Dissecting the germline variants in breast cancer tumors: Polygenic risk scores alter tumor evolution under a two-hit hypothesis for breast cancer.

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Abstract

Breast cancer is the leading cause of cancer death worldwide. Previous methods attributed the heritable risk of breast cancer diagnosis to common germline variants quantified using Polygenic Risk Scores (PRS). Previous research shows prostate cancer PRSs are associated with fewer somatic alterations in tumors. This association corroborates the notion of increased germline risk reduces the needed genomic instability for tumorigenesis as a consequence from Knudson's "two-hit" hypothesis. PRSs have also been associated with earlier age at diagnosis, and favorable survival outcomes. Our project seeks to understand if similar associations between breast cancer PRS and tumor molecular features exist. Using tumor samples (n = 1,076) from The Cancer Genome Atlas, we calculated breast cancer PRS using Mavaddat *et al.*'s PRS_{313}. Then, we identified associations with clinical and molecular features using generalized linear models adjusting for ancestry, age at diagnosis, sex, and existing prognostic clinical factors. Results reveal a moderate association between PRS and age at diagnosis; association between somatic features and age at diagnosis; no association between PRS and somatic features.

Background & Workflow

Breast Cancer & Polygenic Risk Score (PRS)

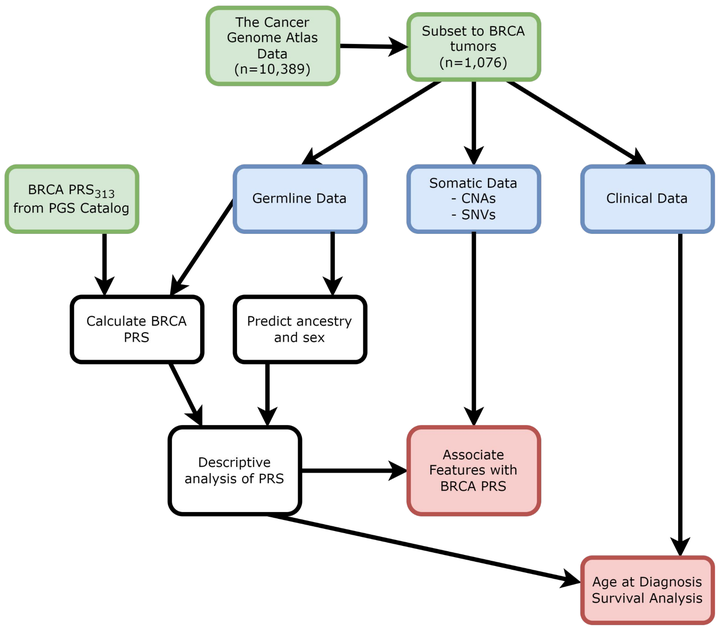
- A portion of breast cancer risk is explained by heritability.
- Polygenic risk scores (PRSs) can be used to estimate genetic risk.
  - Before diagnosis – predicting aggressive tumorigenesis.
  - After diagnosis – personalized avenues for treatment.

Previous Work

- Our research group (Houlahan *et al.*, 2023) associated tumor somatic features with PRS in prostate cancer.
- Provides broader implications to tumor evolution indicative of cancer aggression

Goals:

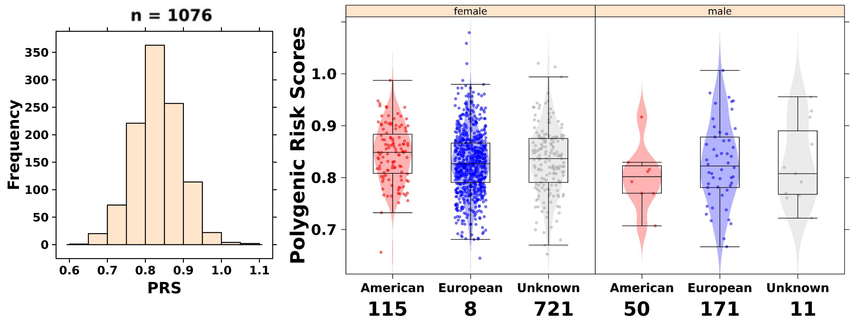
- Associate somatic features in tumors with PRS in breast cancer
- Account for covariates such as age in our clinical data and ancestry and sex predicted from our germline data



[1] Kathleen E Houlahan, PhD and others, A polygenic two-hit hypothesis for prostate cancer, *JNCI: Journal of the National Cancer Institute*, Volume 115, Issue 4, April 2023, Pages 468–472, https://doi.org/10.1093/jnci/djad001

Results

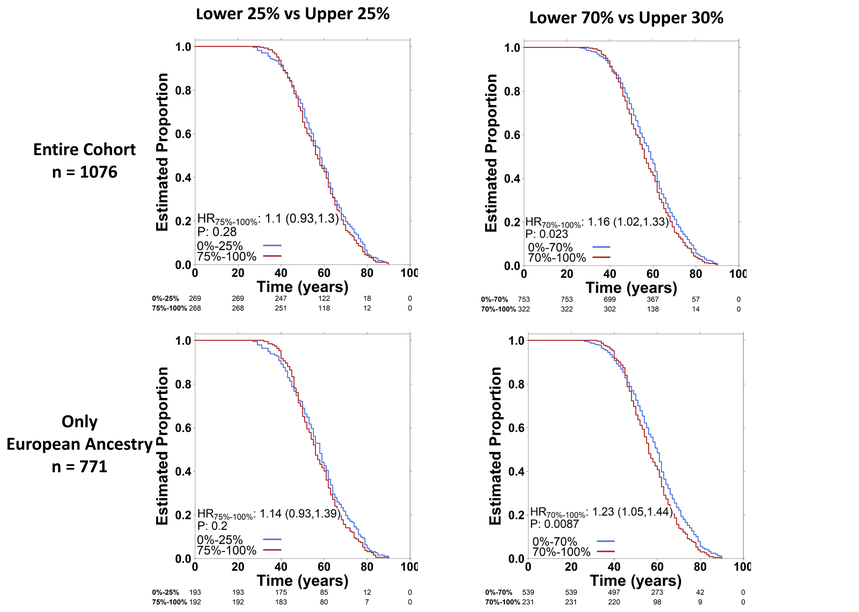
Distribution of polygenic risk scores vary by patient ancestry



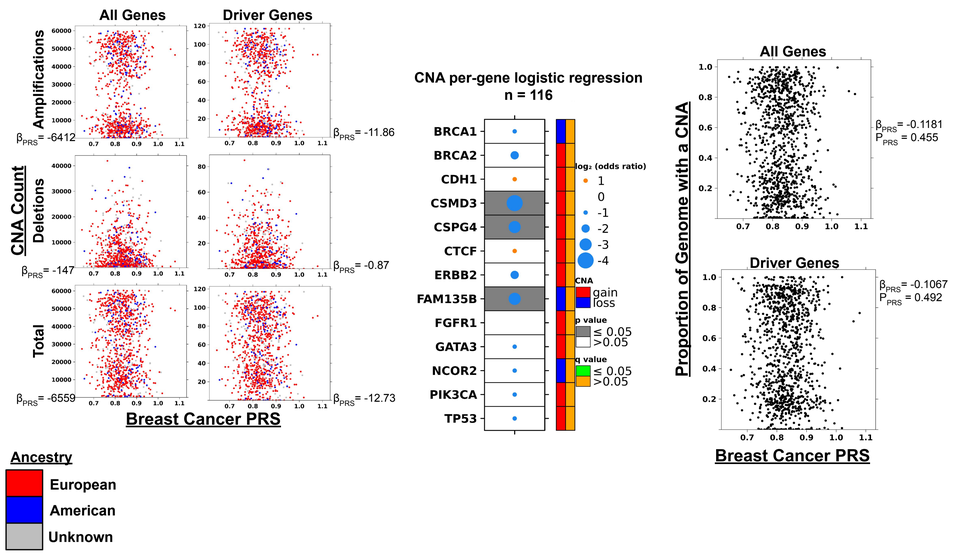
Two-Way ANOVA	P-value
Ancestry	0.059
Sex	0.333
Ancestry:Sex	0.210

Tukey's HSD	P-value	Δμ
EUR-AMR	0.050	-0.014
UNK-AMR	0.329	-0.010
UNK-EUR	0.734	-0.004

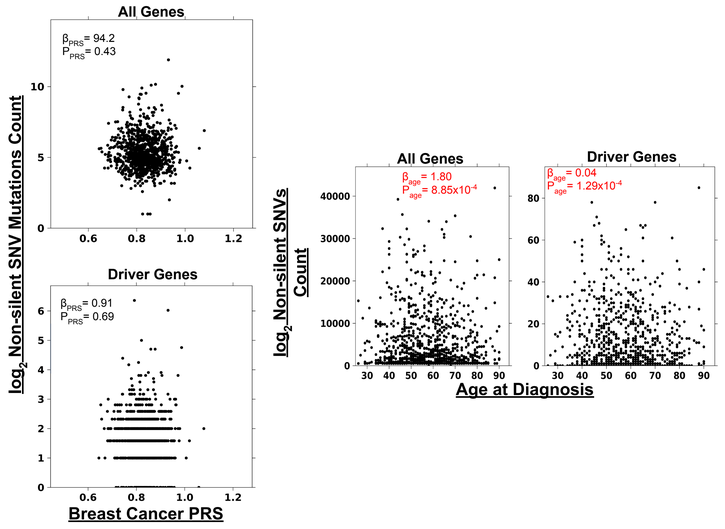
Polygenic risk scores moderately correlate with patient age at diagnosis



Copy number aberrations (CNAs) do not associate with polygenic risk scores



Single nucleotide variants (SNVs) associate with age at diagnosis and not polygenic risk scores



Conclusion & Next Steps

Conclusions:

- Do tumor somatic features associate with PRS in breast cancer?
  - Tumor somatic features (CNAs and SNVs) do not associate with PRS.
  - Non-silent SNVs associate with age at diagnosis.
- Does tumor somatic features associate with clinical data?
  - Polygenic risk scores moderately correlate with patient age at diagnosis
  - Nominal p-values suggest a correlation between age of diagnosis and breast cancer PRS.
    - This association seen in previous work in our lab with prostate cancer (Houlahan *et al.*, 2023).
  - Multiple testing correction using False Discovery Rate (FDR) reduces significance of survival analysis.

Next Steps:

- Associate additional tumor somatic features with PRS and additional clinical data
- Benchmark different PRS models for our breast cancer tumor germline data
- Apply these methods to other types of heritable cancers

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