

# 149P-Associations between the 313-SNP Polygenic Risk Score and Breast Cancer Risk in women from Crete

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## INTRODUCTION

Breast cancer is the most common cancer among females worldwide. Personalized breast cancer risk estimation could stratify women at different levels of the disease risk, and thus could guide targeted preventative measures and population screening. Polygenic Risk Scores (PRSs) combines the effects of common low-risk variants and could be used for the prediction of breast cancer risk in women. Recently, a 313-SNP PRS (PRS<sub>313</sub>) has been constructed for the estimation of overall and ER-specific breast cancer risk in women of European ancestry [1].

However, the performance of PRS across populations within Europe has not been extensively evaluated, which is important for accurate population-specific risk predictions. This, is crucial before the utility of PRS in clinical decisions.

## OBJECTIVES

In this study, we evaluated of the predictive performance of the PRS<sub>313</sub> in women from the Greek island of Crete, using 667 female breast cancer cases and 332 female healthy controls from the Crete Cancer Genetics Program (CCGP study), for overall disease and estrogen receptor (ER) status.

## MATERIALS & METHODS

**Study population and Genotyping:** CCGP study is a case-control study including 332 female controls, and 667 females invasive breast cancer cases, from which 486 women were diagnosed with ER-positive disease and 177 with ER-negative disease. All samples were genotyped on the Infinium OncoArray-500K.

**Statistical methods:** PRS<sub>313</sub> was calculated in each participant, using the following formula:

$$PRS = \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k + \dots + \beta_{313} x_{313}$$

In this formula, x is the dosage of the risk allele in each individual, and  $\beta$  is the log OR of the risk allele taken from Mavaddat et al 2019. For the calculation of ER-specific disease, the  $\beta$  was taken from the hybrid method, as described in Mavaddat 2019 [1].

Logistic regression analysis was performed to evaluate for associations between overall and ER-specific breast cancer risk, and by quartiles of PRS<sub>313</sub> distribution, using the 2<sup>nd</sup> (25-50<sup>th</sup>) quartile as reference.

Areas Under the Curve (AUC) was calculated as a measure of the discriminatory ability of the PRSs.

## RESULTS

PRS<sub>313</sub> was associated with an increased risk of developing breast cancer with OR (95% CI) 2.40 (1.92-3.03), p-value =  $3.31 \times 10^{-14}$  and AUC = 0.653 for overall breast cancer, 2.72 (2.16-3.47), p-value =  $1.02 \times 10^{-16}$  and AUC = 0.681 for ER-positive disease and 2.18 (1.58-3.03), p-value =  $2.72 \times 10^{-06}$  and AUC = 0.628 for ER-negative disease.

Compared to women in the reference quartile of PRS<sub>313</sub> risk distribution, women in the lowest quartile had a 0.66-fold, 0.54-fold, and 0.89-fold risk; while those in the highest quartile had a 2.73-fold, 3.11-fold, and 2.74-fold risk for overall, ER-positive and ER-negative disease respectively (Figure 1). The 1<sup>st</sup> quartile of the PRS<sub>313</sub> risk distribution for ER-positive and ER-negative disease, included 8.8% and 13.6% of cases respectively, while the 4<sup>th</sup> quartile of the distribution for ER-positive and ER-negative disease included 51.2% of cases and 41.8%, respectively (Table 1).

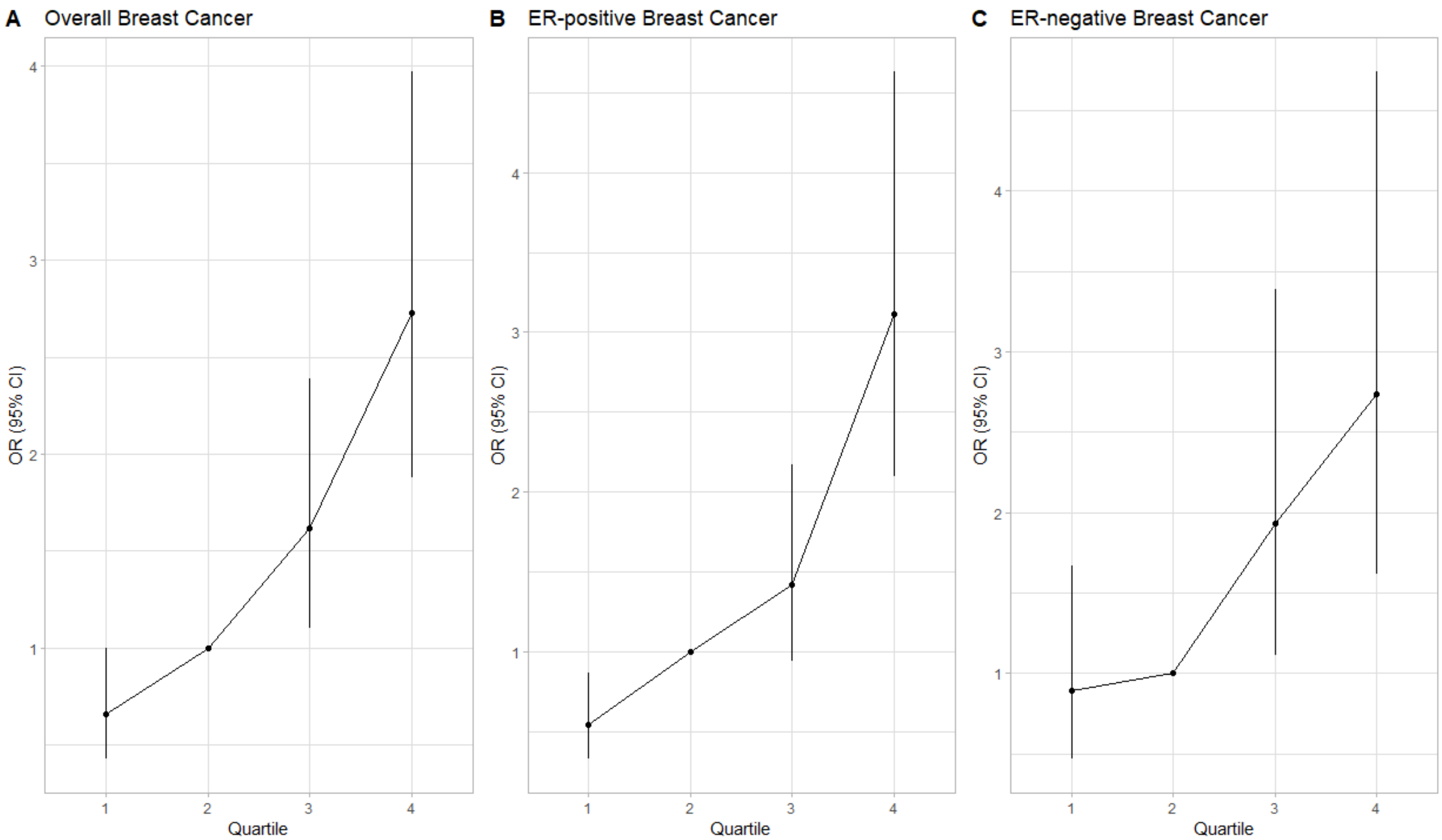


Figure 1: OR (95% CI) by quartiles of PRS<sub>313</sub> risk distribution for (A) overall disease, (B) ER-positive, and (C) ER-negative disease, using the 2<sup>nd</sup> quartile as reference.

**Table 1:** Total number (%) of controls and cases in each quartile of PRS<sub>313</sub> risk distribution for overall breast cancer (BC), ER-positive and ER-negative disease.

Quartiles	Controls (%)	Overall BC Cases (%)	ER-positive BC Cases (%)	ER-negative BC Cases (%)
1	83 (25)	73 (10.9)	43 (8.8)	24 (13.6)
2	83 (25)	111 (16.6)	80 (16.5)	27 (15.3)
3	83 (25)	180 (27.0)	114 (23.5)	52 (29.4)
4	83 (25)	303 (45.4)	249 (51.2)	74 (41.8)

## CONCLUSIONS

PRS<sub>313</sub> could stratify Cretan women based on their individualized overall and ER-specific breast cancer risk, at the extreme quartiles. However, risk is probably overestimated, since the CCGP study was part of the training set used for the construction of PRS<sub>313</sub> [1]. ER-positive breast cancer is better predicted by PRS<sub>313</sub> compared to ER-negative disease.

In the future, combination of PRS<sub>313</sub> with classical breast cancer risk factors could potentially provide a more comprehensive risk prediction and thus improve risk stratification of Cretan women. If these results confirmed in a bigger dataset, it has the potential to be evaluated in the clinic.

## REFERENCES

[1] Mavaddat N, et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. American journal of human genetics. 2019.

**Conflicts of interest:** The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS



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