Pregnancy and Breast Cancer

Elena Provenzano

Addenbrookes Hospital

Cambridge

Pregnancy and Breast Cancer

Pregnancy and Breast Cancer

1. Pregnancy associated breast cancer:

   Histology, management, clinical outcomes

2. Pregnancy as a breast cancer risk factor

3. Pregnancy following a diagnosis of breast cancer

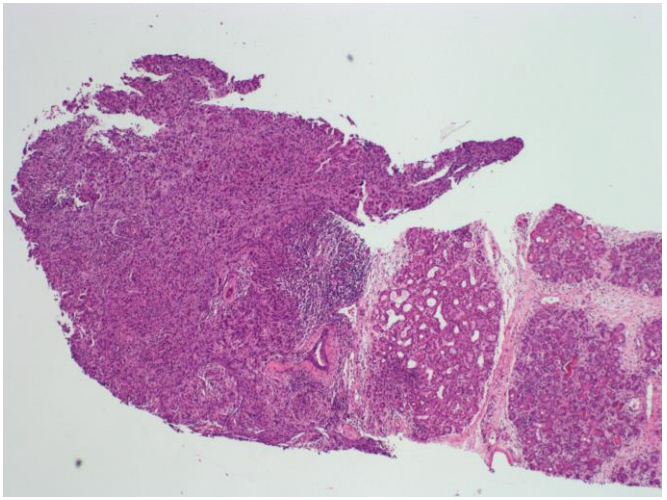
Pregnancy Associated Breast Cancer

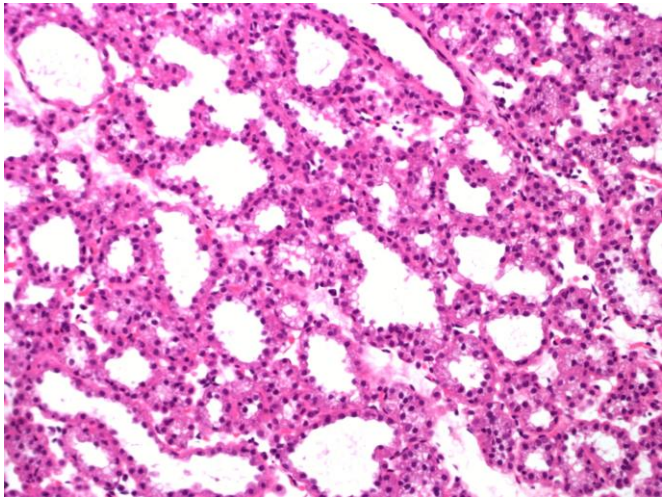
- Breast cancer diagnosed during pregnancy or 12 months post partum
- 0.2-4% of breast cancers
- 1/3,000-10,000 women
- Under 40 – 1/3-4 women diagnosed with BC
- Increasing incidence as maternal age at first birth increasing

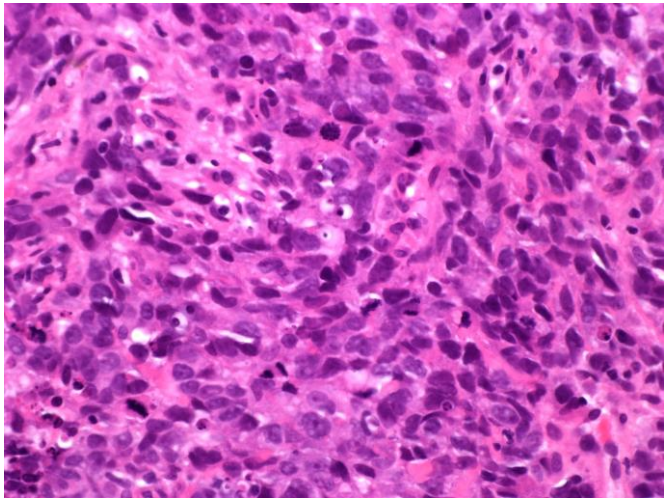
PABC: Histology

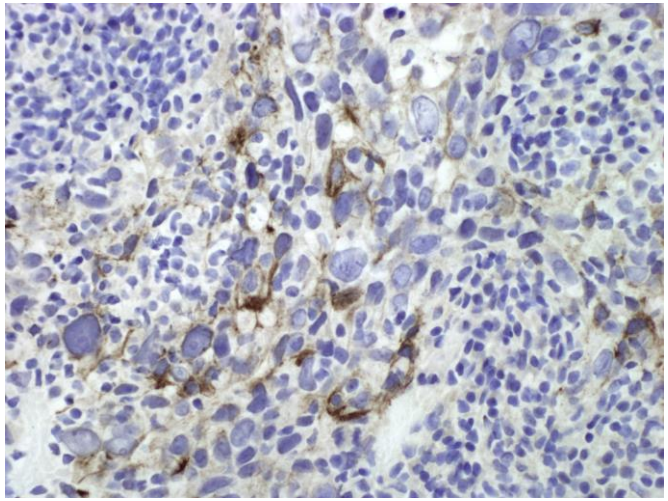
- Ductal NST – 78-100%
- Grade 3 – 40-84%
- ER+ - 20-66%
- HER2+ - 17-39% (early series include 2+)
- TNBC – 22-41%
- Lymphovascular invasion – 61%
- N1+ - 52-79%
- Stage IV – up to 10%
- Conflicting results in age-matched series as to whether there is a significant difference with non-PABC

PABC: Histology



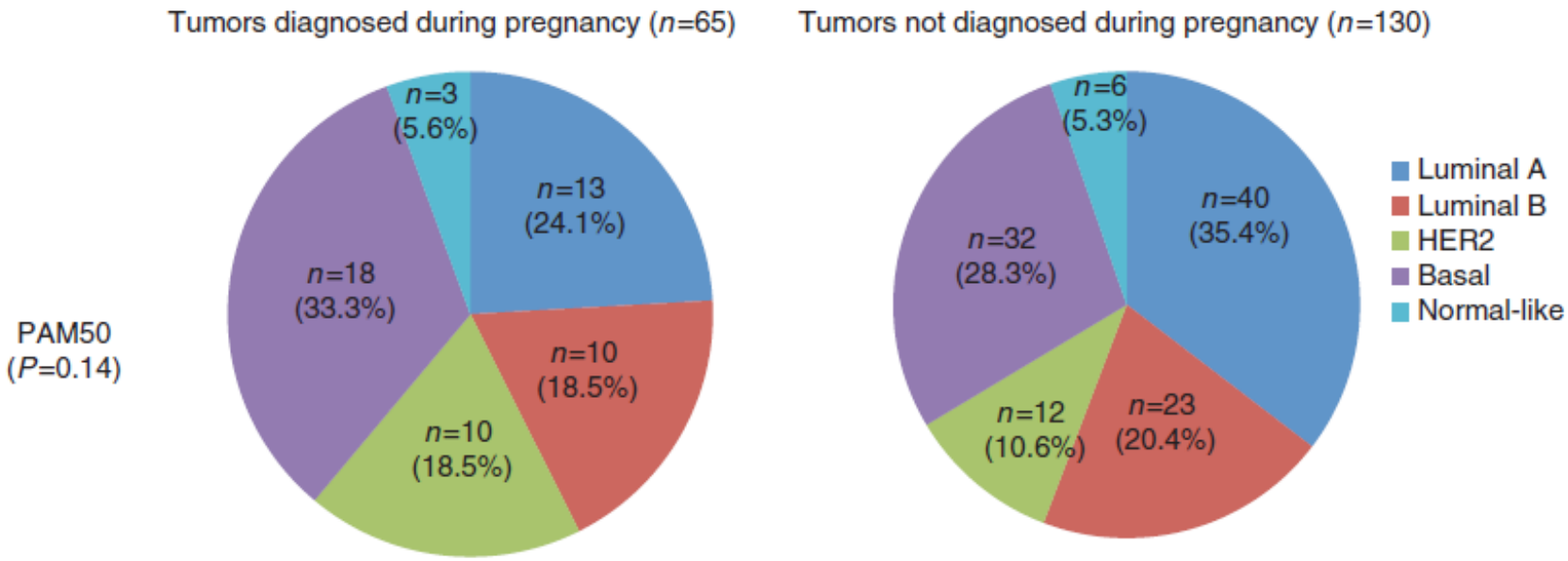






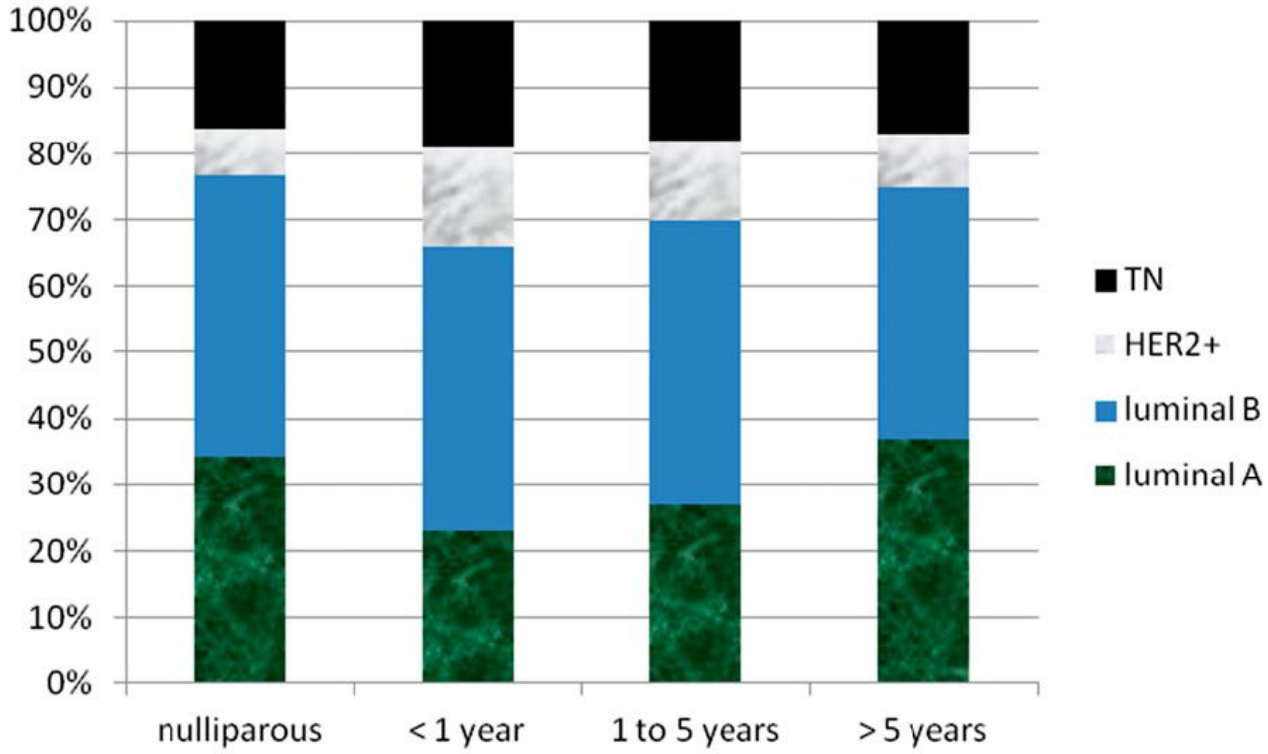
PABC: Molecular subtypes

- Breast cancer during pregnancy
- No difference in molecular subtypes compared with age matched controls



Azim et al., Endocrine related cancer 2014;21:545-54.

PABC: Molecular subtypes



Collins et al., Oncologist 2015;20:713-18.

PABC: Molecular changes

- Increase in total number of non-silent mutations – 20 v 12 (p=0.027)
- Commonest somatic mutations PIK3CA (19%) and p53 (4%)
- Increased frequency MUC gene mutations (46% v 11%) leading to hyperglycosylation
- Increase in cosmic signature 20 – DNA mismatch repair

Nguyen et al., NPJ Breast Ca 2018;4:23.

PABC: TILs

- Azim et al., Breast 2015
- Lower TILs levels in breast cancer during pregnancy across all molecular subtypes
- Average TILs 3% - 12% versus 20% in non-PABC
- 5% TILs rich (>50%)

- Different to microenvironment post partum

PABC: Diagnosis

- Often delay in diagnosis – difficult clinically, not considered
- Mammography with abdominal shielding safe during early pregnancy
- Issues of reduced sensitivity due to density
- Series of 117 PABC – 55% mass, 10% asymmetry, 6% distortion, 55% Ca++ (17% Ca++ alone)
- 19% BIRADS 1/2/3 – 12% normal
- Ultrasound – improved sensitivity in pregnancy
- Mass 89%; 23% BIRADS 1/2/3
- MRI possible in pregnancy without Gadolinium
- CT / bone scan / PET contraindicated

Langer et al., Diag and Interventional Imaging 2014;95:435-41.

PABC: Management

SURGERY

- Up to 60% mastectomy rate as often advanced stage at diagnosis
- Breast conservation safe with similar survival to mastectomy but must consider delay in RT
- Autologous reconstruction contraindicated due to long operative time and risk to foetus
- Recommendation for delayed implant based reconstruction
- SLN safe during pregnancy; negligible exposure to foetus with radioisotope, blue dye contraindicated due to risk of prophylaxis

Toesca et al., Gynae Surg 2014;11:279-84.

PABC: Management

RADIOTHERAPY

- Contraindicated in pregnancy
- Safer during 1st and 2nd trimester as lower dose to foetus; dose largest during 3rd due to proximity
- Delay in RT until after delivery must be considered in BCS decisions – 1% increased risk of local failure with each month delay. Not an issue if chemotherapy required

Table 1 Radiation dosages along with the effect on the fetus and in relation to the gestational age

Radiation dosages	Effect on the fetus
<0.1 Gy	No major effect
0.1–0.15 Gy	Increased risk for malformations
2.5 Gy	Malformations in most cases
>30 Gy	Abortion
From conception to 10 days	Lethal
Weeks 2–12	Malformations in almost all cases, growth retardation
Weeks 13–16	Mental and growth retardation
Weeks 17–26	Malignancies, sterility, genetic defects

Zagouri et al., ESMO Open 2016

PABC: Management

MEDICAL THERAPY

- As similar as possible to non-pregnant female
- Chemotherapy contraindicated in 1st trimester – 17% risk of malformation
- Safe in 2nd and 3rd trimester including anthracyclines and taxanes
- Trastuzumab contraindicated – assoc with oligo- and anhydramnios
- Tamoxifen contraindicated – high risk of foetal malformations (up to 20%)
- Lack of data on novel targeted agents

Zagouri et al., ESMO Open 2016.

PABC: Survival

- Variable results in literature – equivalent or worse prognosis
- Theories for worse prognosis:

1. Delayed diagnosis resulting in advanced stage
2. Hormonal milieu
3. Tumour biology – more aggressive tumour phenotype
4. Microenvironment/ immunity
   during pregnancy – immune suppression
   post partum involution – pro inflammatory state which promotes tumour growth and metastasis
5. Undertreatment in the past

PABC: Survival

- Meta-analysis of 30 studies
- OS worse for PABC – pHR 1.37 (1.21-1.55)
- Difference remained significant in multivariate analysis including stage and other pathological variables
- Increase greatest in cancer diagnosed during the post partum period – pHR 1.84 (1.2-2.65) cf during pregnancy 1.29 (0.74 – 2.24)
- Subsequent study – mortality highest in women diagnosed 4-6/12 post partum OR = 3.8 (2.4-5.9)
- Increase in liver (63 v 37%) and brain mets (73 v 27%)

Azim et al., Cancer Treat Rev 2012;38:834-42.
Lee et al., Breast Ca Res Treat 2017;163:417-21.

PABC: Survival

- More recent studies show equivalent survival outcomes when matched for pathological variables and treatment
- Amant et al., J Clin Onc 2013
- Case control study with 311 PABC – 47% received chemotherapy with taxanes
- 5yr DFS 65%, OS 78% - no difference to non-pregnant controls
- Modern guidelines advocate equivalent chemotherapy in pregnant patients – may reflect under treatment in the past
- No evidence of long term deleterious effect on child development

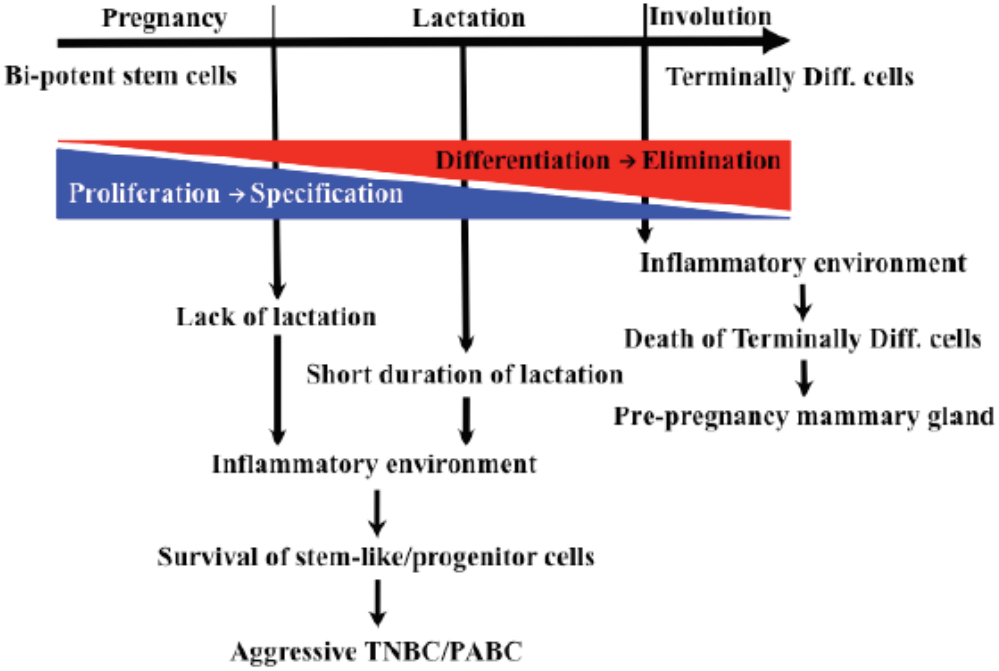
Involution changes

- Increase in immune response and wound healing gene signatures
- Degradation of stromal and basement membrane proteins
- Lymphatic and vascular remodelling
- May explain differences between breast cancer during pregnancy and post partum – different biology confounding analysis
- Gene expression signatures reflecting these pathways identified in breast cancers from parous women up to 10 years post partum

Asztalos et al., SpringerPlus 2015.

Involution changes

- No or short period of lactation: persistence of stem cells in pro inflammatory environment – development and progression of TNBC
- Prolonged lactation – cells terminally differentiated and eliminated by pro inflammatory environment



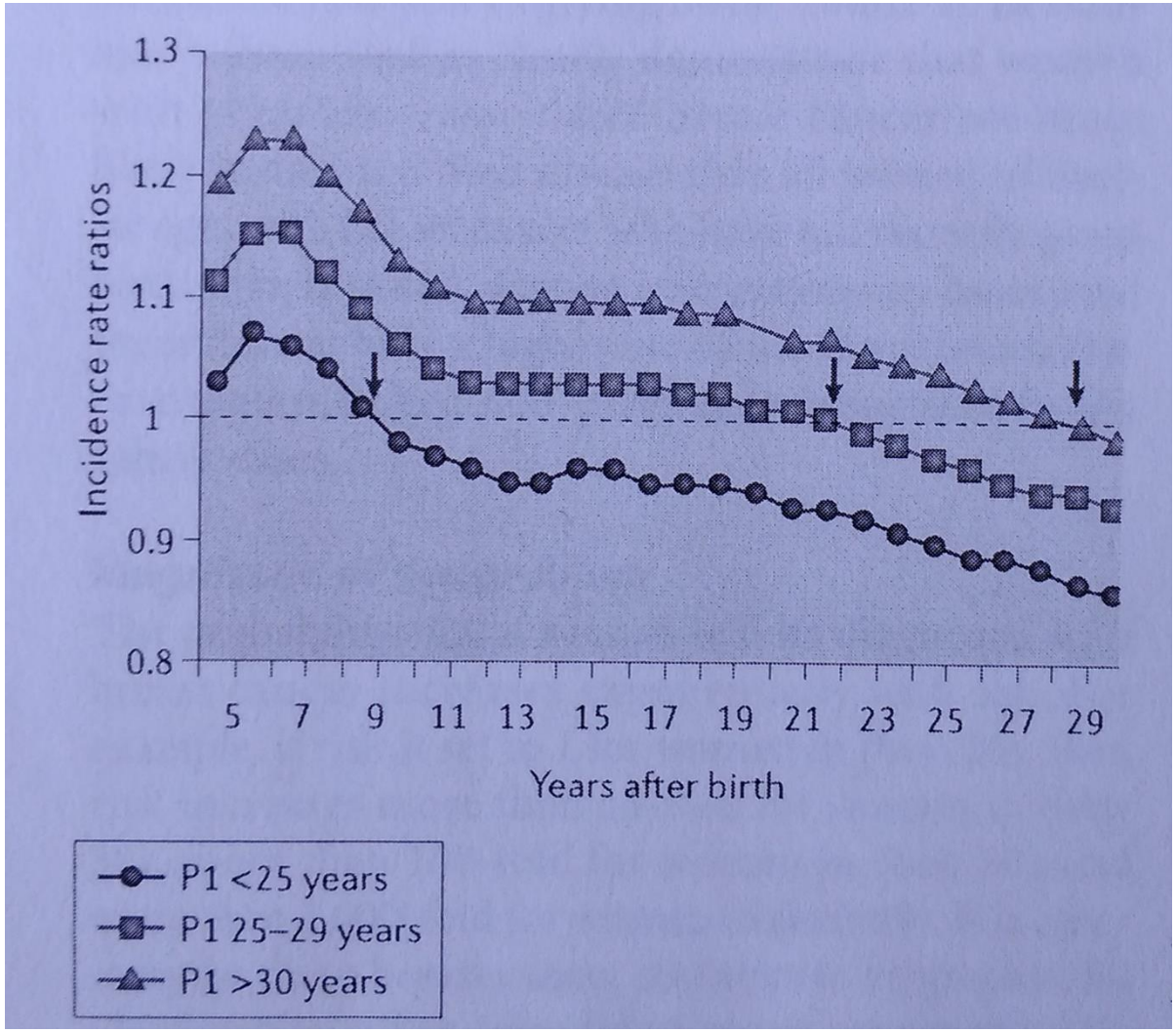
ElShamy W. Oncotarget 2016;7 (33):53941-50.

Pregnancy and Risk

- Dual effect:
  short term increased risk
  long term protective effect
- Peak increase in risk 3-5 years post partum; persists for 15 years
- Maternal age at first pregnancy important modifier – risk more pronounced over 30
- First pregnancy < 25 – 50% decreased risk
- First pregnancy > 35 – 22% increased risk
- Each year childbirth delayed risk increases 3.5%

Shedin P. Nature Rev Cancer 2006; Lambe et al., NEJM 1994.

Pregnancy and Risk



Shedin P. Nature Rev Cancer 2006;6:281-91.

Pregnancy and Risk

- Risk factors vary according to molecular subtype
- Parity – decreased risk in parous versus nulliparous women for luminal cancers (pOR 0.75) but not HER2+ / TNBC
- Age at first birth – older age at first birth increases risk for luminal and HER2+ BC; TNBC decrease or N/S
  luminal A – OR=1.40
  luminal B – N/S
  HER2E – OR =2.84
- Breast feeding – extended breast feeding reduces risk for luminal (pOR 0.77) and TNBC (pOR 0.79); HER2+ N/S but numbers comparatively small.

Lambertini et al., Ca Treat Rev 2016;49:65-76.
Sisi et al., Int J Ca 2016;138:2346-56.

Pregnancy After Breast Cancer

- No increase in risk of recurrence or death
- 3 meta-analyses – all showed a survival benefit for pregnancy >10/12 after breast cancer diagnosis
- One study showed 41% reduction in risk of death but issue of 'healthy mother bias'
- Most national guidelines advocate 2 year wait
  - return of ovarian function
  - highest relapse rate
- ER positive cancers – need to counsel regarding risks of stopping endocrine therapy

Raphael et al., Current Oncol 2015.