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 PRS 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. 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.

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.

Results

Distribution of polygenic risk scores vary by patient ancestry

<table>
<thead>
<tr>
<th>Ancestry</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>American</td>
<td>0.059</td>
</tr>
<tr>
<td>European</td>
<td>0.333</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.210</td>
</tr>
</tbody>
</table>

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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