COLUMBIA UNIVERSITY | MAILMAN SCHOOL of PUBLIC HEALTH

BREAST CANCER FAMILY REGISTRY

Epithelial Podoplanin Co-expression in Postpartum Breast Cancer: An Exploratory Tumor Microenvironment Analysis

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PUBLIC HEALTH IMPORTANCE

The incidence of early-onset breast cancer is rising nationally and globally (1.2). Women diagnosed under age 45 years are often diagnosed with aggressive breast cancer subtypes (3). Within the class of early-onset breast cancer is postpartum breast cancer (PPBC) defined as diagnoses within 5-10 years postpartum. PPBC tumors have an approximate 3-fold higher metastasis risk than nulliparous or ≥10 years postpartum cases. PPBC tumors are also suggested to have a differential tumor biology that is under explored but likened to wound-healing features (4,5). Etiological elucidation that informs tertiary treatment for women diagnosed with PPBC are needed.

OBJECTIVE

Human data on the PPBC tumor microenvironment (TME) are limited. We aim to classify TME phenotype(s) associated with PPBC status.

STUDY POPULATION

A matched case-case analysis of 180 invasive ductal carcinoma cases diagnosed ≤50 years within the New York subset of the Breast Cancer Family Registry (BCFR) (**Figure 1**). Matches were as follows and controls were not mutually exclusive across Lists.

- List 1. BC <5 years postpartum | BC ≥10 years postpartum

9 cases 1:2 matches, 11 cases 1:1 matches, 4 pairs controls only, 1 pair case only

- List 2. BC <5 years postpartum | BC nulliparous

13 cases 1:2 matches, 12 cases 1:1 matches, 2 pairs controls only

- List 3. BC ≥5-<10-years postpartum | BC ≥10 years postpartum

19 cases 1:2 matches, 13 cases 1:1 matches, 4 pairs controls only, 2 pairs cases only

- List 4. BC within ≥5-<10-years postpartum | BC nulliparous

14 cases 1:2 matches, 12 cases 1:1 matches, 7 pairs controls only, 1 pair cases only

MATERIALS & METHODS

EPIDEMIOLOGICAL DATA

Self-reported sociodemographic and reproductive data.

MULTIPLEX QUANTITATIVE IMMUNOFLUORESCENCE (MQIF)

- MQIF (Opal/Vectra Polaris) conducted blinded to patient clinicopathologic data for Podoplanin (PDPN), Macrophages (CD68), Endothelial Cells (CD31/CD34 antibody mixture), panCK, SEMA7A, PD-L1, and DAPI.
- Slides scanned with a 10X objective.
- Tumor containing regions annotated by pathologists.

DIGITAL COMPUTATIONAL PATHOLOGY

- Cell phenotyping, cell counts, and signal intensities were quantified in HALO (full magnification), with fluorescent intensities normalized to 0-255.
- Phenotypes defined by co-/anti-coincidence logic.
- Within tumor regions, we computed densities (cells/mm^2) for markers and 20 colocalized phenotypes, normalized by DAPI$^+$ nuclear density to yield unitless ratios, and log-transformed these ratios to approximate normality.
- Phenotypes with ≥25% zero values were dichotomized as present/absent.
- Continuous predictors were z-scored within cross validation (CV) folds.

STATISTICAL ANALYSIS

- We used least absolute shrinkage and selection operator-penalized logistic regression (LASSO LR) to identify tumor phenotypes associated with PPBC groups.
- The tuning hyperparameter λ was selected via 5*5 repeated cross-validation maximizing area under the receiver operating characteristic curve (AUC).
- We assessed LASSO stability using 200 bootstrap iterations, recording the frequency of retained features.
- Within each of four matched subsamples, LASSO models were run twice: once with all candidate features (Model A) and once with tumor phenotypes only (Model B).
- We then fit post-LASSO LR models with generalized estimating equations (GEE) to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for tumor phenotypes retained by LASSO.

RESULTS

Figure 1. Consort Diagram

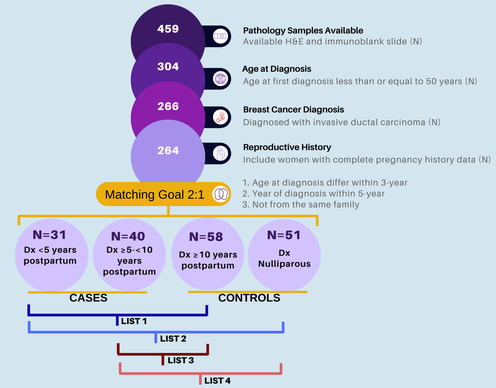


Figure 2. Post-LASSO LR w/ GEE ORs & 95% CIs for retained tumor phenotypes and matching variables, ≤5 years/ <10 year since last FTP vs. > 10 years since last FTP

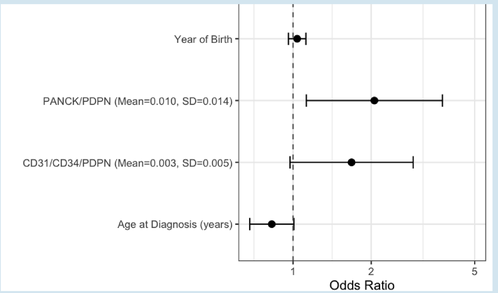


Table 1. Classification performance of LASSO LR models

Model	PPBC Outcome	AUC	λ
1a: All Candidate Features	< 5 years vs ≥10 years since last FTP	0.97	0.343
1b: Tumor Phenotypes Only	< 5 years vs ≥10 years since last FTP	0.58	0.015
2a: All Candidate Features	< 5 years since last FTP vs Nulliparous	0.52	0.0002
2b: Tumor Phenotypes Only	< 5 years since last FTP vs Nulliparous	0.5	10
3a: All Candidate Features	≤ 5 years/< 10 years vs ≥10 years since last FTP	0.78	0.085
3b: Tumor Phenotypes Only	≤ 5 years/< 10 years vs ≥10 years since last FTP	0.66	0.107
4a: All Candidate Features	≤ 5 years/< 10 years since last FTP vs Nulliparous	0.72	0.009
4b: Tumor Phenotypes Only	≤ 5 years/< 10 years since last FTP vs Nulliparous	0.057	0.015

SUMMARY

Model 3 performed better than chance when all candidate features were included in the Lasso Model (AUC 0.78) *and* when only the tumor phenotypes were included in the Lasso model (AUC 0.66) (**Table 1 and Figure 2**).

CONCLUSION

- Phenotypes examined did not classify our conservative clinical definition of PPBC (<5 y postpartum) better than chance.
- The lymphatic vasculature, a feature of wound healing, classified our epidemiologic definition of PPBC (≥5-<10 y postpartum) better than chance compared to parous controls.
- Additional BCFR samples will be used to increase power to re-examine analyses as well as a conduct a cohort analysis to facilitate comparison across estimate magnitude and direction.

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