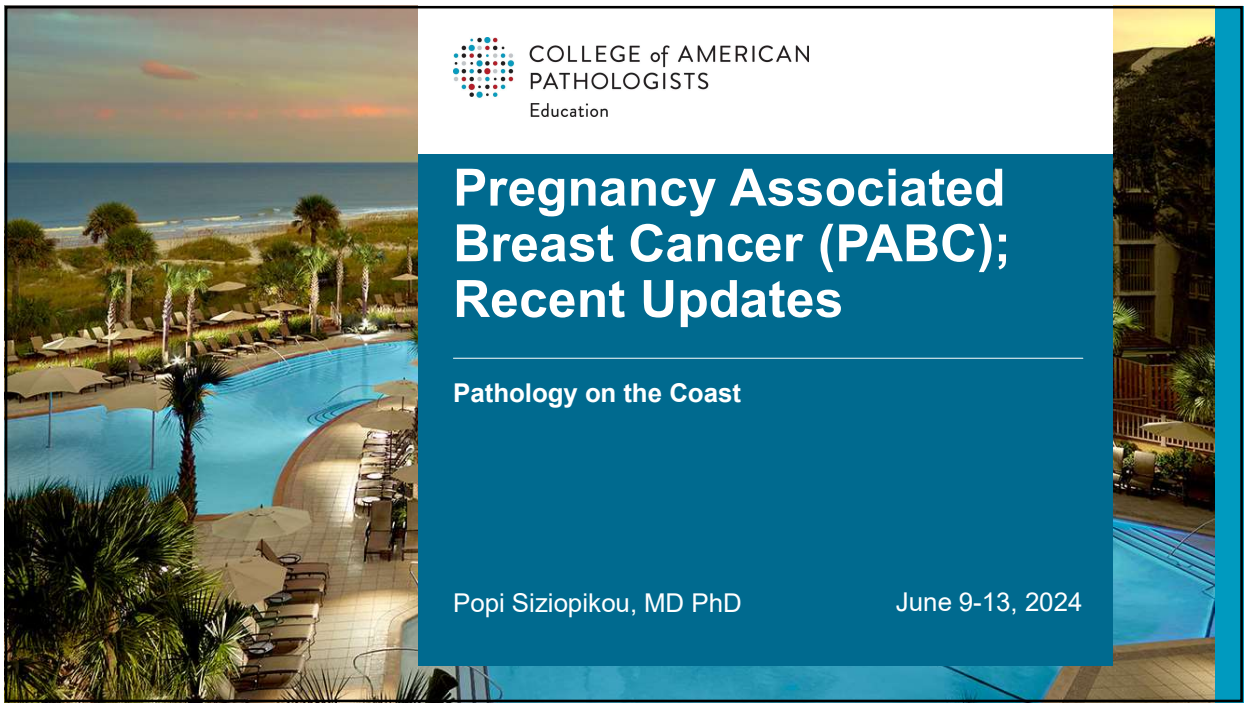

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Objectives

- Define PABC including recent updates
- Describe epidemiology, pathophysiology, and clinical presentation of PABC
- Identify the unique histopathologic features and tumor marker expression of PABC
- Recognize the unique genomic signatures of these tumors
- Cite key ongoing studies on PABC.

2

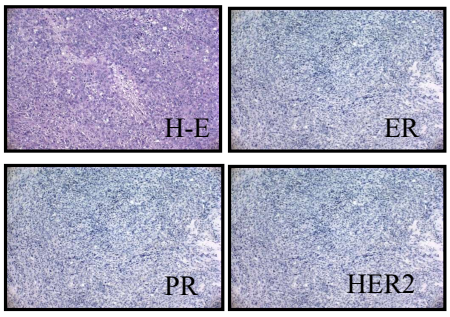
Outline

- Clinical case
- Definitions including recent updates
- Epidemiology
- Pathophysiology
- Clinical presentation
- Pathologic features and immunohistochemistry
- Molecular pathology and genomic signatures
- Ongoing studies

3

Clinical Case

- 33 yo G1P1 female presented with self-detected right breast mass at 3 months post partum
- Breast Imaging showed a 2.9 cm mass at 1 o'clock and 3 cm from the nipple and an enlarged axillary lymph node
- Breast Pathology showed a poorly differentiated (Grade 3) invasive ductal carcinoma, negative for ER, PR and HER2 (score 0) and a positive LN



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PABC: Definition

- Breast cancer diagnosed during gestation, lactation and within 1 to 5 years postpartum
- Recently new definition of PABC has been proposed:
  - PrBC: PABC diagnosed during pregnancy
  - PPBC: PABC diagnosed during the post-partum period

5

PABC: Historic Background

CORRESPONDENCE.

INFLUENCE OF PREGNANCY ON CANCER OF THE BREAST.

EDITOR ANNALS OF SURGERY:

SIR:—The symposium on cancer of the breast in your July number covers the ground very satisfactorily except in one particular, viz: the relations of pregnancy to the disease in question. All surgeons are aware, and the point is emphasized in many text books, that cancer of the breast under the stimulus of pregnancy takes on a specially malignant character and runs a furiously rapid course.

Cheesman WS. Annals of Surgery. 1907 September; 46(3): 487–488

6

Epidemiology

- Malignancy in pregnancy
  - 1:2000 in 1964 to 1:1000 deliveries in 2000

Table 3
Incidence of malignant tumors per pregnancies or deliveries.

Tumor type	Incidence
Breast cancer	1:3000–10,000
Cervical cancer	1:2000–10,000
Hodgkin's lymphoma	1:1000–6000
Melanoma	2–5:100,000
Leukemias	1:75,000–100,000
Ovarian cancer	4–8:100,000
Colorectal cancer	1:13,000
Thyroid cancer	14:100,000

Voulgaris E, Pentheroudakis G and Pavlidis N. Cancer and pregnancy: a comprehensive review. *Surg Oncol* 2011;20:e175-85.

7

Epidemiology

TABLE 1. Estimated New Female Breast Cancer Cases and Deaths by Age: United States, 2017

	IN SITU CASES		INVASIVE CASES	
AGE, Y	NO.	%	NO.	%
<40	1,610	3%	11,160	4%
40-49	12,440	20%	36,920	15%
50-59	17,680	28%	58,620	23%
60-69	17,550	28%	68,070	27%
70-79	10,370	16%	47,860	19%
80+	3,760	6%	30,080	12%
All ages	63,410		252,710	

DeSantis C, Ma J, Sauer AG, and Newman LA, et al. Breast Cancer Statistics, 2017, Racial disparity in mortality by state. *CA: A Cancer Journal for Clinicians* 2017;67:439-448.

8

Breast Cancer and Pregnancy

- >6,000,000 pregnancies/year in the US
- 1 in 3,000 to 1 in 10,000 are associated with BC
- PABC constitutes 0.2-3.8% of all breast cancer cases
- PABC constitutes 25-30% of all premenopausal women diagnosed with breast cancer
- Mean age: 33 years
- Two thirds of the cases are diagnosed postpartum
- Breast cancer is the leading cause of cancer death in US women age 15-29

SEER DATA

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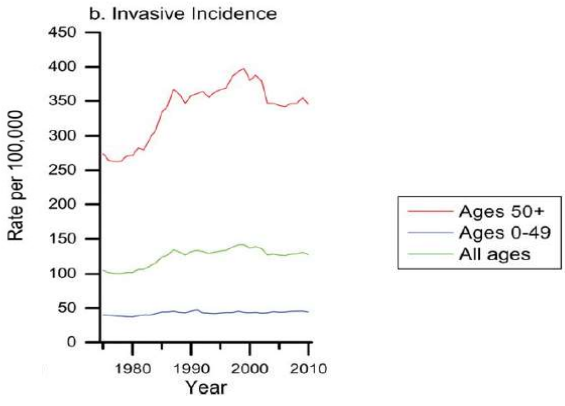
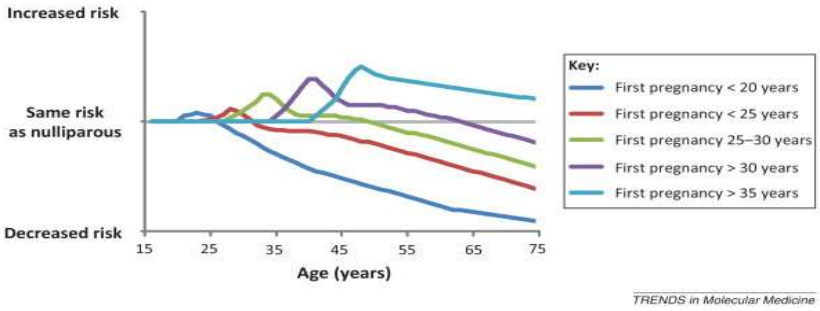
Epidemiology (cont'd)



DeSantis C, Ma J, Bryan L and Ahmedin J. Breast Cancer Statistics, 2013. *CA: A Cancer Journal for Clinicians* 2013;64(1):52-62.

10

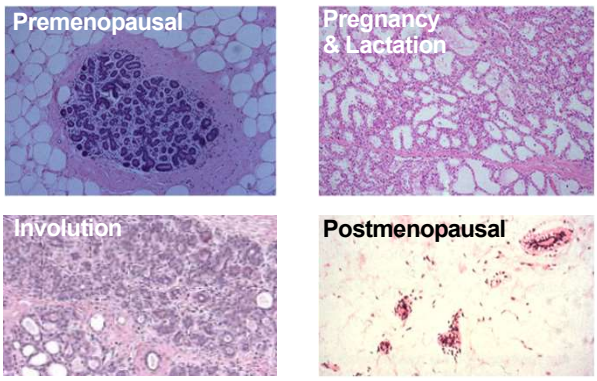
The Dual Effects of Pregnancy on Breast Cancer Development



Meier-Abt. Trends Mol Med. 2014 Mar; 20(3):143-53

11

Stages of Breast Development



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Dual Effect of Pregnancy on Breast Cancer Development

Protective

- Pregnancy induced terminal epithelial cell differentiation (gland less susceptible to tumorigenesis)
- Changes in estrogen responsiveness of parous gland
- Diminution in number of mammary stem cells
- High parity reduces lifetime menstrual cycles and exposure to cycling hormones

Britt et al. Pregnancy and the risk of breast cancer. Endocrine-Related Cancer (2007) 14 907–933

13

Dual Effect of Pregnancy on Breast Cancer Development

Promoting

- Pregnancy related hormones (ER, PR, IGF-1) promote previously initiated cells
- Altered hormone levels in parous women especially GH and prolactin
- Immunosuppressive effects of pregnancy
- Involutional changes post pregnancy, simulate wound healing/inflammatory environment increasing propensity for metastasis

Britt et al. Pregnancy and the risk of breast cancer. Endocrine-Related Cancer (2007) 14 907–933

Schedin, P. Pregnancy-associated breast cancer and metastasis www.nature.com/reviews/cancer (2006) 6 281-291

14

Involution Hypothesis

- Mammary gland involution: fully differentiated milk-producing breast regresses to a pre-pregnant-like state
- Involves apoptotic cell death of 50-80% of the mammary epithelium
- Tissue-remodeling programs similar to wound healing and inflammation
- Wound healing and inflammation ➔ tumor progression, dissemination and metastasis

Lyons et al, Pregnancy and breast cancer: when they collide. J Mammary Gland Biol Neoplasia 2009; 14:87

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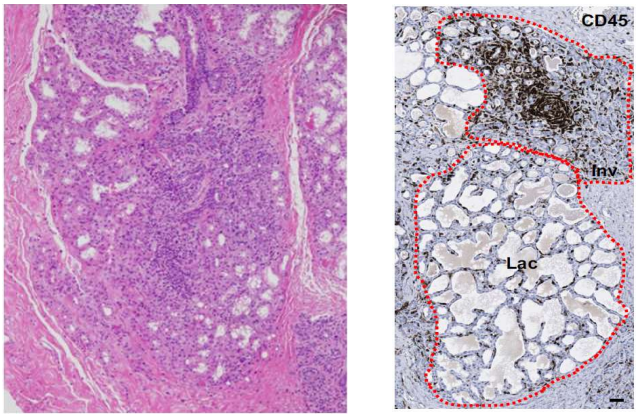
Involution Hypothesis



Lyons et al, Pregnancy and breast cancer: when they collide. J Mammary Gland Biol Neoplasia 2009; 14:87

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PABC: Clinical Presentation

- Palpable breast mass
- Physiologic changes of pregnancy
  - Increased breast volume
  - Palpable nodularity
  - Firmness
  - Increased parenchymal density
- Often delay in diagnosis
- Usually presents as advanced disease
  - Largest proportion of stages II-IV breast cancers

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Pathologic Features of PABC

- Can be any subtype of BC
  - Invasive ductal carcinoma (75-90%)
- Larger tumor size (average 3.5 cm vs 2.0 cm in non-PABC)
- Higher grade (usually grade 3)
- Higher stage at presentation
- Higher rates of lymph node involvement (56-89%)
- Increased risk of metastatic disease at diagnosis (2.5x more likely than non-PABC)

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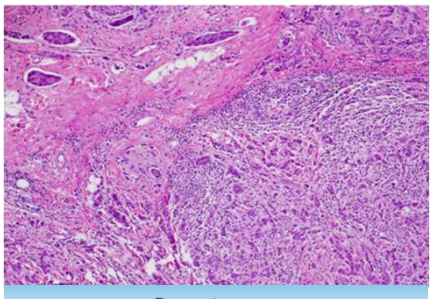
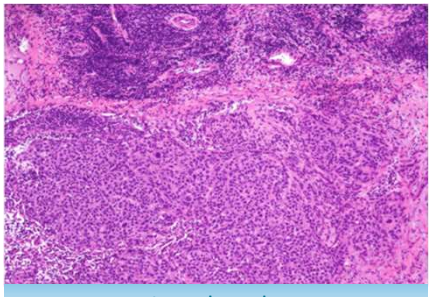
PABC: Histologic Features



Breast mass



Lymph node

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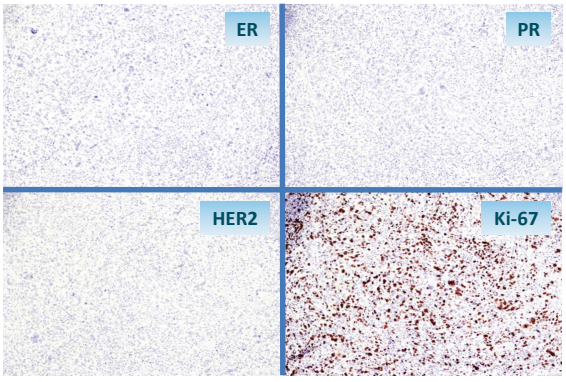
PABC: IHC

- High frequency of hormone negative status
  - ≈70% ER and PR negative with high ki67
- More frequently triple negative
  - ER, PR and HER2
- If not TN, then often overexpression of HER2



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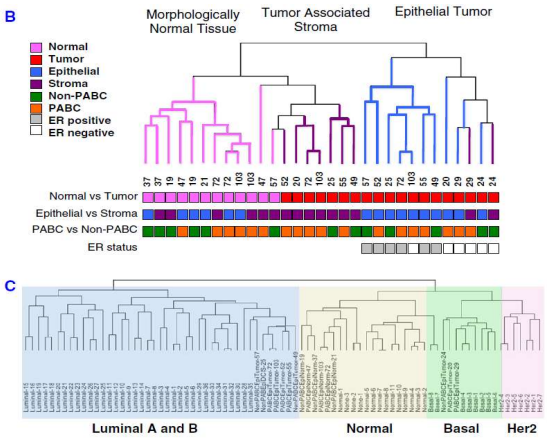
PABC: Genomic Signatures

- Hormonal milieu of pregnancy contributes to the advanced stage at diagnosis and the aggressiveness of PABC
- PABC samples clustered with established breast cancer subtypes

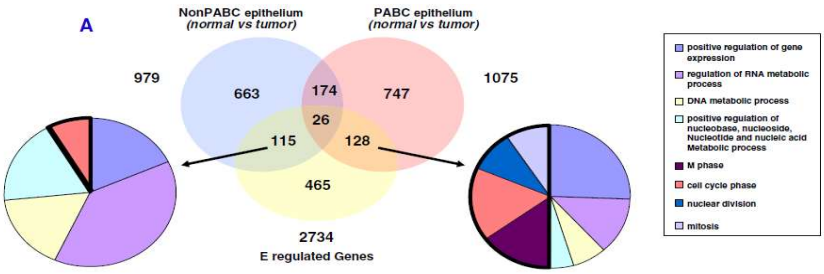


Harvell DME, Kim J, O'Brien J, et al. Genomic signatures of pregnancy-associated breast cancer epithelia and stroma and their regulation by estrogens and progesterone. Horm Canc 2013;4:140-53.

21

PABC: Genomic Signatures of Tumor Cells

- Hormone-regulated genes differed in PABC vs. non-PABC (malignant epithelium)



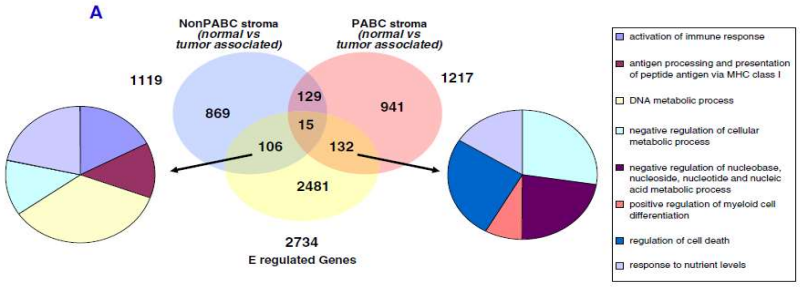
- Cell proliferation
- Cell metabolism
- Lipid metabolism
- Immune response

Harvell DME, Kim J, O'Brien J, et al. Genomic signatures of pregnancy-associated breast cancer epithelia and stroma and their regulation by estrogens and progesterone. *Horm Canc* 2013;4:140-53.

22

PABC: Genomic Signatures of Stroma

- Hormone-regulated genes differed in PABC vs. non-PABC (tumor-associated stroma)



- ↑ immune-related genes (macrophage response)

Harvell DME, Kim J, O'Brien J, et al. Genomic signatures of pregnancy-associated breast cancer epithelia and stroma and their regulation by estrogens and progesterone. *Horm Canc* 2013;4:140-53.

23

PABC: Genomic Signatures

- 1,097 genes differentially expressed between PABC and non-PABC
- Overrepresented in PABC
  - Cellular proliferation
  - Cellular lipid catabolism
  - Positive regulation of the immune system
  - Lymphocyte activation
  - Leukocyte differentiation

The significant differences in genomic pathways support the involution hypothesis

- Development and prognosis of PABC
- May aid in the identification of unique therapeutic targets

Harvell DME, Kim J, O'Brien J, et al. Genomic signatures of pregnancy-associated breast cancer epithelia and stroma and their regulation by estrogens and progesterone. *Horm Canc* 2013;4:140-53.
Wang D, Peng H, Hu Y et al. Distinctive gene expression patterns in pregnancy associated breast cancer. Frontiers in Genetics 2022, DOI 10.3389/fgene.2022.850195

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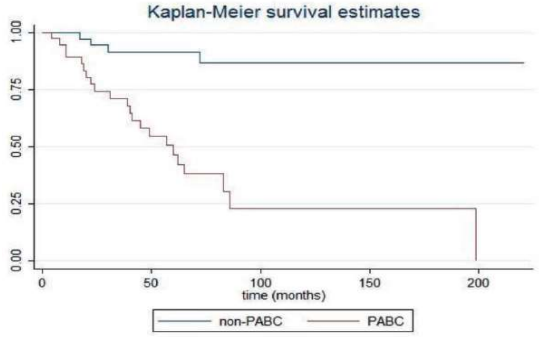
Prognosis

- Worse prognosis in a matched case study (stage, age and year of diagnosis)
- 5-year OS 30.7% PABC vs. 48.7% non-PABC ($p < 0.0001$)



Dimitrakakis C, Zagouri F, Tsigginou A et al. Does pregnancy-associated breast cancer imply a worse prognosis? A matched case-case study. *Breast Care* 2013;8:203-7

25

Prognosis of PABC during Pregnancy vs Postpartum

- Meta-analysis: 41 studies: breast cancer before, during and after pregnancy
  - increased overall risk of death in PABC vs non-PABC
  - Pts diagnosed during the postpartum period are most at risk for disease progression or relapse
- Colorado Young Women Breast Cancer Cohort
  - postpartum status is the main driver of poor prognosis in young women with BC, especially those <35y and stage I disease

Hartman E and Eslick GD: The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Res Treat 160:347-360, 2016.
Jindal S et al. Postpartum breast cancer has a distinct molecular profile that predicts poor outcomes. Nature Communications, 12:6341, 2021.
Shagisultanova E et al. Overall survival is the lowest among young women with postpartum breast cancer. Eur J Cancer 168:1190127, 2022.

26

Proposed New Terminology and Revised Definition of PABC; PrBC vs PPBC

- The original PABC terminology is outdated and should no longer be used
- PrBC: Breast cancer occurring during pregnancy
- PPBC: Breast cancer occurring in the postpartum period (extending to 5-10 years after birth)

Amant F, Lefrere H, Cardonick E, Lambertini M, Loibl S, Peccatoni F, Partidge A and Schedin P. The definition of pregnancy-associated breast cancer is outdated and should no longer be used. Lancet Oncology 22:753-754, 2021.

27

Proposed New Terminology and Revised Definition of PABC; PrBC vs PPBC

- PrBC: Breast cancer occurring during pregnancy
  - 4% of BC in women <45 years
  - Outcomes are equivalent based on age-matched, stage-matched non-pregnant controls
- PPBC: Breast cancer occurring in the postpartum period (extending to 5-10 years after birth)
  - 35-55% of BC in women <45 years
  - increased metastasis and death independent of age, tumor stage, tumor biologic subtype, BMI, education, race and socioeconomic status

Amant F, Lefrere H, Cardonick E, Lambertini M, Loibl S, Peccatoni F, Partidge A and Schedin P. The definition of pregnancy-associated breast cancer is outdated and should no longer be used. Lancet Oncology 22:753-754, 2021.

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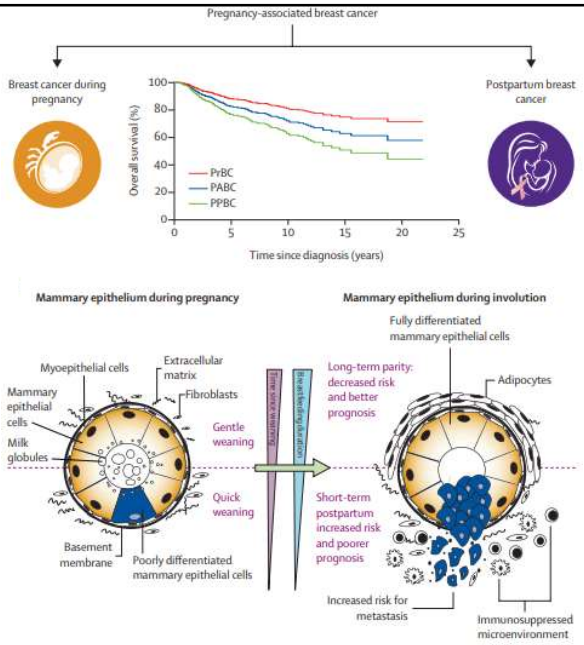
PrBC vs PPBC



Amant F, Lefrere H, Cardonick E, Lambertini M, Loibl S, Peccatoni F, Partidge A and Schedin P. The definition of pregnancy-associated breast cancer is outdated and should no longer be used. Lancet Oncology 22:753-754, 2021.

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Proposed New Terminology and Revised Definition of PABC; PrBC vs PPBC

- Additional studies looking separately into the PrBc and PPBC are urgently needed in order to:
  - Improve our understanding of the biology of breast cancer during the different stages of pregnancy, lactation, involution and afterwards
  - Decipher the pathways underlying the differences in tumor biology and prognosis
  - Optimize therapeutic management for our young patients

Amant F, Lefrere H, Cardonick E, Lambertini M, Loibl S, Peccatoni F, Partidge A and Schedin P. The definition of pregnancy-associated breast cancer is outdated and should no longer be used. Lancet Oncology 22:753-754, 2021.

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PABC: Management

- Careful consideration of the best interests of mother and the fetus
- Multidisciplinary team approach (Obstetrician, MFM specialist, Radiologist, Pathologist, Medical Oncologist, Surgical Oncologist, Geneticist, Neonatologist, Psychosocial Support expert, others)
- Treatment decisions are individualized and consider disease extent, best treatment plan for the mother, minimizing harm to the fetus based on gestational age, and addressing issues of future family planning

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Summary

- PABC is BC diagnosed during or after a recent pregnancy or lactation
- PABC affects 25-30% of premenopausal women with breast cancer
- PABC tends to present at a more advanced stage, with larger, higher grade, triple negative or HER2-positive tumors
- New terminology and revised definitions were recently introduced separating PrBC and PPBC

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Summary

- Pregnancy results in a transient increase risk in breast cancer followed by a decrease risk (protection) over time
- Multiple hypotheses for pregnancy's tumor promoting and tumor protective effects exist
- Tissue remodeling pathways during mammary gland involution are similar to wound healing and inflammation and may facilitate tumor progression and metastasis
- Better understanding of the molecular pathways of tumor initiation and progression and prompt diagnosis and treatment in these tumors may lead to better therapies for these young breast cancer patients.

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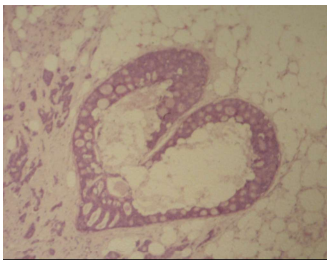
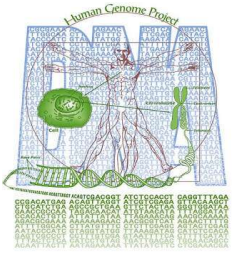
Thank you!





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Questions?

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