Breast Cancer Polygenic Risk Scores Derived in White European Women Overestimate Risk in Women of Black Origin

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Introduction

- Polygenic Risk Scores (PRS) are tools for disease risk prediction and have been particularly well validated in breast cancer [1][2]
- PRS consider the combined risk of common variants seen in the population and determine an individual's personalised risk of developing breast cancer.

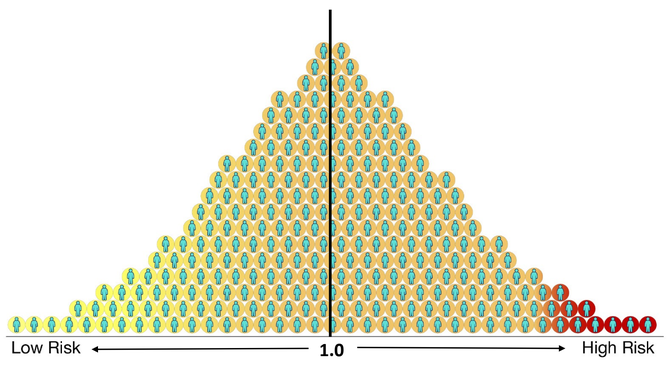


Figure: Polygenic risk scores explain the relative risk of a person developing a disease, compared to population level (~1.0). [3]

- A well calibrated PRS has a population mean of ~1.0 whilst a well discriminated PRS has a case mean > control mean.
- Recently, it has been shown that PRS which are developed in predominantly White European populations require ethnicity specific recalibration [4][5]
- It is widely accepted that genetic risks discovered in one population are not directly transferable to another population.
- We have previously estimated that for SNP143 there is a 91% overprediction of breast cancer risk in the Black group (n=18) and a 26% overprediction in the Ashkenazi group (n=31). [5]
- We have significantly expanded our dataset in this analysis and seek to examine the calibration and discrimination of SNP142 in these two populations from Greater Manchester, UK.

Sample identification

PROCAS: Predicting Risk of Cancer at Screening
BCINIS: Breast Cancer in Northern Israel Study
MCGM: Manchester Centre for Genetic Medicine
[6][7]

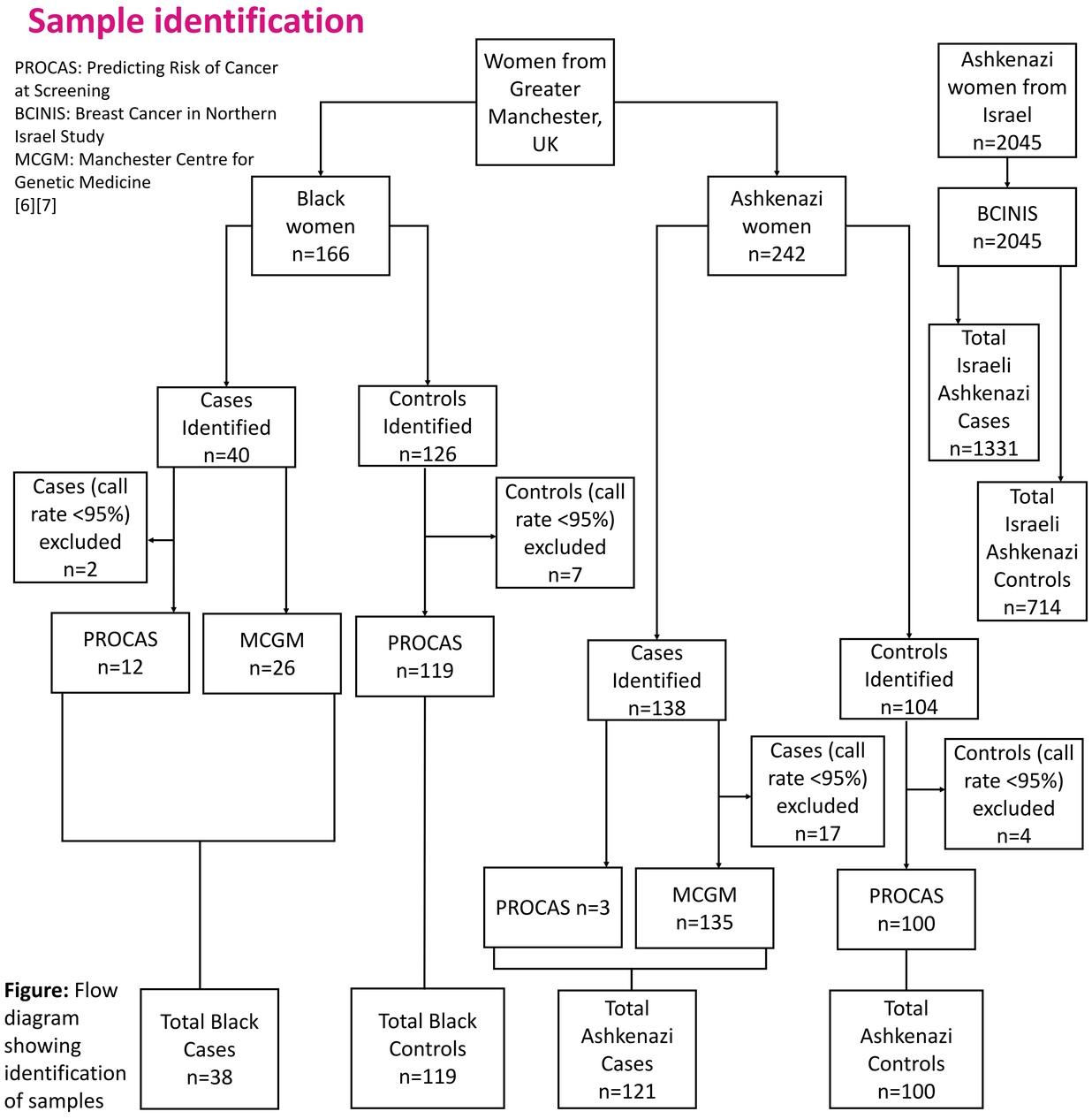
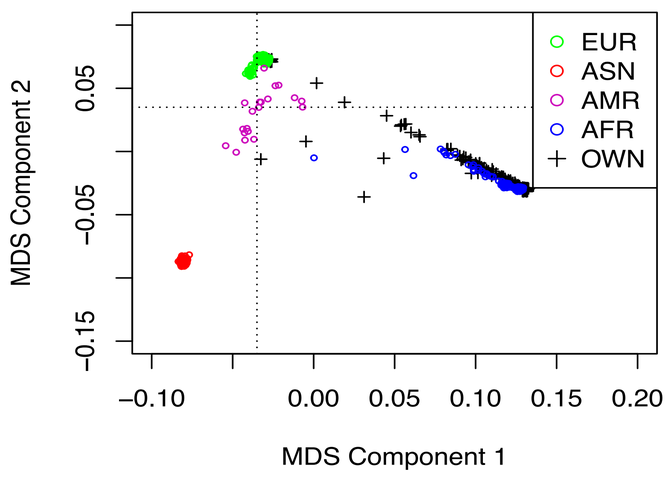


Figure: Flow diagram showing identification of samples

Unsuccessful correction in women of Black descent

SNP142	White European women (n=221, 111 cases, 110 controls)	Black women unadjusted (n=157, 38 cases, 119 controls)	Black women adjusted (n=134, 33 cases, 101 controls)
	Mean PRS (95% CI)	Mean PRS (95% CI)	Mean PRS (95% CI)
Cases	1.33 (1.18-1.48)	1.52 (1.14-1.90)	0.91 (0.63-1.19)
Controls	1.01 (0.89-1.13)	1.62 (1.47-1.77)	0.89 (0.82-0.96)

Table: Mean PRS for cases and controls in White European women, Black women whose EAFs are unadjusted and Black women whose EAFs have been adjusted for ethnicity.



EUR: European
ASN: Asian
AMR: Ad Mixed American
AFR: African
OWN: Our own Black samples
Comparison data from 1000 Genomes project [8]

- OWN samples all Black
- Heterogeneous and spread out
- Genetically very different to green European cluster
- White European PRS cannot be adjusted and used in a Black population

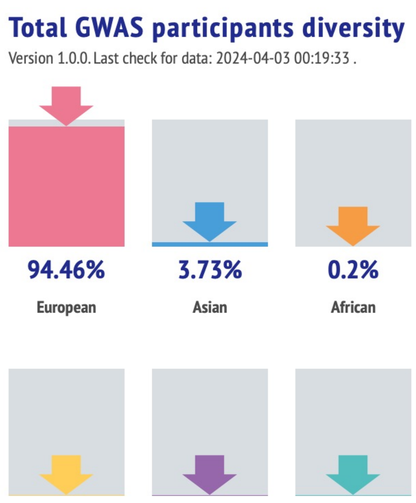
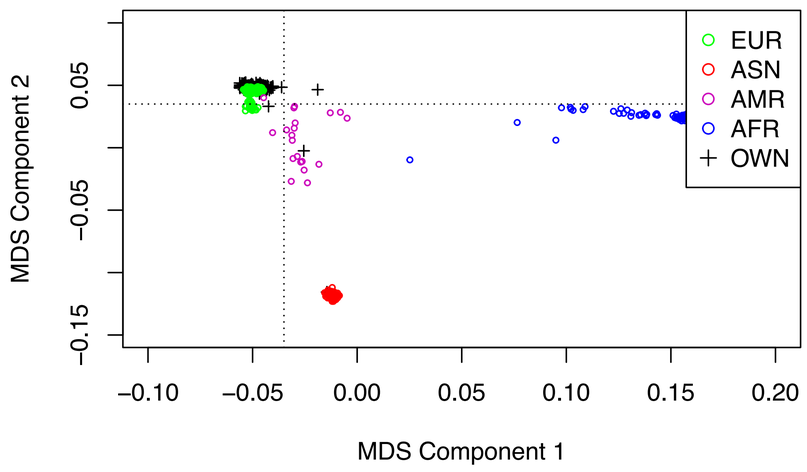


Figure: To date, <1% of research linking genetics to diseases has occurred in Black populations. [9]

Successful correction in women of Ashkenazi Jewish descent

SNP142	Manchester White European (n=221, 111 cases, 110 controls)	Manchester Ashkenazi Jewish unadjusted (n=221, 121 cases, 100 controls)	Manchester Ashkenazi Jewish adjusted (n=221, 121 cases, 100 controls)	Israeli Ashkenazi Jewish unadjusted (n=2045, 1331 cases, 714 controls)	Israeli Ashkenazi Jewish adjusted (n=2045, 1331 cases, 714 controls)
	Mean PRS (95% CI)	Mean PRS (95% CI)	Mean PRS (95% CI)	Mean PRS (95% CI)	Mean PRS (95% CI)
Cases	1.33 (1.18-1.48)	1.54 (1.38-1.70)	1.30 (1.16-1.44)	1.47 (1.43-1.51)	1.25 (1.21-1.29)
Controls	1.01 (0.89-1.13)	1.20 (1.08-1.32)	1.02 (0.92-1.12)	1.15 (1.10-1.20)	0.98 (0.94-1.02)

Table: Mean PRS for cases and controls in White European women, Ashkenazi Jewish women whose EAFs are unadjusted and Ashkenazi Jewish women whose EAFs have been adjusted for ethnicity.



EUR: European
ASN: Asian
AMR: Ad Mixed American
AFR: African
OWN: Our own Ashkenazi samples
Comparison data from HapMap

- OWN samples all Ashkenazi
- Homogeneous in a tight cluster
- Genetically similar to green European cluster
- White European PRS can be adjusted and used in an Ashkenazi population

Acknowledgements

This work was funded by Cancer Research UK via the funding to ACED (C19941/A27859). This research was also supported by the Manchester National Institute for Health Research (NIHR) Biomedical Research Centre (IS-BRC-1215-20007). To find out more email eleanor.roberts-2@manchester.ac.uk. I would like to thank my supervisors, particularly Dr Sacha Howell and Professor Gareth Evans for their constant support and guidance.

Conclusions

- These findings have important implications for multi-ethnic population-based risk prediction programmes
- Failure to calibrate appropriately for women of non-White European heritage will potentially lead to harms through overprediction of breast cancer risk
- Continued research to improve the accuracy of ethnicity specific breast cancer risk prediction algorithms is required, for example GWAS should be carried out in larger populations of African descent

Future work

- As more interracial mixing occurs between individuals of all races, it becomes increasingly difficult to determine the best ethnically relevant PRS to use
- Instead of relying on self-reported ethnicity, one approach could be to design an assay which determines ethnicity by genetic markers on DNA alongside BC risk alleles. Integration of SNP-based ethnicity into PRS design may hold promise for future risk prediction

References

[1] Pashayan, N., et al. (2011). "Polygenic susceptibility to prostate and breast cancer: implications for personalised screening." Br J Cancer 104(10): 1656-1663.
[2] Mavaddat, N., et al. (2019). "Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes." Am J Hum Genet 104(1): 21-34.
[3] https://www.genome.gov/Health/Genomics-and-Medicine
[4] Ho, W. K., et al. (2020). "European polygenic risk score for prediction of breast cancer shows similar performance in Asian women." Nat Commun 11(1): 3833.
[5] Evans, D. G., et al. (2022). "The importance of ethnicity: Are breast cancer polygenic risk scores ready for women who are not of White European origin?" Int J Cancer 150(1): 73-79.
[6] Evans, D. G., et al. (2016). "Improvement in risk prediction, early detection and prevention of breast cancer in the NHS Breast Screening Programme and family history clinics: a dual cohort study." NIHR Journals Library. Chapter 4.
[7] Rennert, G., et al. (2017). "Oral Bisphosphonates and improved survival of breast cancer." Clin Cancer Res 23(7): 1684-1689.
[8] The 1000 Genomes Project Consortium. (2015). "A global reference for human genetic variation." Nature 526, 68-74.
[9] https://gwasdiversitymonitor.com