Can we improve ovarian cancer risk prediction for women with *BRCA1/2* mutations using polygenic risk scores?

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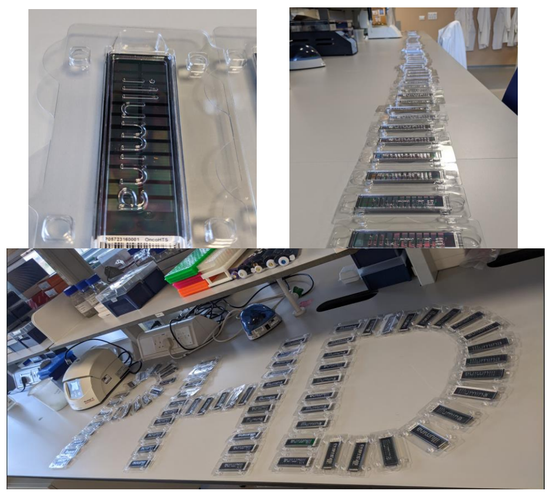
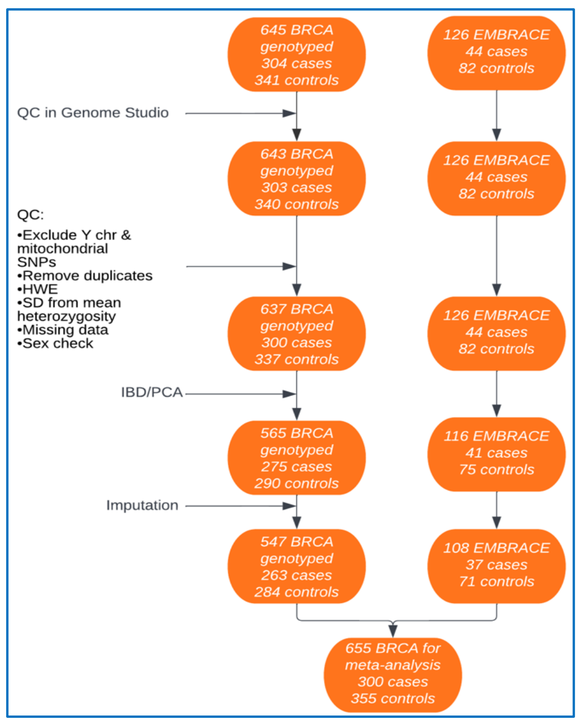
BACKGROUND AND OBJECTIVES

- 1/3 of familial epithelial ovarian cancer (EOC) is explained by *BRCA1/2* pathogenic variants (PVs).
- Polygenic risk scores (PRSs) for *BRCA1/2*-heterozygotes associated with EOC have been created by Barnes et al
- EOC risk is also affected by clinical/hormonal factors.

METHODS

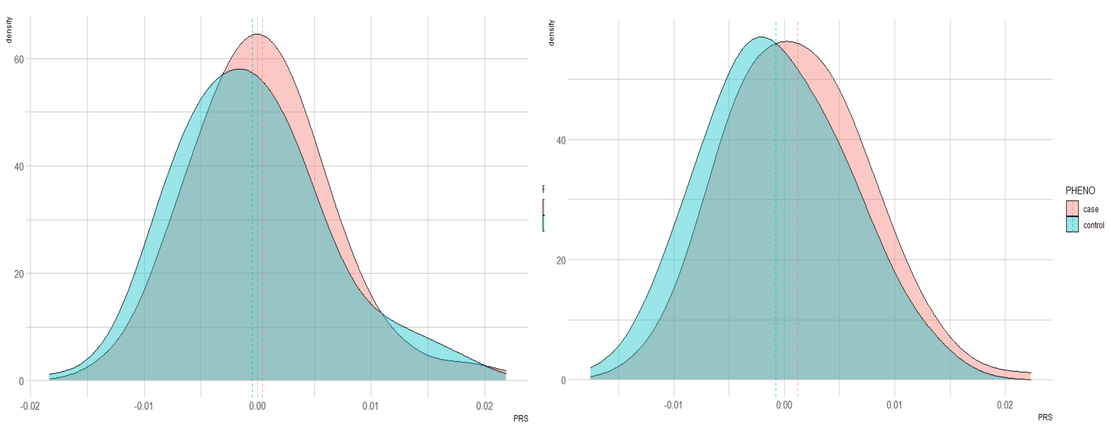
- Samples from 300 cases and 355 controls were genotyped using the Illumina Oncoarray Iscan and in the EMBRACE study
- GWAS-standard QC of the data was performed
- Modified PRSs were constructed based on the Barnes et al PRS.
- Model discrimination and EOC risk was assessed by area under the curve (AUC) values and lowest-highest quintile odds ratio (ORs) difference.
- We investigated model optimisation using logistic regression to combine models with clinical & hormonal data.



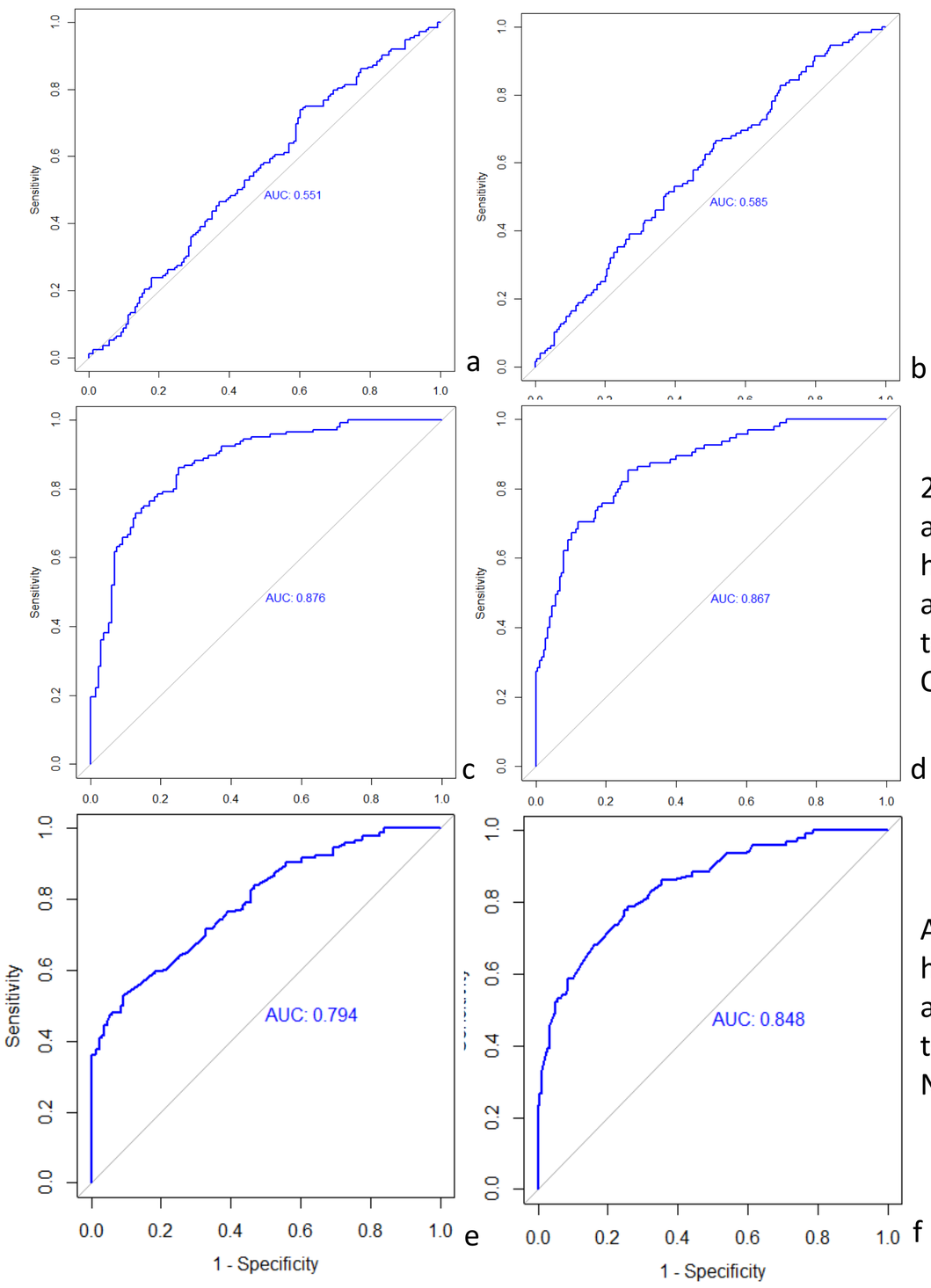


RESULTS

- 547 women (263 cases with EOC and 284 controls) were included in the *BRCA* dataset and 108 women (37 cases and 71 controls) in the EMBRACE dataset.
- Age at diagnosis, family history and survival differed between the datasets, hormonal factors were similar.
- Mean age at EOC diagnosis was 52.2 for *BRCA1*-heterozygotes and 59.8 for *BRCA2*-heterozygotes.



Density plots for BRCA1 and BRCA2 heterozygotes using a 27-SNP PRS model



27-SNP PRS model only

27-SNP PRS plus age, family history, parity and age at first full term pregnancy – OPTIMAL MODEL

Age, family history, parity and age at first full term pregnancy – NO PRS

ROC curves and AUC values for *BRCA1* (a, c and e) and *BRCA2* (b, d and f) heterozygotes

Table of differences between lowest and highest quintiles in different risk models

	Difference between highest and lowest quintile										
Risk model	Unadj	Age	FH of EOC	Age at menarche	Age at menopause	Age at FTP	Parity	OCP use	Combined hormonal factors*	Age at death	Optimised model⁺
***BRCA1* overall**	2.2x	2.5x^	3.8x	3.0x	1.9x^	19.2x' 2.4x^	1.7x	2.3x	23.0x' 2.8x^	23.6x' 2.9x^	46.3x
***BRCA1* serous**	2.3x	1.9x^	3.5x	2.7x	13.5x' 2.3x^	13.5x' 2.3x^	1.5x	2.4x	21.9x' 3.8x^	27.9x' 4.8x^	20.8x
***BRCA2* overall**	6.3x	5.9x^	7.4x	5.2x	20.9x' 5.6x^	43.3x' 11.7x^	3.2x	7.6x	41.5x' 11.2x^	37.7x' 10.2x^	52.1x
***BRCA2* serous**	7.7x	20.4' 6.6x^	8.2x	4.8x	21.4x' 6.9x^	31.8x' 10.3x^	4.1x	12.6x	40.1x' 12.9x^	28.9x' 9.3x^	Not calculable

* Combined hormonal factors included age at menarche, menopause, first full term pregnancy and parity
^ uses unadjusted values for 0-20% percentile as adjusted variable incalculable
' value for 0-20% percentile for adjusted value calculated as 0 so 0.1 used as conservative estimate for difference between highest and lowest quintile
⁺ optimised model includes PRS, age, family history, parity and age at first full term pregnancy

DISCUSSION

- PRS alone does not have good predictive ability for EOC for women with *BRCA1/2*, but in combination with risk factors the risk discrimination ability is significantly improved.
- However the contribution of PRS to the risk model is small.
- It is also possible that in *BRCA1/2*-heterozygotes who already have a significant proportion of their genetic risk explained by these high-risk genes, the impact of PRSs is less than in women with no explained genetic cause.
- Larger prospective studies could assess if combined PRS models inform risk-reducing decisions for women at risk of EOC.

References
- Flaum N, et al. Optimisation of polygenic risk scores in BRCA1/2 pathogenic variant heterozygotes in epithelial ovarian cancer, Genetics in Medicine (2023), doi: https://doi.org/10.1016/j.gim.2023.100898.
- Barnes DR, et al. Polygenic risk scores and breast and epithelial ovarian cancer risks for carriers of BRCA1 and BRCA2 pathogenic variants. Genet Med. 2020;22(10):1653-66.

Conflicts of interest: none. Email: Nicola.flaum@manchester.ac.uk Dr Niki Flaum