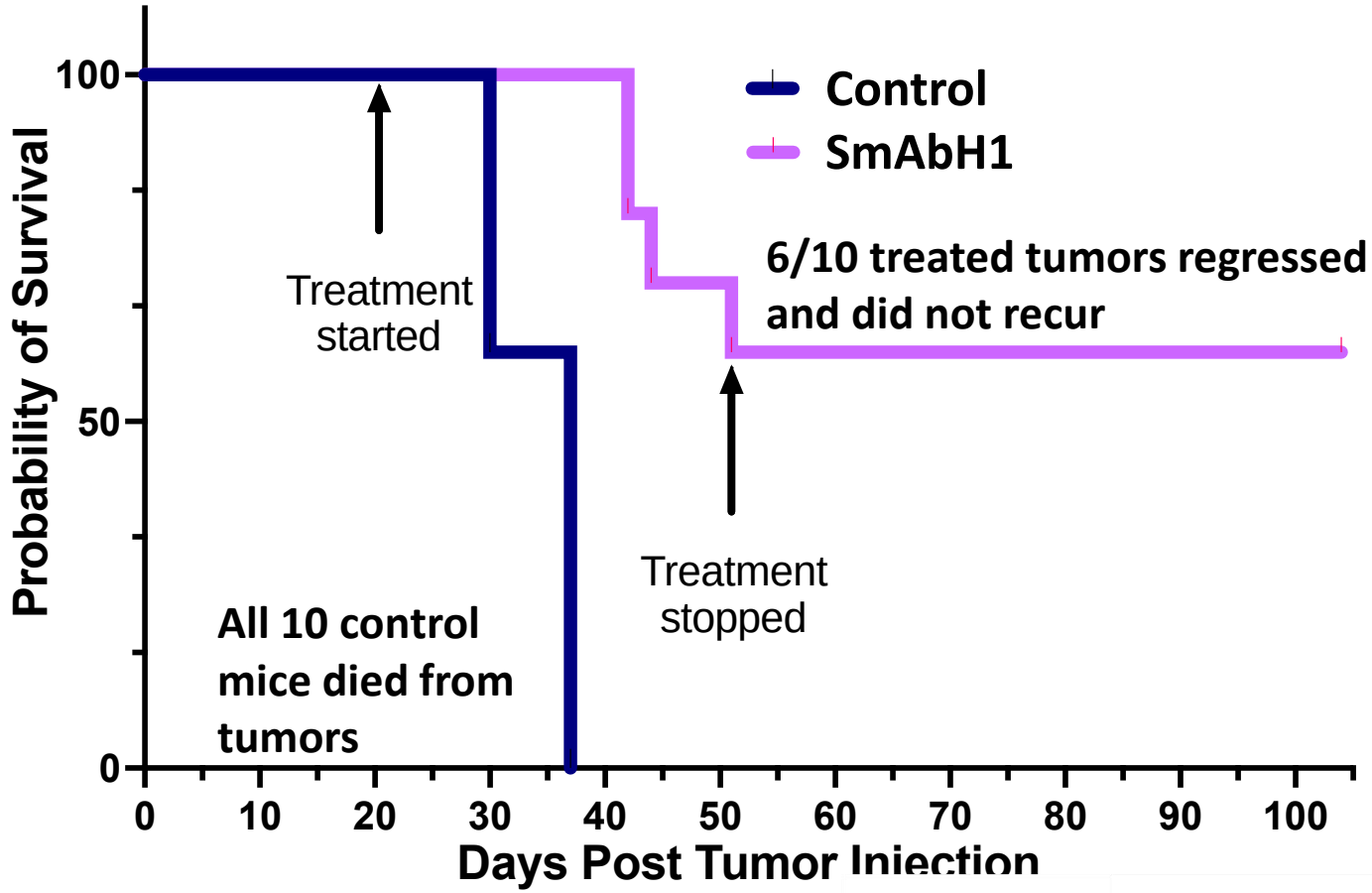
Rachel Steinmetz (CANB)

Can we directly target SEMA7A to improve outcomes for breast cancer patients?

SmAbH1 cures cancer in mice and prevents recurrence



SmAbH1 works like Her2 targeted therapy (such as Herceptin/trastuzumab) by both binding the target on the cancer cell and activating the immune system to attack.



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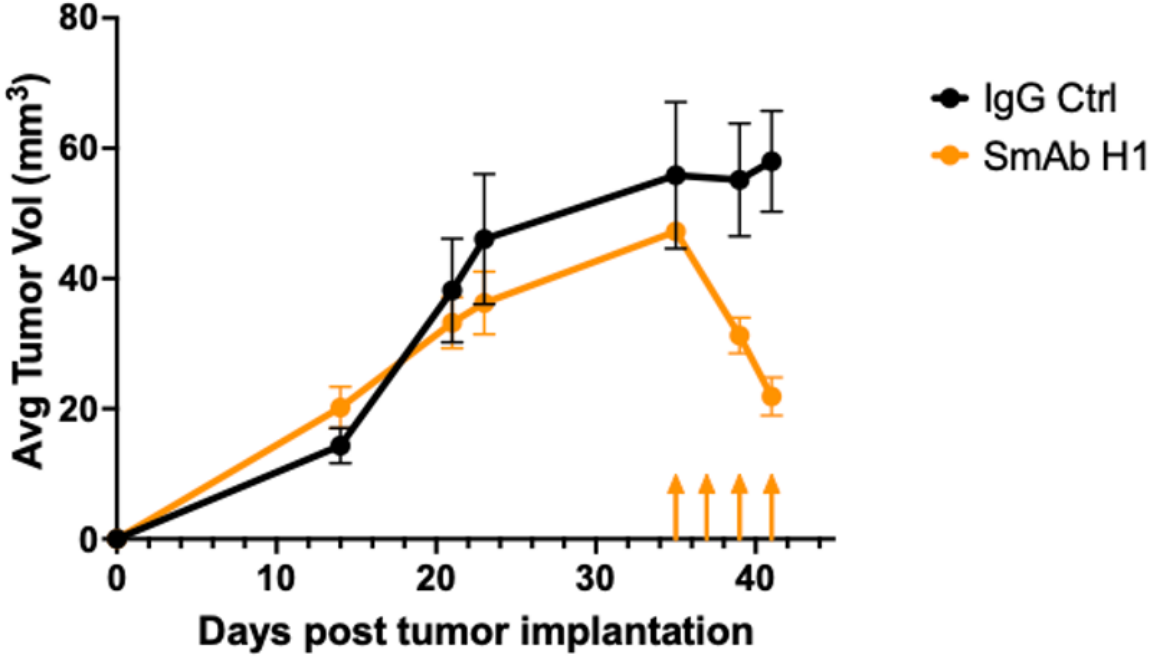
Alan Elder, PhD (CANB)

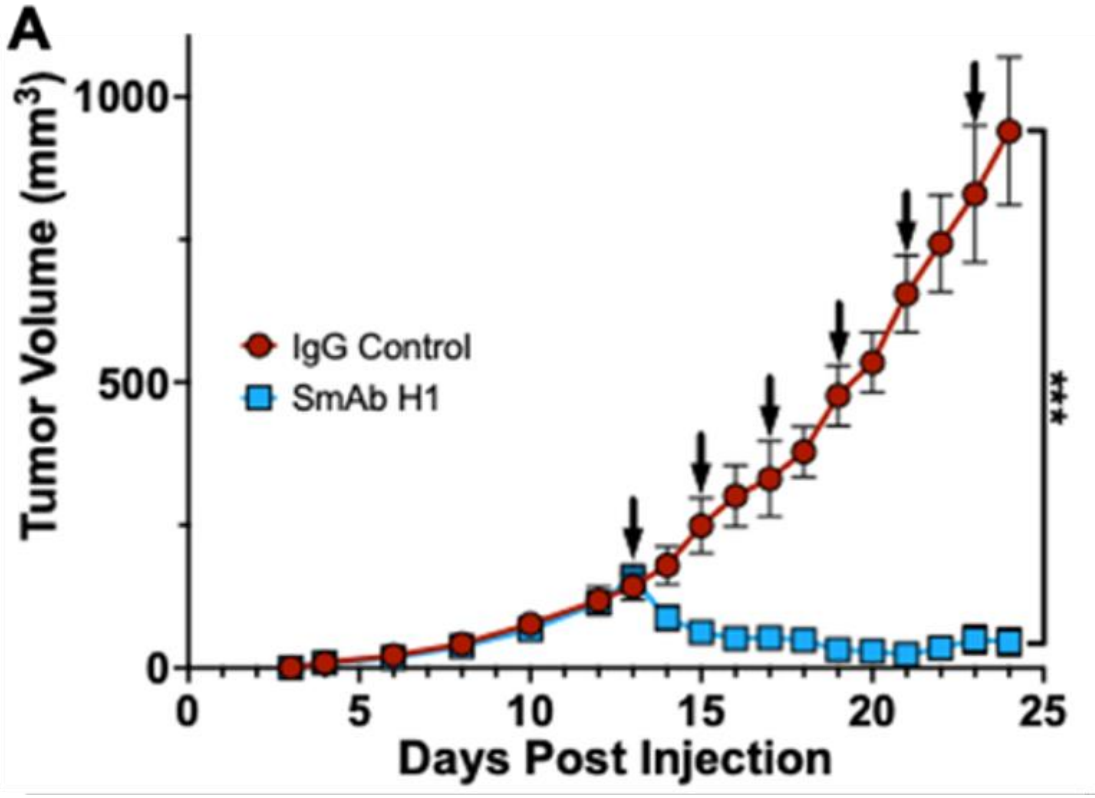
ER- and ER+ tumors are **sensitive to our monoclonal antibody.**

SSM2 cells (129)
(ER+ mouse mammary carcinoma)



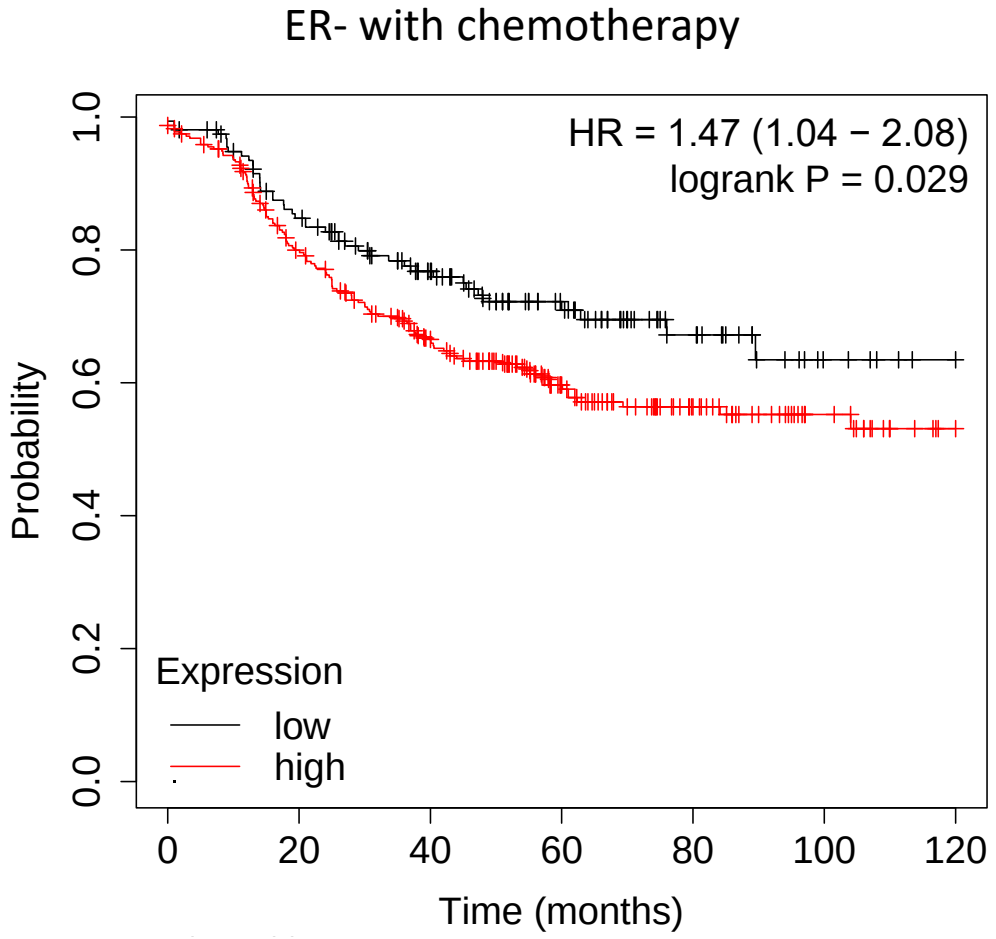
smab start = d+35
100ug/injection

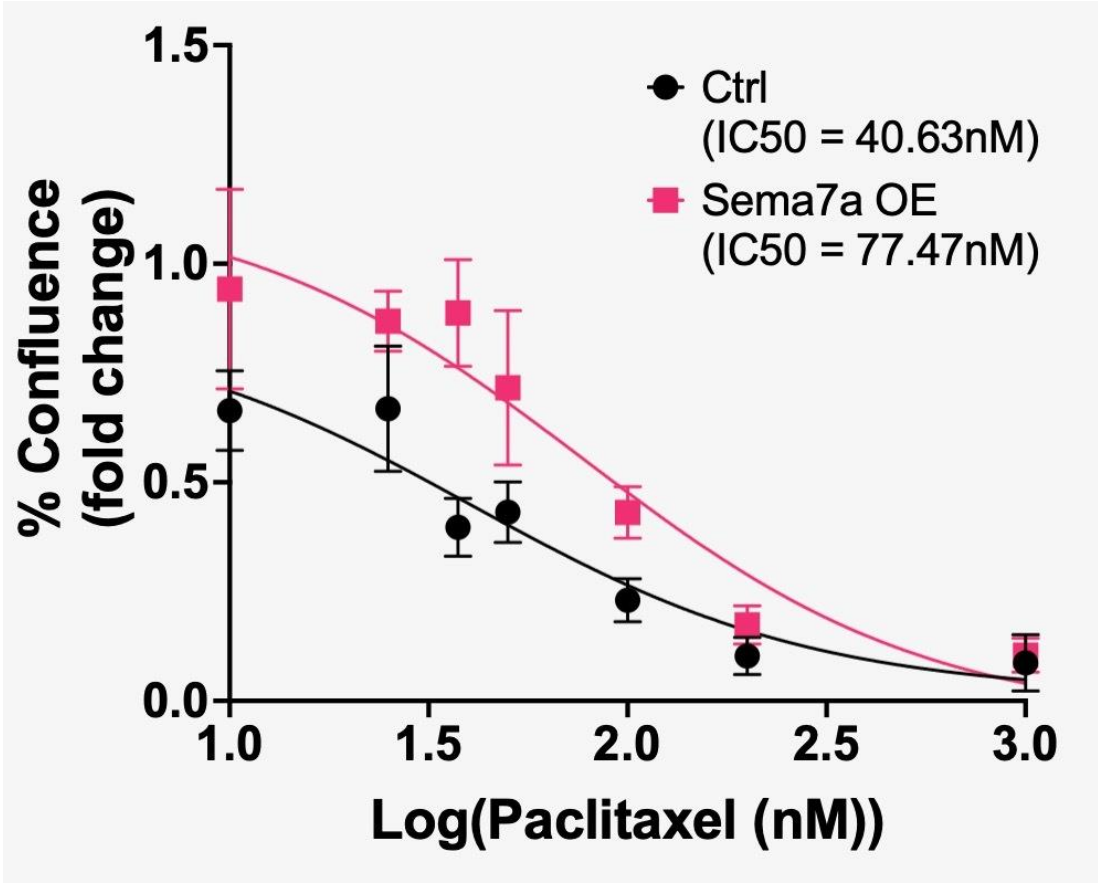
E0771 cells (C57)
(ER- mouse mammary carcinoma)



Alan Elder, PhD (CANB) and Rachel Steinmetz

SEMA7A+ER-BC are resistant to chemotherapy

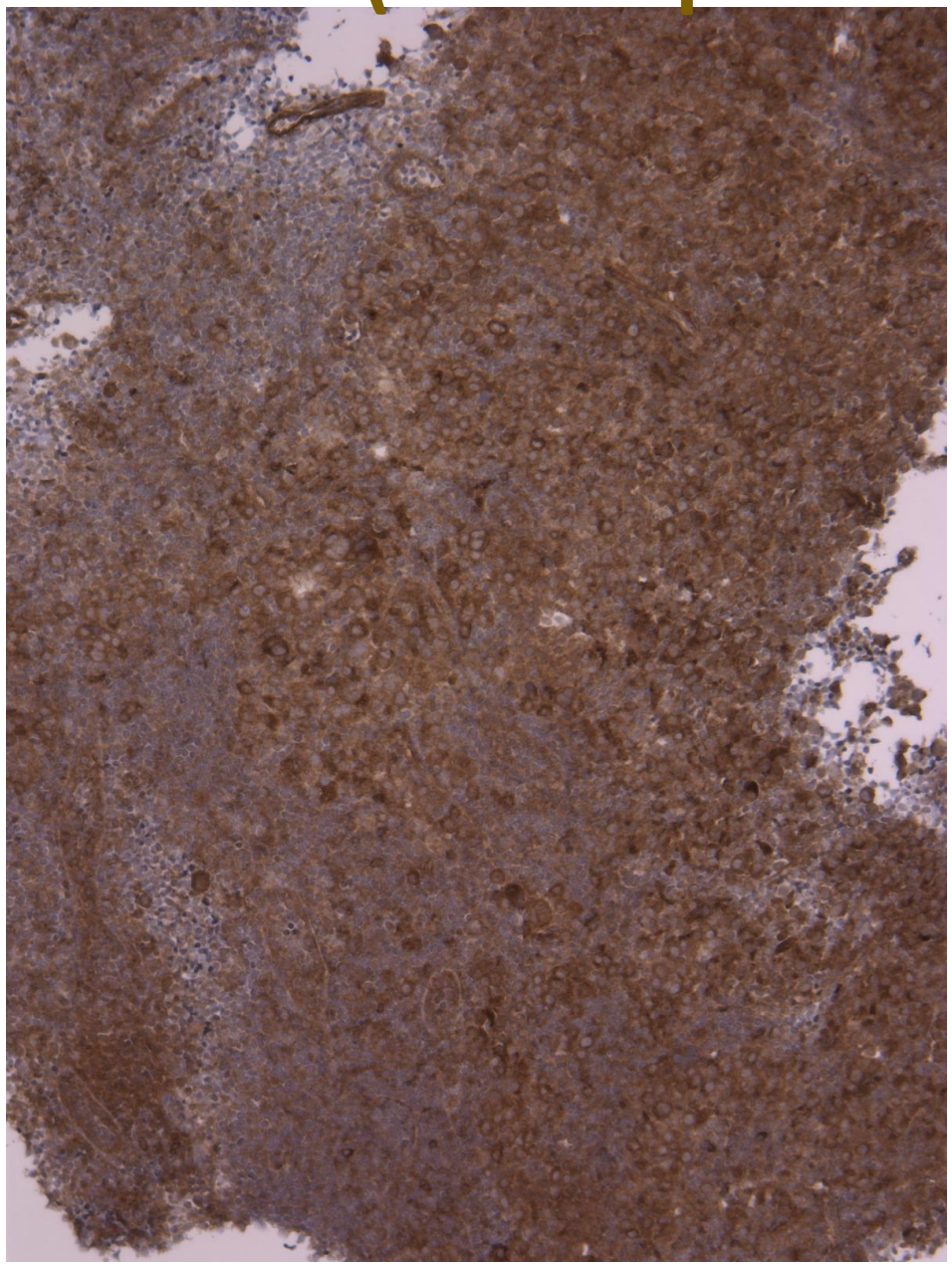




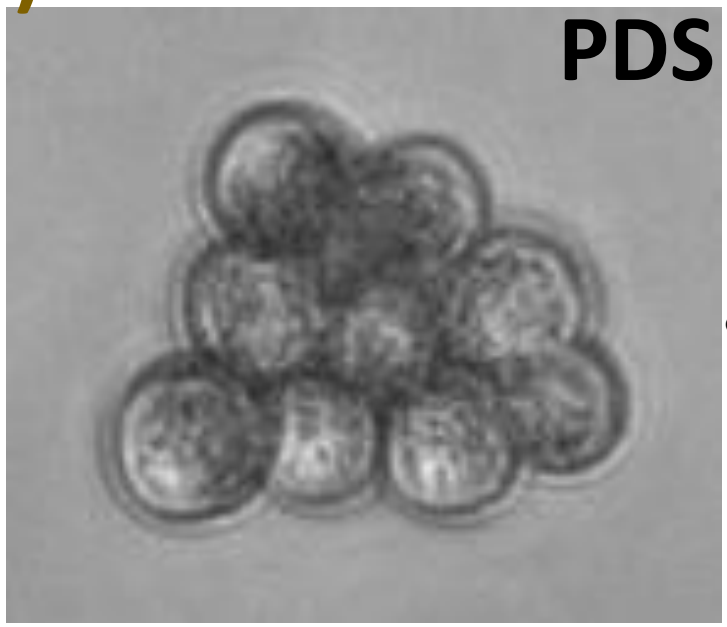
Black et al Oncogene 2016; Kelsey Kines, PhD (CANB/MSTP)

IMM618 (33 yr old, TNBC, chemo-, immuno and radio-resistant)

SEMA7A (~100% positive)



PDS



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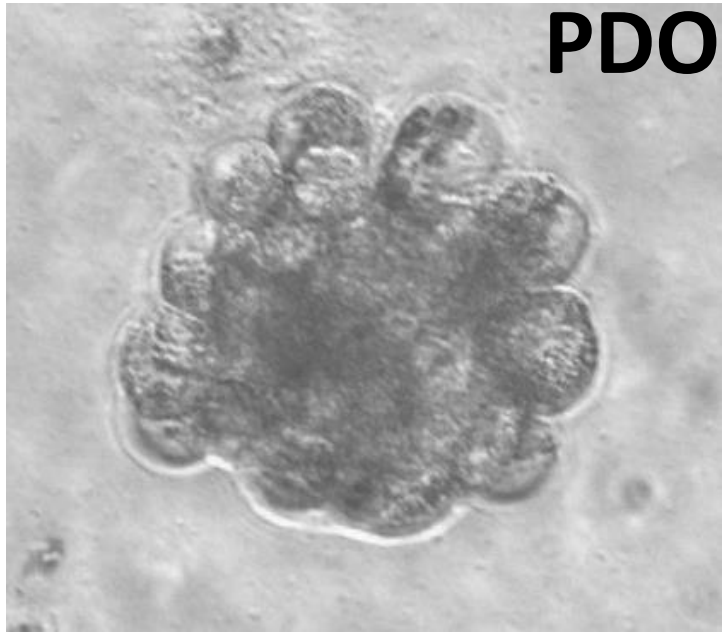

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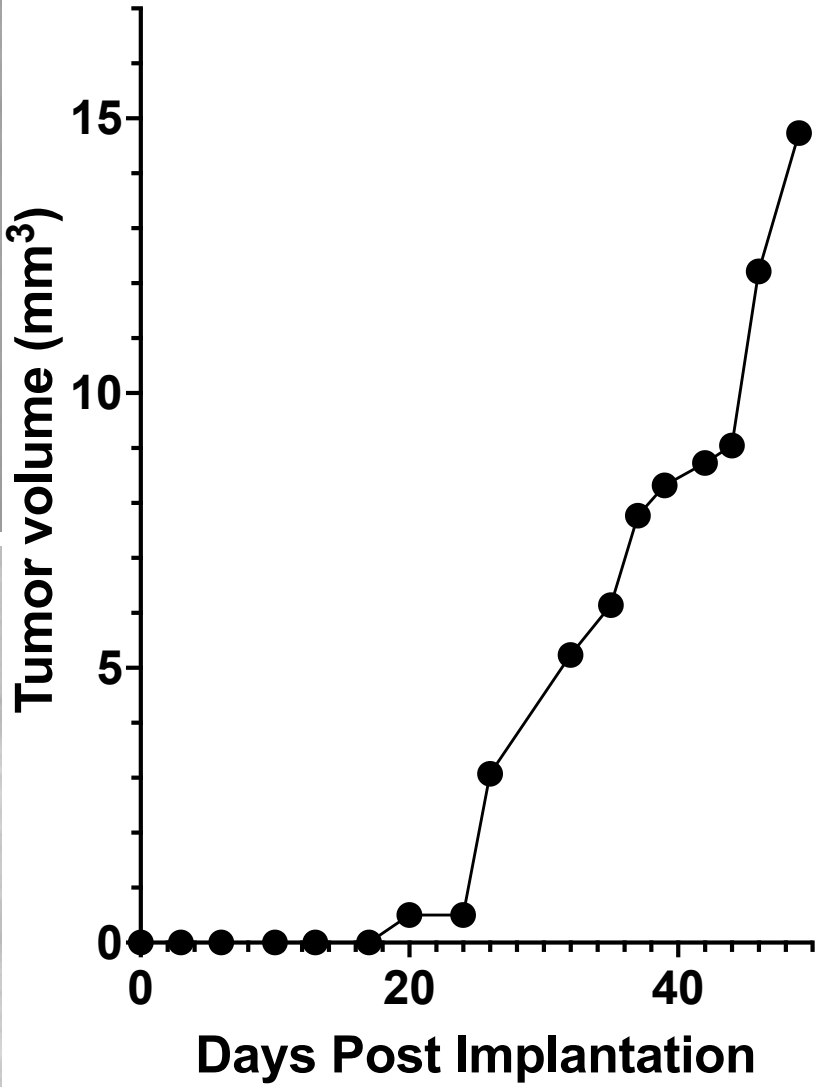
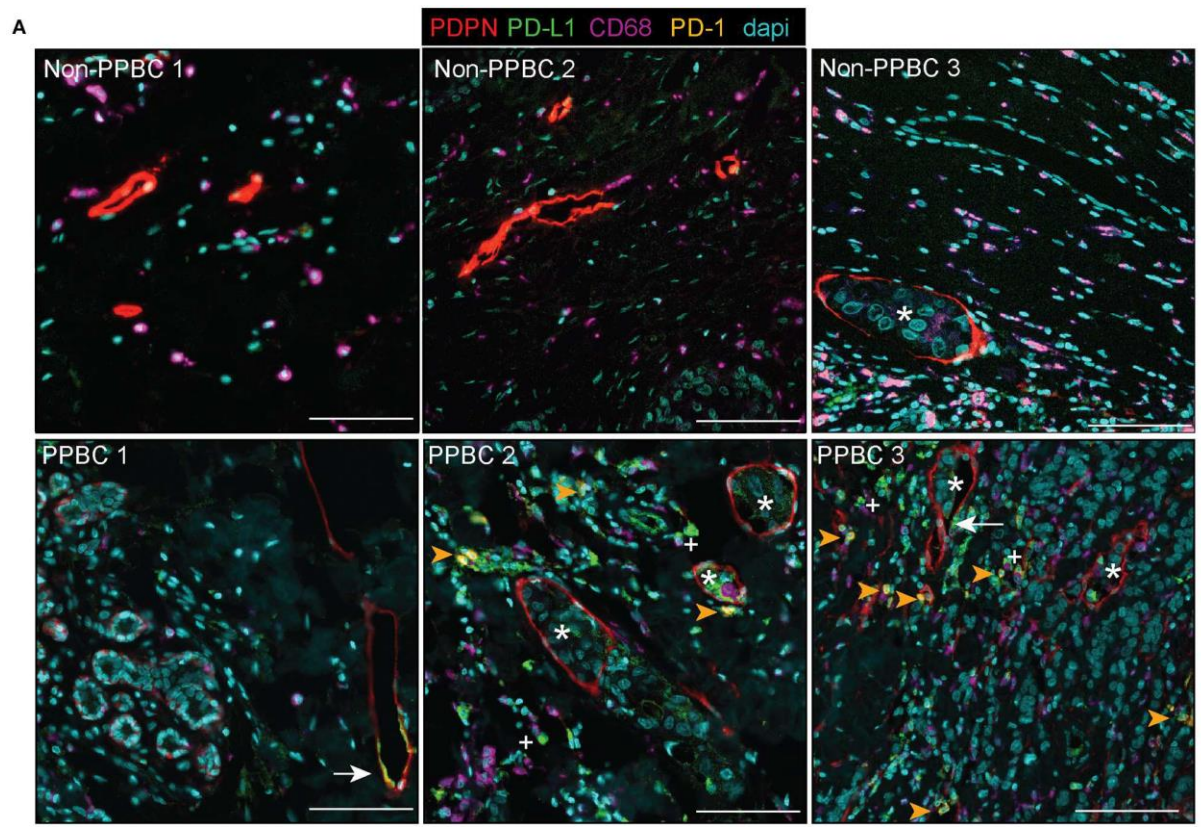


Lyons lab (unpublished)

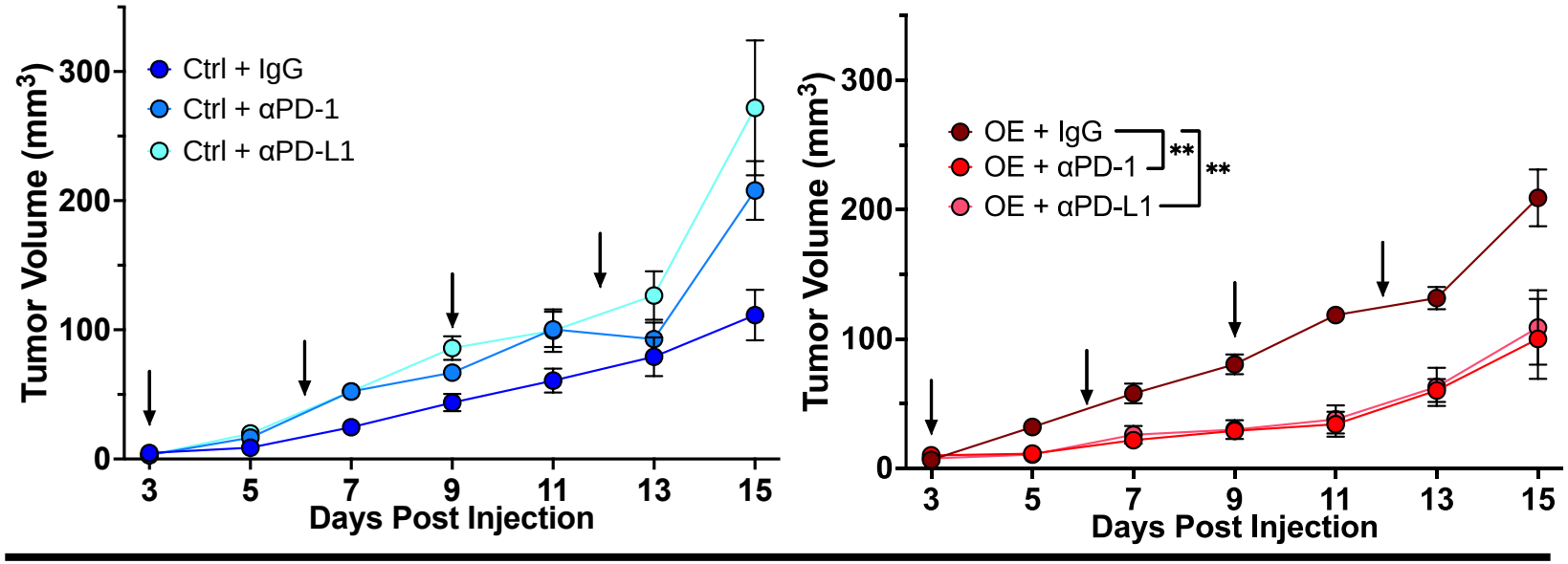
Breast cancer cells survive chemotherapy by activating targetable immune-modulatory programs characterized by PD-L1 or CD80

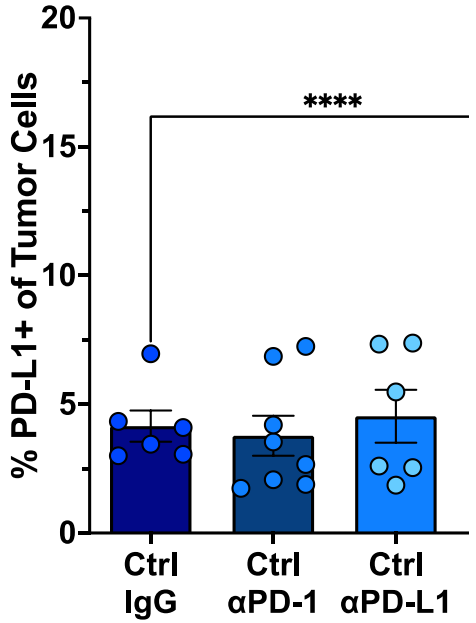
Ashkan Shahbandi, Fang-Yen Chiu, Nathan A. Ungerleider, Raegan Kvadas, Zeinab Mheidly, Meijuan J. S. Sun, Di Tian, Daniel A. Waizman, Ashlyn Y. Anderson, Heather L. Machado, Zachary F. Pursell, Sonia G. Rao & James G. Jackson

Nature Cancer **3**, 1513–1533 (2022) | Cite this article



SEMA7A promotes sensitivity/resistance to immune checkpoint blockade in vivo

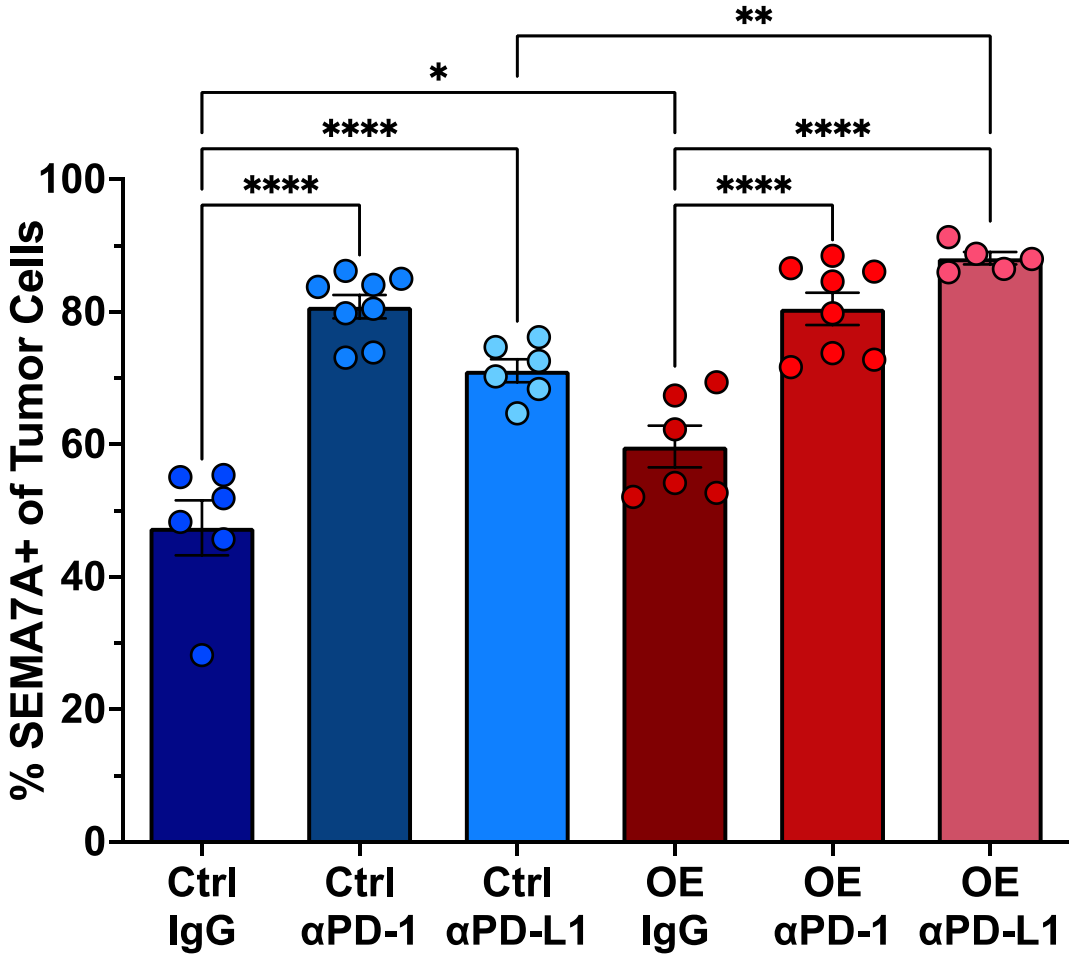


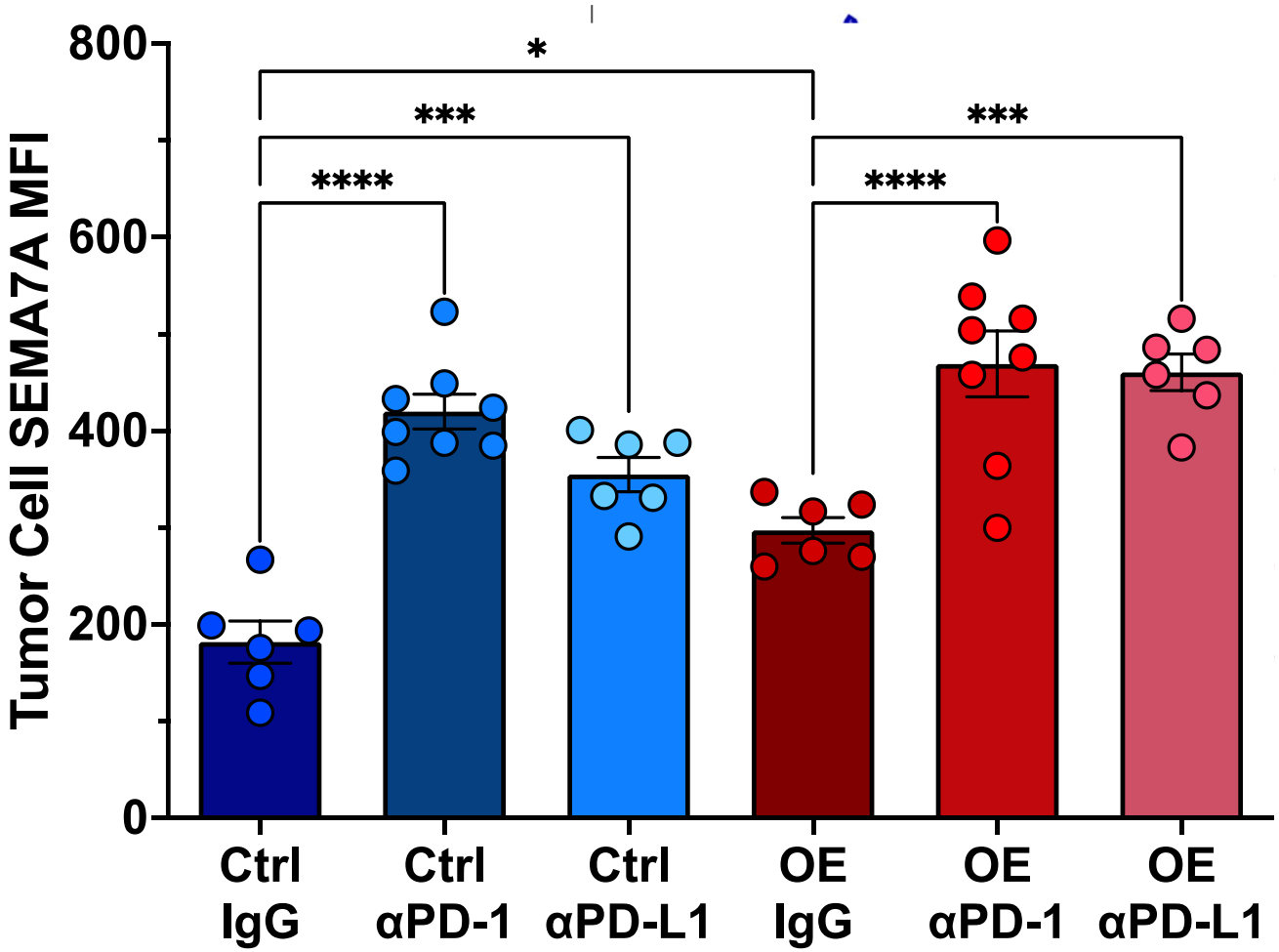


E0771 Tumor Cells
C57/Bl6 Mice

Alan Elder, MS (CANB)

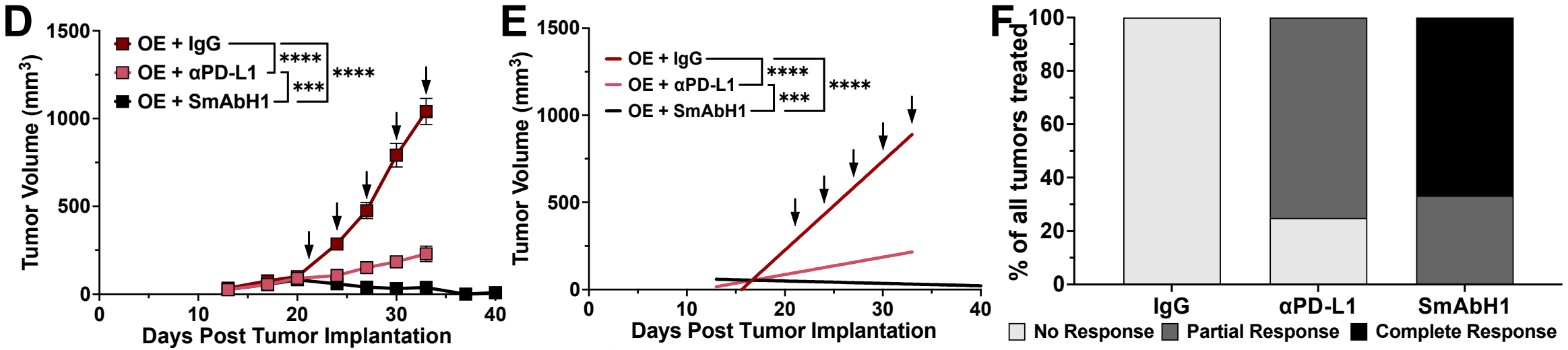
αPD-1/PD-L1 increases SEMA7A+ tumor cells





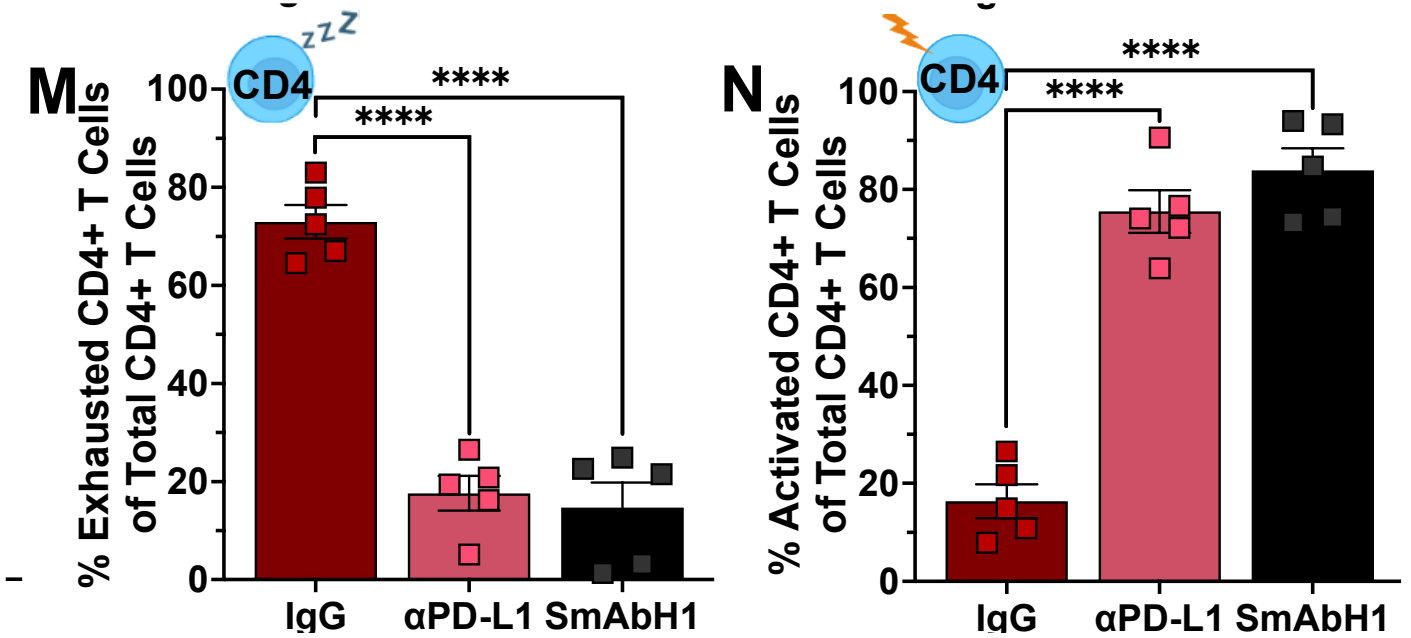
Alan Elder, MS (CANB)

Treatment with SmAb may be more efficacious than αPD-L1



SmAbH1 may work like immunotherapy

PD-1^{high}
Lag-3+
IFNγ–
TNFα–



PD-1^{mig}
Lag-3-
IFNγ+
TNFα+

Alan Elder, MS (CANB)

Conclusions

- PPBCs need novel treatment options based on the unique biology
  - The unique biology of PPBCs can inform studies of many treatment refractory breast cancers
- SEMA7A is a potential novel target that is predictive, prognostic and druggable
- **Our novel monoclonal antibody may be a solution for PPBC patients and all patients that are SEMA7A+ (~47% of all BC)**

PearlSci

https://www.bigwheelpress.com/products/semaphore-thank-you-mini

Lyons Lab

Alan Elder, MS, PhD (CANB)
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Petra Dahms (CANB)
Kelsey Kines, PhD (CANB/MSTP)
Rachel Steinmetz (CANB)
Heather Fairchild, MS, MBA (PRA)
Veronica Wessells (PRA)
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Taylor Wallace, PhD
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Sarah Black (PRA)
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Jill Slansky, PhD
Steve Anderson, PhD
UCCC Tissue Biobank

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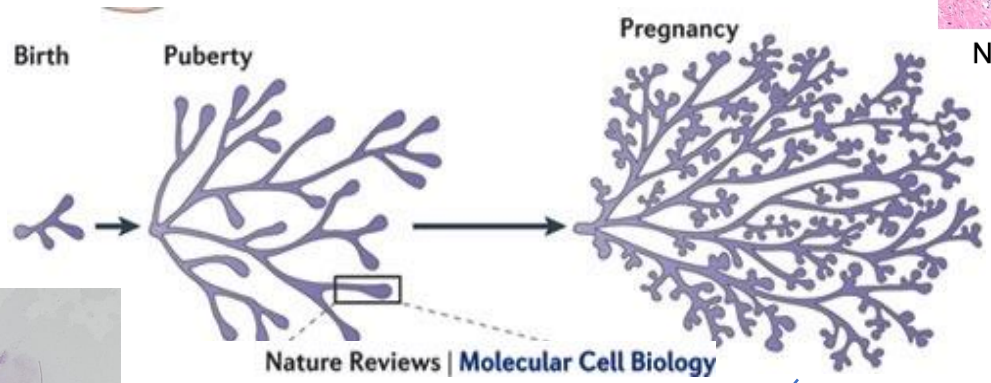
ABN Ohana Gates Grubstake Award

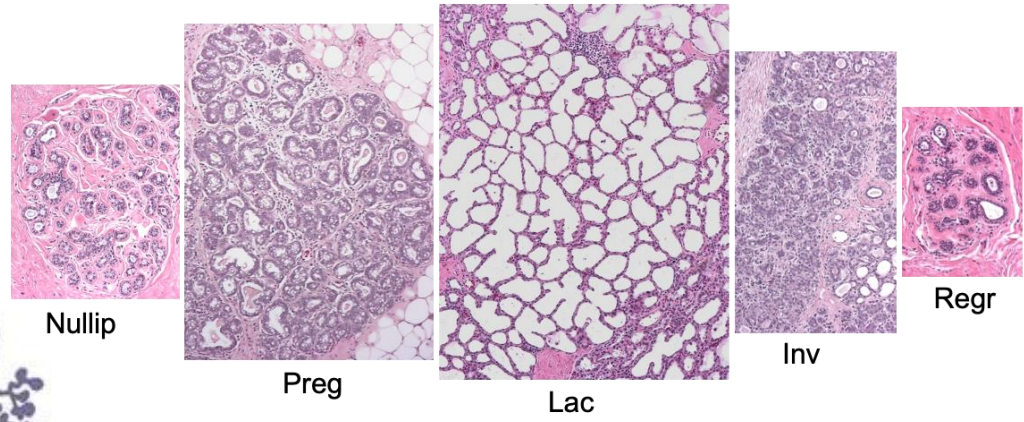
NIH/NCI Cancer Center Support Grant P30CA046934 and the Colorado CTSI UL1 RR025780 **Additional support provided by The Young Women's Breast Cancer Translational Program, UCCC, Gates Center, Department of Medicine (OECSP and ASPIRE), and Division of Medical Oncology**

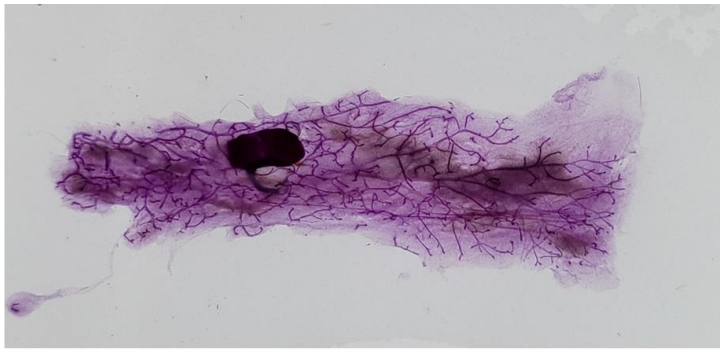
NIH

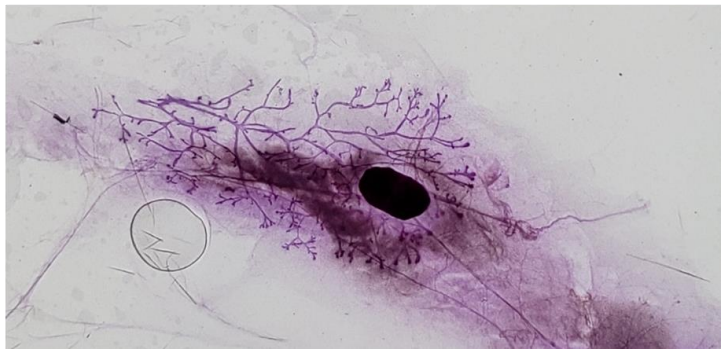
NICHD

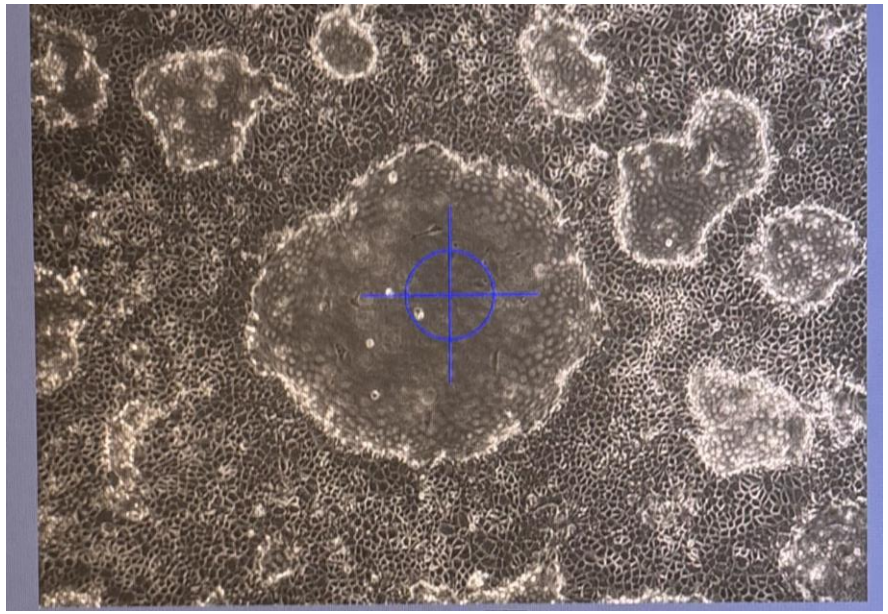
Studies of normal mammary development











Petra Dahms (CANB)

Lauren Cozzens (CANB)

The contribution of differences in breastfeeding duration and age at first birth to racial disparities in TNBC incidence

Lajos Pusztai, M.D., D.Phil. (Yale Cancer Center)

On behalf of

Rachel Jaber Chayeb, M.D. (now at U. Penn) and Nicole Odzer (Yale School of Medicine class 2025)

Pusztai Disclosure

Personal financial interests:

Honoraria and Consulting fees from Pfizer, Merck, Astra Zeneca, Bristol Myers Squibb, Novartis, Personalis, Exact Sciences, Radionetics, Natera

Institutional financial interests:

Clinical trial or research funding from Pfizer, Merck, AstraZeneca, Seagen, Bristol Myers Squibb, Menarini-Stemline, Exact Sciences

Age-adjusted incidence rates of TNBC are higher in Black than in White women, TNBC account for a greater proportion of breast cancers in Black versus White women (19-28% vs 9-14%)*

Suggested Causes		Caveats
• Genetic – Duffy Antigen Receptor for Chemokines (Atypical Chemokine Receptor 1) DARC/ACKR1 rs2814778 SNP *(Newman LA et al. Annals Surg. 2019;270:484-92)* – Ancestry-specific polygenic risk score (*Hughes E et al. JCO Precision Oncology. 2022;6:e2200084*)	→	Weak effect Large genetic variation within Africa Population admixture
• Environmental – Hair dye and relaxing agents *(Llanos AA, et al. Carcinogenesis. 2017;38:883-92)* – Regular alcohol intake *(Howard FM, Olopade OI. The Cancer Journal. 2021;27:8-16.)*	→	Contradictory literature, limited biological plausibility Small effect Lack of subtype-specific effect
• Risk factor distribution – Breast Feeding *(Islami F, et al. Ann Oncol. 2015;26:2398–2407)* – Pregnancies *(Yang XR, et al. J Natl Cancer Inst. 2011;103:250–263)*	→	Variable effect sizes

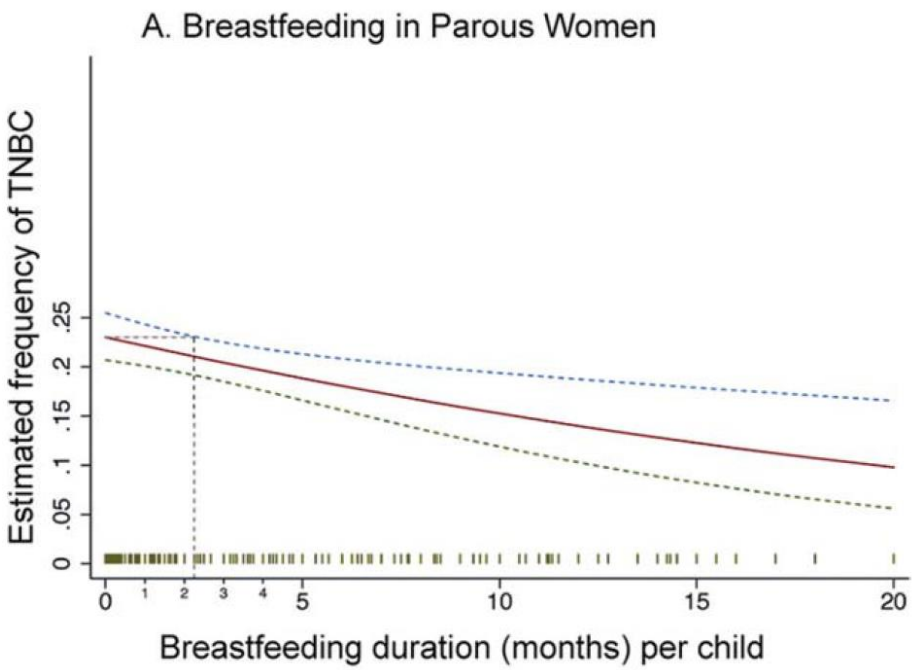
* Kong X, et al. Variation in breast cancer subtype incidence and distribution by race/ethnicity in the United States from 2010 to 2015. JAMA Network Open 3:e2020303, 2020

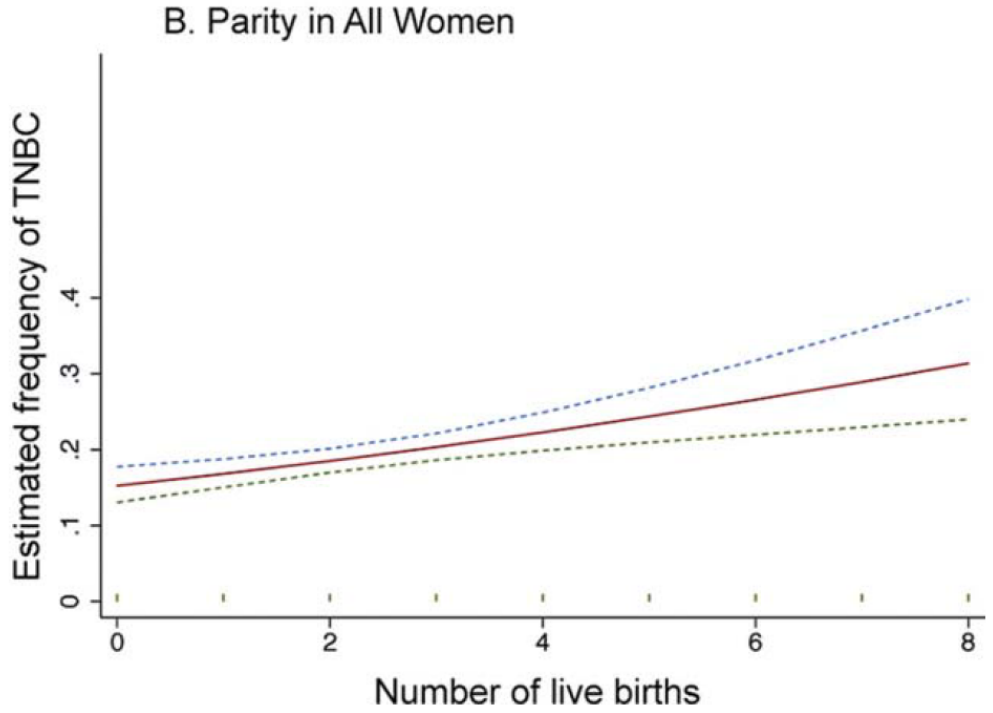
Original Article *Cancer* 2010;116:4933–43.

Higher Parity and Shorter Breastfeeding Duration

Association With Triple-Negative Phenotype of Breast Cancer

Shivani S. Shinde, MD[1,2]; Michele R. Forman, PhD[2,3]; Henry M. Kuerer, MD, PhD[4]; Kai Yan, PhD[5]; Florentia Peintinger, MD[1,4]; Kelly K. Hunt, MD[4]; Gabriel N. Hortobagyi, MD[6]; Lajos Pusztai, MD, DPhil[6]; and W. Fraser Symmans, MD[1]





Black women have lower rates of breastfeeding and are younger at first birth than White women in the USA

USA CDC National Immunization Survey Breast Feeding prevalence and trends (https://www.cdc.gov/breastfeeding/data/nis_data/results.html):
74% of Black women report having ever breastfed and 44% continue to breastfeed for 6 months, compared to 85% and 60% respectively, for White women(16).

Socio-demographic Factors	Any Breastfeeding				Exclusive Breastfeeding		
	n	Ever Breastfed Mean ± ½ of 95% Confidence Intervals	Breastfed at 6 months Mean ± ½ of 95% Confidence Intervals	Breastfed at 12 months Mean ± ½ of 95% Confidence Intervals		Exclusive Breastfeeding through 3 Months Mean ± ½ of 95% Confidence Intervals	Exclusive Breastfeeding through 6 Months Mean ± ½ of 95% Confidence Intervals
US National	20906	83.2 ± 1.0	55.8 ± 1.3	35.9 ± 1.2	20217	45.3 ± 1.3	24.9 ± 1.1
Race/Ethnicity							
Hispanic	3991	83.0 ± 2.3	51.4 ± 2.9	33.2 ± 2.7	3903	43.8 ± 2.9	23.5 ± 2.5
Non-Hispanic White	11465	85.3 ± 1.3	59.9 ± 1.7	39.4 ± 1.6	11060	49.0 ± 1.7	26.9 ± 1.5
Non-Hispanic Black	2144	74.1 ± 3.7	44.0 ± 3.7	24.1 ± 2.8	2075	36.3 ± 3.5	19.1 ± 2.8
Non-Hispanic Asian	1119	90.8 ± 2.9	70.2 ± 4.9	45.7 ± 5.1	1076	42.5 ± 5.1	28.5 ± 4.5

USA CDC National Survey of Family Growth 2015-2019 (https://www.cdc.gov/nchs/nsfg/index.htm):
77% of Black women are < 25 years of age at first birth
51% of White women are < 25 years of age at first pregnancy

Raju TN. Achieving healthy people 2030 breastfeeding targets in the United States: challenges and opportunities. Journal of Perinatology. 2023 Jan;43(1):74-80.

Aim

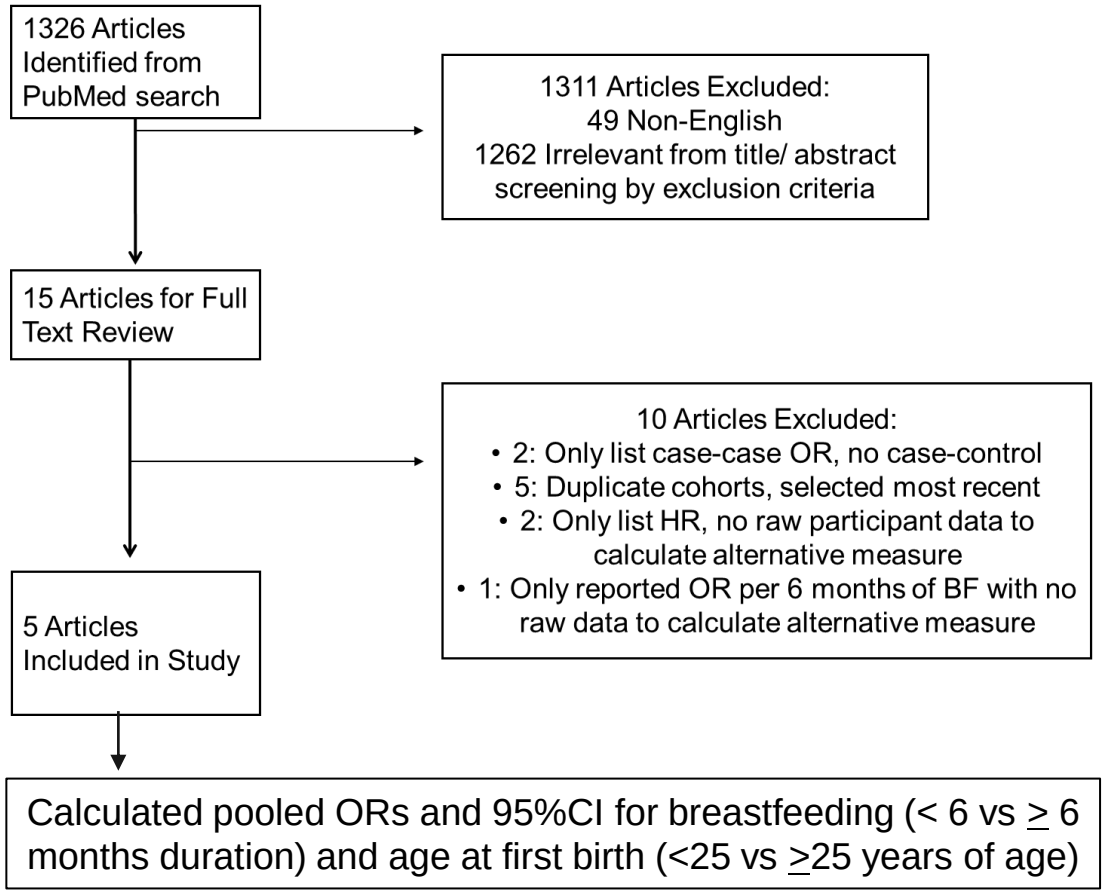
To determine to what extent differences in the prevalence of reproductive risk factors contribute to differences in TNBC incidence between Black and White women through calculating the population attributable fraction (PAF) of short breastfeeding duration and younger age at first birth

Population attributable fraction (PAF) is the proportion of disease that is due to a particular risk factor exposure in a population

Research Strategy

PubMed search inclusion criteria:

i) prospective cohort or case-control study in the US
ii) examine breastfeeding risk in relation to TNBC
iii) report odds ratio (OR), relative risk (RR), or hazards ratio (HR)



PAF Calculation

PAF = "PRF × (RR−1)" /"1+PRF ×(RR−1)"

PRF is the % population prevalence of a risk factor
- Breastfeeding estimates were from the **CDC's National Immunization Survey**
- Parity and age at first birth were from the **National Survey of Family Growth**

RR is relative risk approximated by pooled OR from the literature

Combined PAF = 1 – (1 – v(i)PAF1) × (1 – v(i)PAF2)) where
v(i)=1- r, and r is the polychoric correlation coefficient between breast feeding duration and age at first birth

Pooled Odds Ratios for TNBC risk and breastfeeding and age at first birth in Black and White women, respectively

		Risk Factors	
Subgroup		Breastfeeding <6 m	Age at first birth <25
White	**Pooled OR (95% CI)**	1.41(1.15,1.74)	1.06(0.86,1.29)
	I^2 %	67	84
	P^a	0.05	<0.01
Black	**Pooled OR (95% CI)**	1.35(1.06,1.73)	1.39(1.08,1.78)
	I^2 %	0	84
	P^a	0.59	0.01
Overall	**Pooled OR (95% CI)**	Common: 1.39(1.18,1.63) Random: 1.42(1.16,1.75)	Common: 1.19(1.01,1.39) Random: 1.19(0.84,1.69)
	I^2 %	38	81
	P^a	0.17	<0.01

I^2 = heterogeneity
Common = common effect mode, R package *meta*
Random = random effect model, R package *meta*

Population Attributable Risk for TNBC from breastfeeding, age at first birth, and combined in Black and White women, respectively

Risk Factor	White PAF (95% CI)	Black PAF (95% CI)
Breastfeeding < 6 m vs >= 6 m	12(5,20)	15(3,26)
Age at first birth <25	2(-6,11)	21(5,35)
Combined PAF	12	26.7

Conclusion

- We estimated that of all TNBC diagnosed in 2022, 4,850 (17% of 28,785 total) were attributable to breastfeeding shorter than 6 months and/or age at first birth younger than 25.
  - In 2022, **12% of TNBC in White women (n=2,421**) can be attributed to breastfeeding less than 6 months and/or age at first birth less than 25.
  - In 2022, **27% of TNBC in Black women (N=1,533**) can be attributed to breastfeeding less than 6 months and/or age at first birth less than 25.

- Policy changes aimed at supporting and more broadly enabling breastfeeding, addressing structural barriers, and promoting a culture shift could reduce the overall incidence and racial disparities in TNBC incidence in the USA.

- Increasing awareness of the protective role of breastfeeding, improving workplace policies, and limiting the lobbying power of formula companies might increase breastfeeding rates and duration leading to healthier infants and fewer breast cancers.

Acknowledgements

Breastfeeding and Triple Negative Breast Cancer in the US: Preventable Fractions Estimated from Survey Data

Running Head: breastfeeding and racial disparities in TNBC incidence

Rachel Jaber Chehayeb, BS[1], Nicole Odzer, BS[1], Roberta A. Albany[2,3], Leah Ferrucci, PhD[4], Daniel Sarpong, PhD[5], Rafael Perez-Escamilla, PhD[4], Jessica B. Lewis, PhD[5], Amanda I. Phipps, PhD,[6,7] Allison Meisner, PhD[7], Lajos Pusztai, MD, DPhil[1,8*]

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Manuscript under review. npjBreast. 2024 Special section on Health Care Disparities

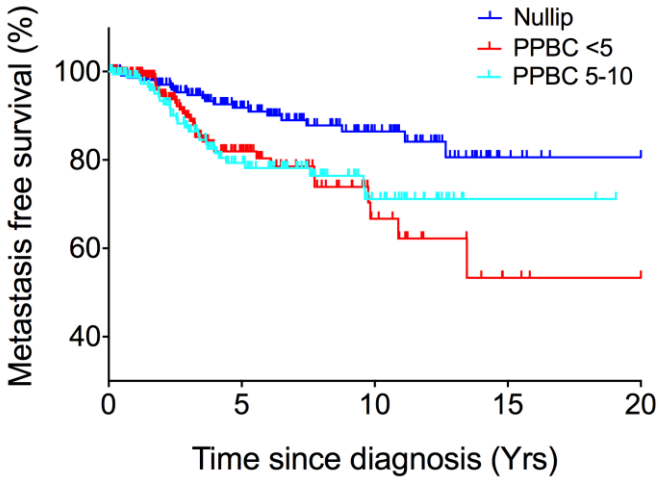
Postpartum Liver Biology
Implications for BrCa Metastasis and Response to Therapy

RISE UP for Breast Cancer Conference
University of California San Francisco
November 1-3, 2024

Pepper Schedin, PhD, Knight Cancer Institute, OHSU,
Portland, Oregon, November 3, 2024

OHSU

Postpartum Breast Cancer-High Risk of Metastasis

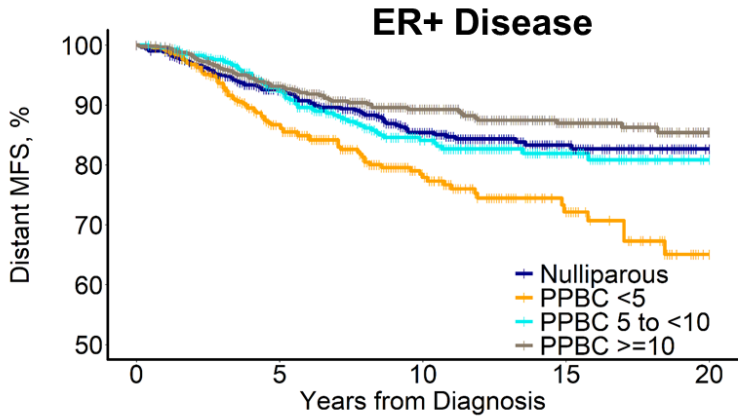


Virginia Borges, MD

Traci Lyons

Erica Goddard

Goddard et al, JAMA Network Open, 2019
n=701 YWBC



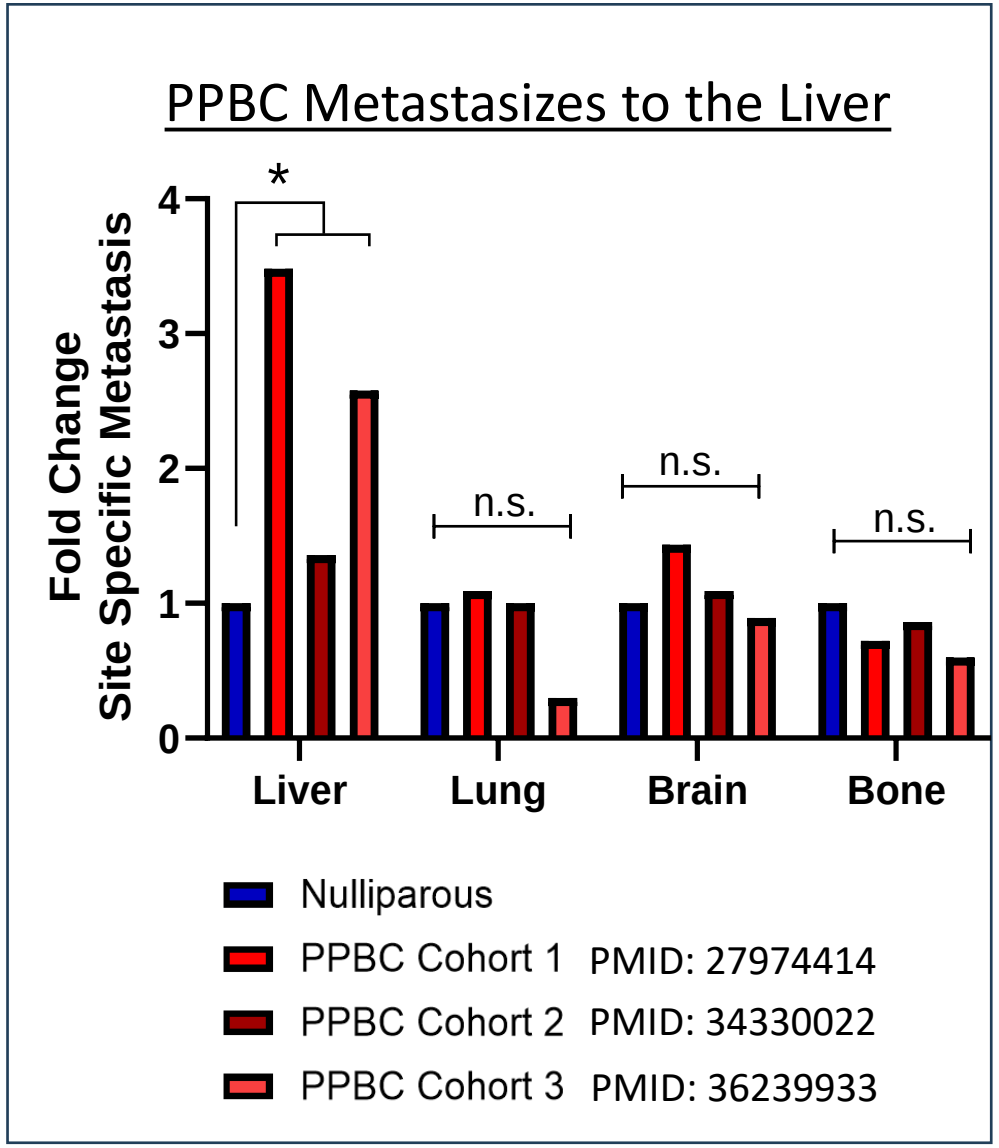
Number at risk

Nulliparous	637	460	266	134	48
PPBC <5	437	291	139	62	16
PPBC 5 to <10	467	323	181	87	32
PPBC >=10	662	456	278	172	64

Ken Smith, UPDB

Zhenzhen Zhang

Zhang et al, JAMA Netw Open, 2022
n=2970 YWBC



Why is PPBC at increased risk for liver metastasis?

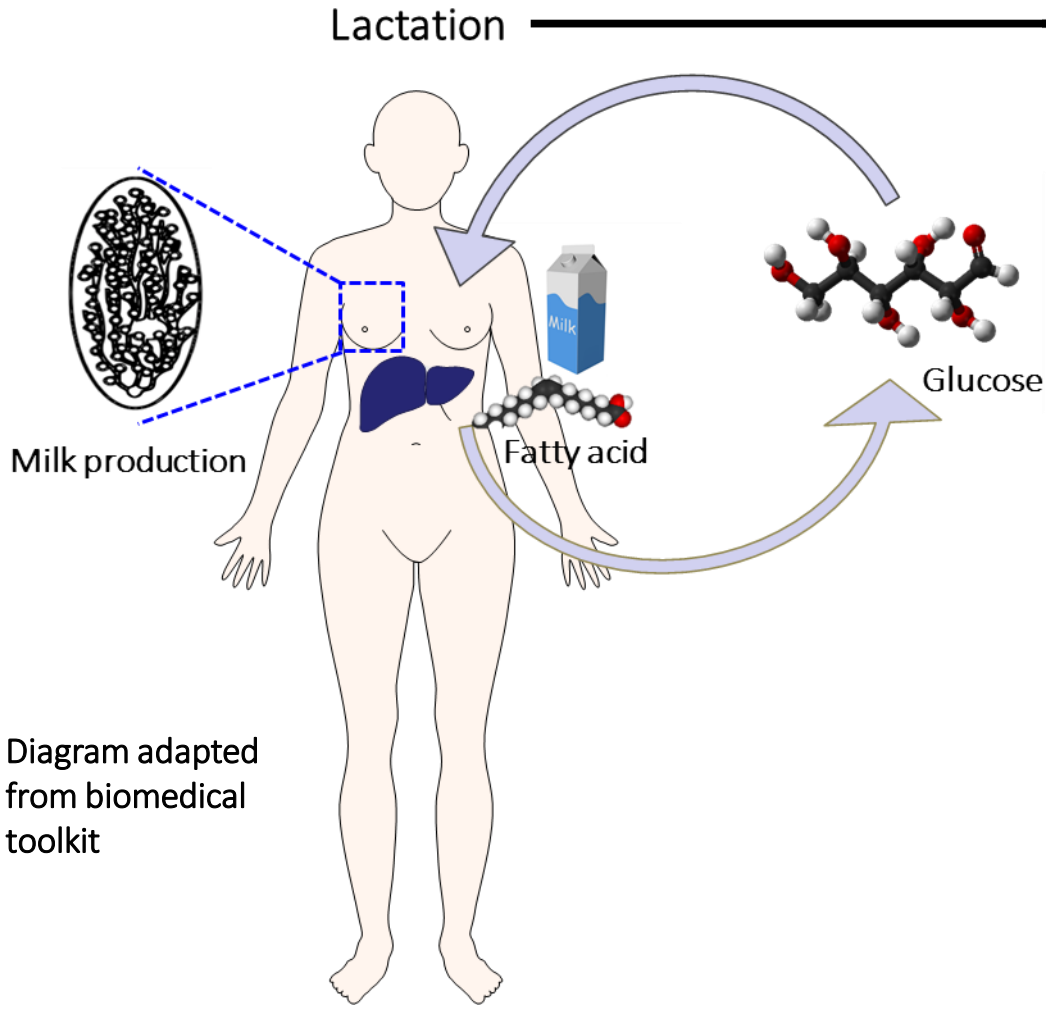
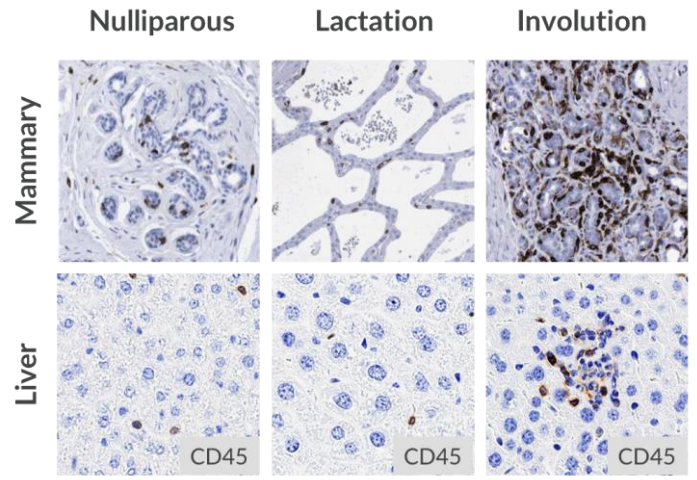


Diagram adapted from biomedical toolkit

<u>Involution</u>

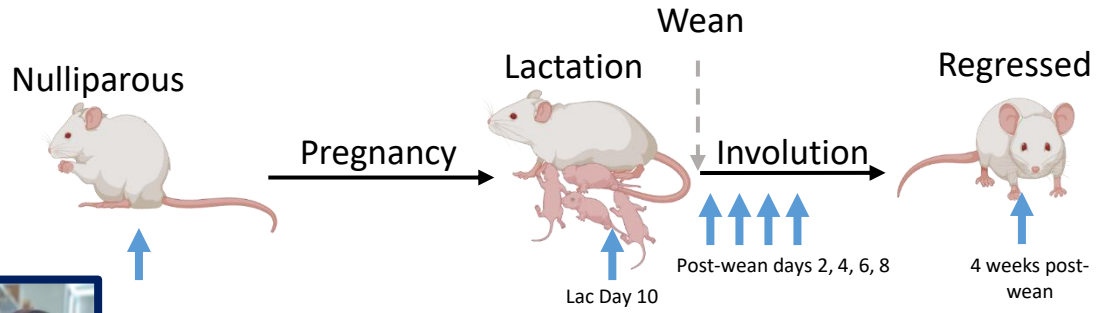
- Tumor Promotional
- Stromal activation
- Immune Suppression

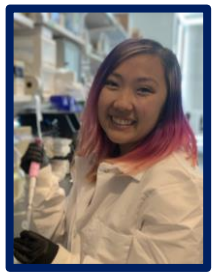


Pennock et. al. (2018) J Immunotherapy Cancer & unpublished liver images.

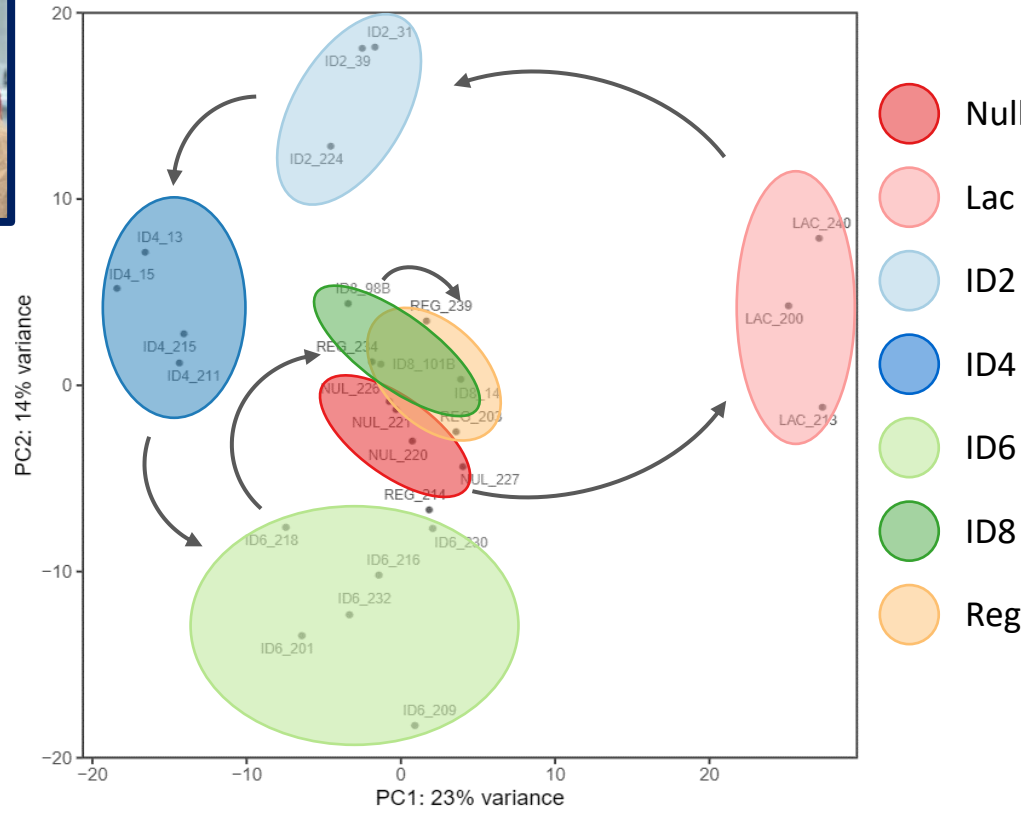
Schedin lab: Goddard et al., Cancer Discovery 2017; Bartlett et al., Cancers 2021, Bartlett et al, PNAS 2021; Zhang, JAMA Netw Open 2022

Liver Biology & Metastatic Niche change with Reproductive State

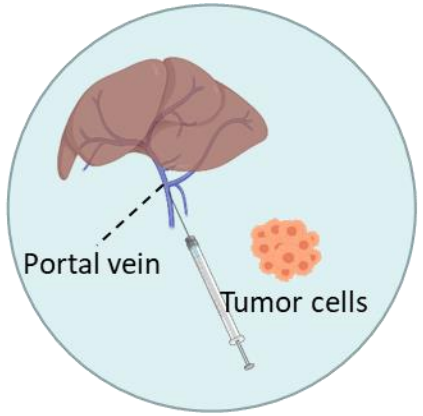


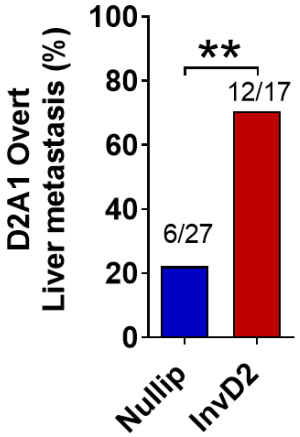


Michelle Ozaki

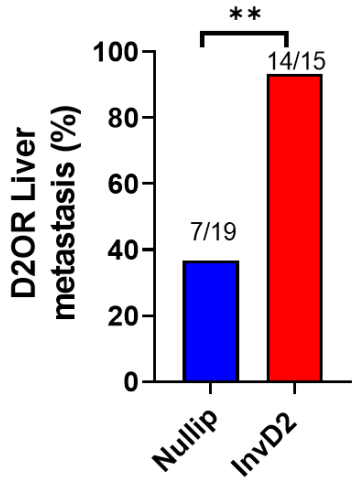


Michelle Ozaki et al, BioRxiv 2024

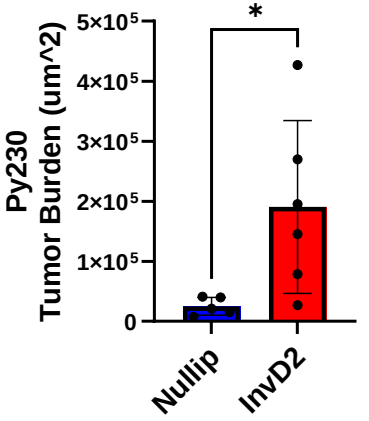




Goddard et al, Cancer Discov 2017



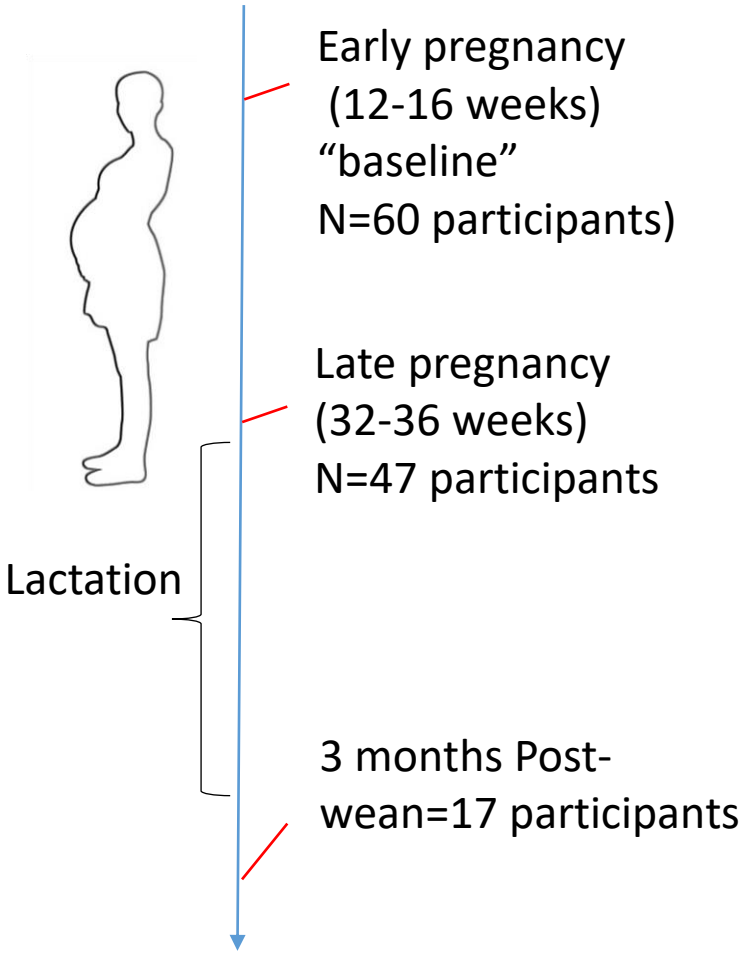
Bartlett et al, Cancers 2021

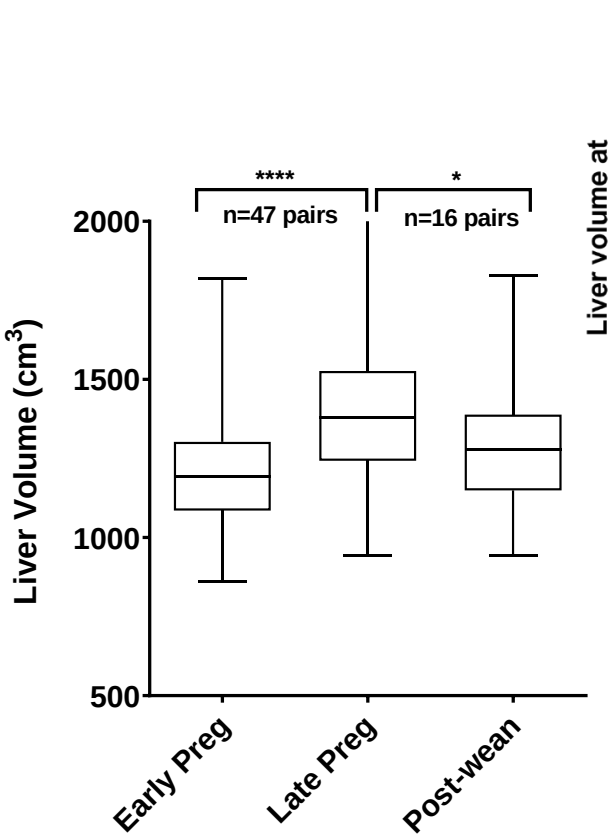


Ozaki, Unpublished

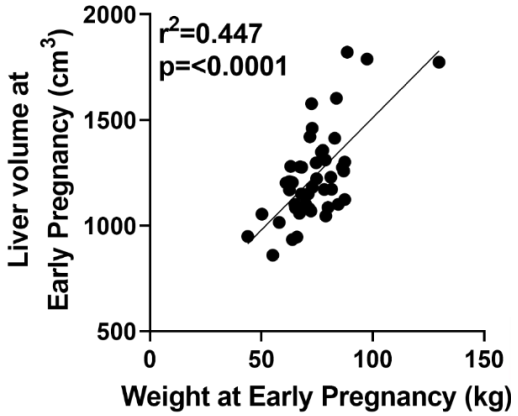
Evidence for Weaning-Induced Liver Involution in Women …..Metastatic Niche?

- Enroll women when they become pregnant;
- 2 study visits with optional post-weaning visit: MRI, blood, glucose tolerance tests

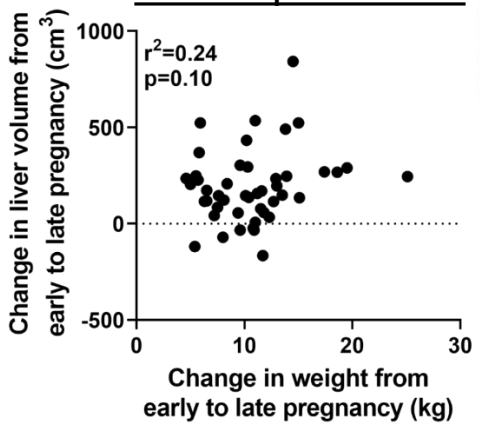




Hepatostasis



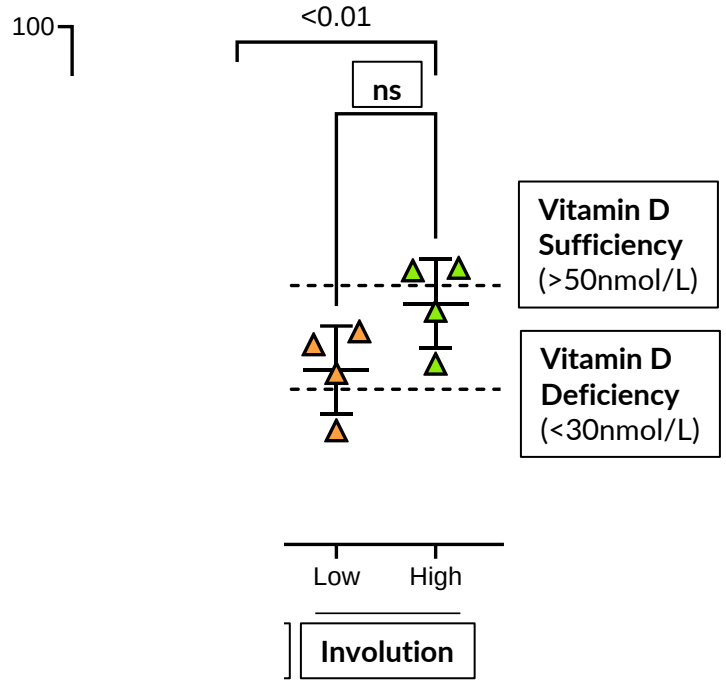
Not Hepatostasis



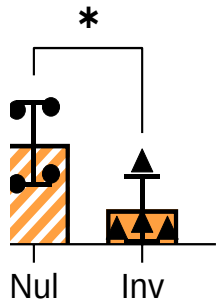
Bartlett et al, PNAS 2021

Vitamin D as Preventive and/or Therapeutic Agent for PPBC

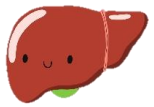
- Vitamin D deficiency associates with poor breast cancer outcomes
- Increased demand for vitamin D during pregnancy and lactation-
  - Vitamin D mobilizes bone calcium for fetal bone & milk
- Vitamin D deficiency is highly prevalent in postpartum women, ranging from 18-84%
- Vitamin D has immune-modulatory and anti-inflammatory activities-but efficacy in PPBC is unknown



ions of active form



Liver involution suppresses xenobiotic metabolism including Vit D

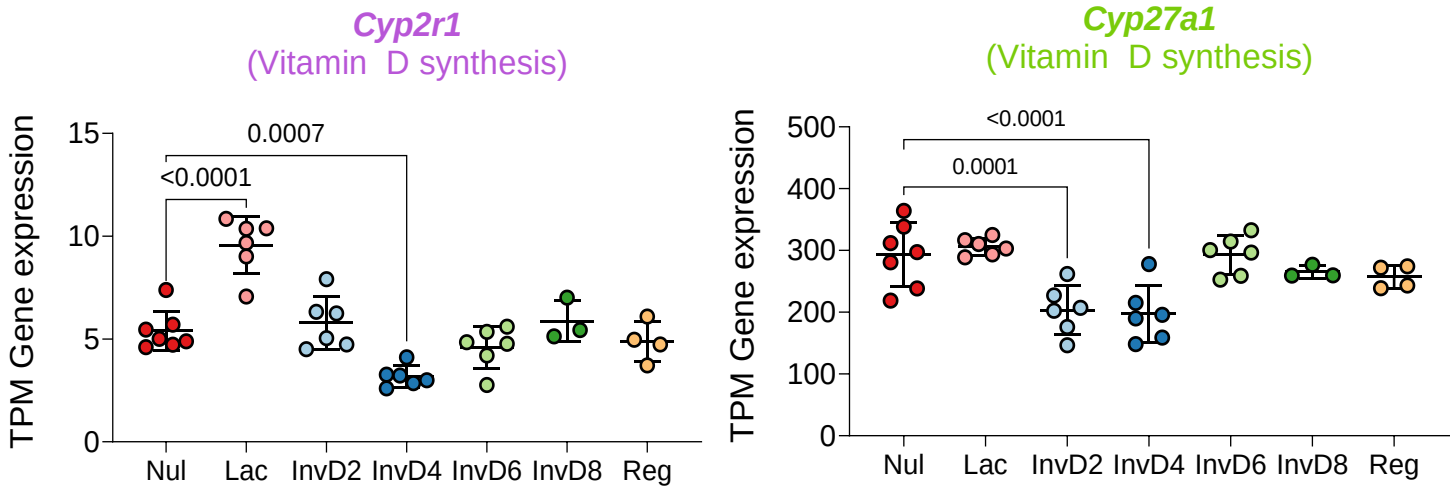


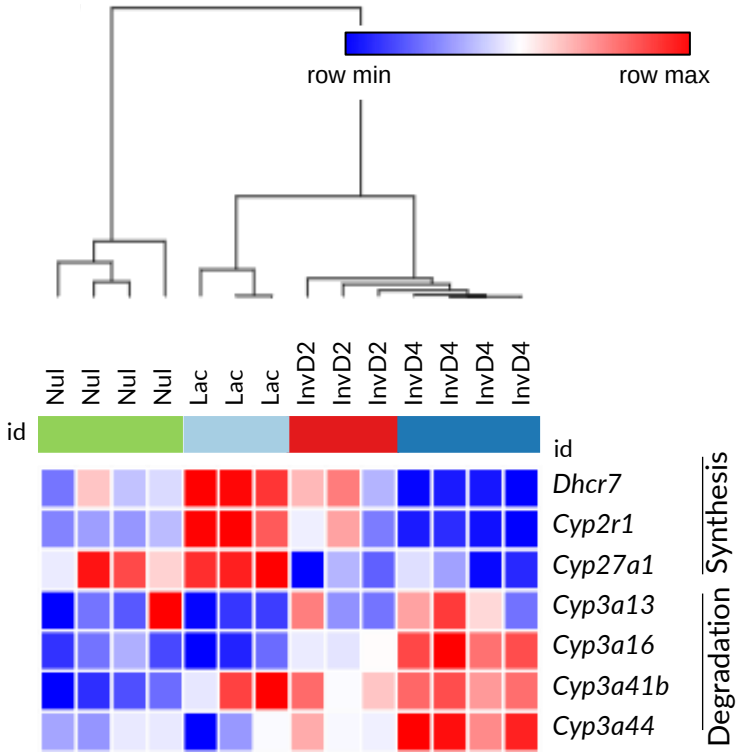
Cyp2r1 *Cyp27a1*

Vitamin D_3 → $25(OH)D_3$ → $1,25(OH)_2D_3$

(Dietary form) (circulating form) (active form)

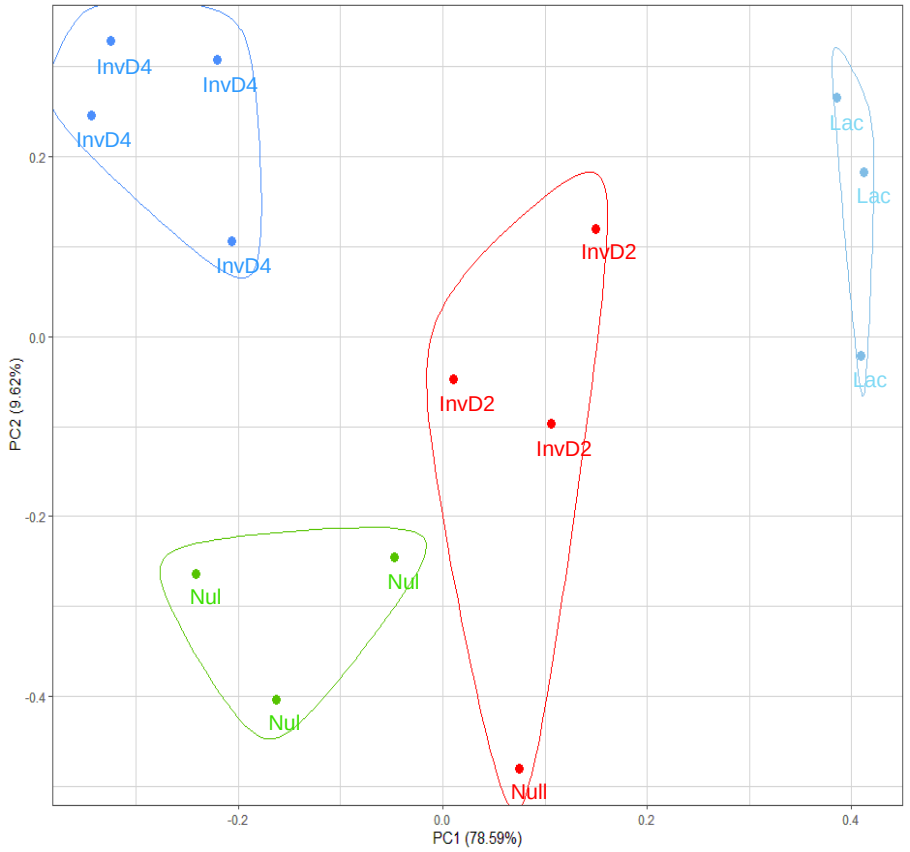
Vitamin D metabolism is altered by reproductive state





Sarah Bernhardt et al, BioRxiv 2024

Expression of 70 CYP450 genes cluster by reproductive state



Summary

- Proximity to recent childbirth predicts metastasis
- BCLM is increased and liver involution likely contributes
- During liver involution, xenobiotic metabolism is suppressed
- Implications for drug efficacy/toxicity in women with recent childbirth?

Sarah Bernhardt et al, BioRxiv 2024

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Jenean O'Brien
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UT Southwestern Medical Center

Identifying Gaps in Care Among Patients With Pregnancy and Post-Partum Associated Breast Cancer

Malcolm Su, MD
UTSW Department of Internal Medicine
November 3rd, 2024

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UT Southwestern Medical Center

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Introduction and Background

- Pregnant and post-partum patients with breast cancer face unique physiological changes associated with pregnancy that require the coordinated care of several specialists to manage.
- About 3% of women with newly diagnosed breast cancers are pregnant, and the incidence of breast cancer diagnosed in pregnancy (PrBC) and breast cancer diagnosed post-partum (PPBC) is rising [1][2].
- There is a need to identify unmet needs of these patients, especially as younger breast cancer patients often present with more progressed disease. We aimed to characterize the barriers to care and unmet needs among women with PrBC and PPBC.

[1] Durrani S, Akbar S, Heena H. Breast Cancer During Pregnancy. *Cureus*. Jul 8 2018;10(7):e2941. doi:10.7759/cureus.2941
[2] Xu S, Murtagh S, Han Y, Wan F, Toriola AT. Breast Cancer Incidence Among US Women Aged 20 to 49 Years by Race, Stage, and Hormone Receptor Status. *JAMA Netw Open*. Jan 2 2024;7(1):e2353331. doi:10.1001/jamanetworkopen.2023.53331

Methods & Cohort Characteristics

- A retrospective study was conducted to evaluate all female patients diagnosed with breast cancer during pregnancy or within 10 years.
- EMR records from 2015 to 2024 were reviewed from UT Southwestern Medical Center and Parkland Health and Hospital System.
- Data on clinical presentation, demographics, and establishment at various specialty clinics (including oncology, maternal fetal medicine, mental health, and cardiology) were gathered.

Characteristic	Cohort (n=71)
Age, years, mean (range)	36 (21-54)
Diagnosis of Breast Cancer	
During pregnancy	23 (32.4%)
Within 1-year post-partum	5 (7.0%)
Between 1 to 5 years post-partum	25 (35.2%)
Between 5 to 10 years post-partum	18 (25.3%)
Insurance status	
Medicare or Medicaid	4 (5.6%)
Private	43 (60.6%)
Uninsured	24 (33.8%)
Race/Ethnicity	
White or Caucasian	29 (40.8%)
Black or African American	17 (23.9%)
Hispanic	18 (25.3%)
Other	7 (9.8%)

Health Outcomes and Delays in Care

- Among both PrBC and PPBC patients, the mean time from date of breast biopsy to establishment with a medical oncologist was 32.5 days.
- Among PrBC patients, the mean time from date of breast biopsy to establishment with a maternal fetal medicine specialist was 42.7 days.
  - 15 (65.2%) PrBC patients experienced at least one maternal or fetal complication during pregnancy. Complications included gestational hypertension, gestational diabetes, pre-eclampsia, fetal anatomic abnormalities, and inviable pregnancies.
- Among PPBC patients, the mean (SD) time from delivery to biopsy date was 4.1 (2.6) years.
  - Ten (14%) PPBC patients had subsequent pregnancies after initiating chemotherapy.
  - Seven (70%) of these pregnancies resulted in at least one complication.

Unique and Unmet Patient Needs

- Forty (56.3%) patients were treated with cardio-toxic anthracyclines or immunotherapy such as trastuzumab.
  - Thirty-two (80%) obtained an echocardiogram prior to therapy
  - Only 12 (30%) established care with a cardiologist
- Thirty (42%) patients sought out care with a psychologist or psychiatrist for anxiety and depression specifically related to pregnancy and breast cancer diagnosis.

- Of PPBC patients, 16 (33.3%) were unaware of infertility risk with chemotherapy or had no documented conversation regarding fertility preservation and were never prescribed fertility preservation medications.

Conclusions and Next Steps

- We characterize a significant delay in the time from diagnosis to establishment with specialists for PrBC and PPBC patients.
- There is a need for improved rates of echocardiogram completion and cardio-oncology establishment to better monitor the cardiovascular risks.
- We plan to create a multidisciplinary team composed of breast medical and surgical oncology, cardio-oncology, MFM, fertility, and psycho-oncology specialists to help address each of these unmet needs and barriers to care.
- Our hospital system is also creating a role for a patient navigator who will help with patient transportation to clinics as well as sharing information about fertility preservation and mental health resources.