Common genetic variants associated with breast cancer risk used in the Athena study to enhance models identifying women for chemoprevention

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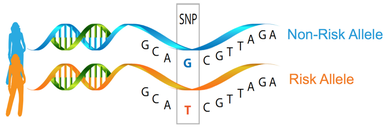
Background

The U.S. Preventive Services Task Force recommends that women with a ≥3% five-year risk of developing breast cancer consider taking selective estrogen receptor modifiers (SERMs) or aromatase inhibitors (AIs) to reduce their risk

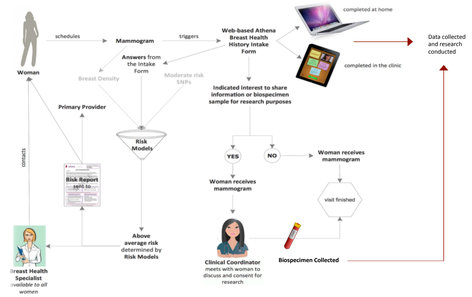
The Gail and Breast Cancer Surveillance Consortium (BCSC) risk models calculate a woman's 5-year breast cancer risk[1,2]



Polygenic risk score (PRS) is calculated by adding up the individual risk associations for 75 identified single nucleotide polymorphism (SNPs) alleles. PRS score has been found to predict women at various levels of risk for breast cancer[3,4]

The Athena Breast Health Network is a research and care collaboration among the five University of California (UC) Medical Centers and Sanford Health that aims to improve care and includes to date 115,000 women

Adaptive Research Model to Improve Patient Care



Objective

To examine the associations between SNP PRS and known breast cancer risk factors (ethnicity, family history of breast cancer and number of biopsies)

To quantify the likely impact on combining a risk factor based risk models with SNP PRS on women's five-year risk estimates

Evaluate how this strategy would affect the proportion of women recommended for chemoprevention

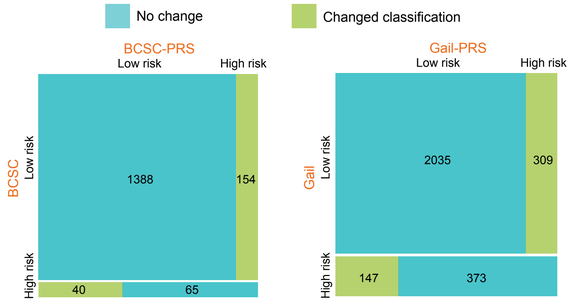
Methods

- 2677 women from Athena with no previous diagnosis of breast cancer were selected
- The cohort was enriched for women determined to be at elevated risk for developing breast cancer by the Gail model
- A panel of 75 breast cancer risk SNPs were evaluated using DNA from saliva and blood samples (Akesogen Inc; COGS Illumina oncochip array).
- The PRS for each patient was calculated by converting the breast cancer odds ratio for each SNP into a likelihood ratio (LR) and combining LR's across SNPs[5]
- BCSC, Gail, BCSC-PRS and Gail-PRS scores (risk models incorporating PRS within a Bayesian framework), were evaluated for each patient
- Associations between variables were assessed using t-test or ANOVA. A threshold of $p<0.05$ was used to assess significance

Results

We found by adding PRS to BCSC or Gail that 10% (154/1542) and 13.6% (309/2274) of patients with a prior BCSC or Gail score <3% five-year risk, respectively, changed classifications to ≥3% five-year risk and would be eligible for chemoprevention

Conversely, 38% (40/105) and 28.3% (147/520) of patients with a BCSC or Gail score of ≥3% five-year risk, respectively, changed classifications by adding PRS and would no longer be eligible for chemoprevention

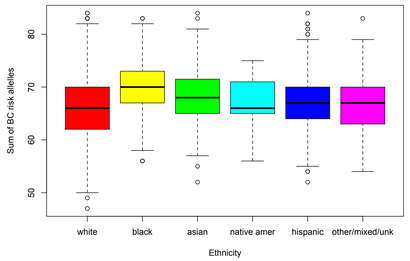


PRS is significantly associated with a family history of breast cancer ($p=1.79E-5$); neither SNP allele count nor PRS associates with previous biopsy status

By ANOVA, there is a statistically significant association between the number of breast cancer risk alleles and race/ethnicity ($p<2E-16$).

Applying Tukey post-hoc analysis to identify which pairs of ethnicities/races have significantly different mean numbers of breast cancer risk alleles, we find that Black, Asian and Hispanic women have significantly more risk alleles than do White women. Black women also have significantly more risk alleles than Asian and Hispanic women

Race/ethnicity	Number of patients	BC risk allele sum (mean [sd])
White	1636	66.0 (5.55)
Black	132	70.2 (5.24)
Asian, Native Hawaiian or Pacific Islander	248	68.2 (5.20)
American Indian or Alaska Native	13	66.6 (5.44)
Hispanic	534	67.2 (5.21)
Other, mixed (2+ races), unknown	119	67.0 (5.34)



Conclusion

- Addition of PRS to breast cancer risk models changes the classification as high risk (5-year risk estimates) for a considerable proportion of women
- BCSC + PRS: 48% of women change risk stratification (net population impact 28%)
- Gail + PRS: 42% of women change risk stratification (net population impact 14.7%)
- PRS is significantly associated with family history of breast cancer
- Number of breast cancer risk alleles is significantly associated with race/ethnicity

Next Steps

- Assess impact of combining PRS with BCSC and 9 genes on breast cancer risk in WISDOM Study (opening 3rd quarter 2016)
- Annual vs. risk-based screening in 100,000 women

Acknowledgements

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