Polygenic Risk Modelling for Prediction of Epithelial Ovarian Cancer Risk

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Running Title: Polygenic Risk Modelling for Prediction of Epithelial Ovarian Cancer Risk

ABSTRACT

Polygenic risk scores (PRS) for epithelial ovarian cancer (EOC) have the potential to improve risk stratification. Joint estimation of Single Nucleotide Polymorphism (SNP) effects in models could improve predictive performance over standard approaches of PRS construction. Here, we implemented computationally-efficient, penalized, logistic regression models (lasso, elastic net, stepwise) to individual level genotype data and a Bayesian framework with continuous shrinkage, "select and shrink for summary statistics" (S4), to summary level data for epithelial non-mucinous ovarian cancer risk prediction. We developed the models in a dataset consisting of 23,564 non-mucinous EOC cases and 40,138 controls participating in the Ovarian Cancer Association Consortium (OCAC) and validated the best models in three populations of different ancestries: prospective data from 198,101 women of European ancestries; 7,669 women of East Asian ancestries; 1,072 women of African ancestries, and in 18,915 *BRCA1* and 12,337 *BRCA2* pathogenic variant carriers of European ancestries. In the external validation data, the model with the strongest association for non-mucinous EOC risk derived from the OCAC model development data was the S4 model (27,240 SNPs) with odds ratios (OR) of 1.38(95%CI:1.28–1.48,AUC:0.588) per unit standard deviation, in women of European ancestries; 1.14(95%CI:1.08–1.19,AUC:0.538) in women of East Asian ancestries; 1.38(95%CI:1.21-1.58,AUC:0.593) in women of African ancestries; hazard ratios of 1.36(95%CI:1.29–1.43,AUC:0.592) in *BRCA1* pathogenic variant carriers and 1.49(95%CI:1.35-1.64,AUC:0.624) in *BRCA2* pathogenic variant carriers. Incorporation of the S4 PRS in risk prediction models for ovarian cancer may have clinical utility in ovarian cancer prevention programs.

Keywords: polygenic risk score, penalized regression model

INTRODUCTION

Rare variants in known high and moderate penetrance susceptibility genes (*BRCA1*, *BRCA2*, *BRIP1*, *PALB2*, *RAD51C*, *RAD51D* and the mis-match repair genes) account for about 40% of the inherited component of EOC disease risk (1,2). Common susceptibility variants, reviewed in Kar et. al. and Jones et. al., explain about 6% of the heritability of EOC (1,3). Polygenic risk scores (PRS) provide an opportunity for refined risk stratification in the general population and in carriers of rare moderate or high risk alleles.

A PRS is calculated as the weighted sum of the number of risk alleles carried for a specified set of variants. The best approach to identify the variant set and their weights to optimize the predictive power of a PRS is unknown. A common approach involves selecting a set of variants that reach a threshold for association based on the p-value for each variant with or without pruning to remove highly correlated variants (4,5). More complex machine learning approaches that do not assume variant independence have also been used (6,7), but these methods have produced only modest gains in predictive power for highly polygenic phenotypes (6,8). Penalized regression approaches such as the lasso, elastic net and the adaptive lasso have also been used with individual level data (9), but a major drawback is the computational burden required to fit the models (9,10).

We present novel, computationally-efficient PRS models using two approaches: 1) penalized regression models including the lasso, elastic net and minimax concave penalty for use with individual genotype data; and 2) a Bayesian regression model with continuous shrinkage priors for use where only summary statistics are available - referred to as the "select and shrink with summary statistics" (S4) method. We compare these models with two commonly used methods, stepwise regression with p-value thresholding and LDPred.

MATERIALS (SUBJECTS) AND METHODS

Model Development Study Population

EOC is a highly heterogeneous phenotype with five major histotypes for invasive disease – high-grade serous, low-grade serous, endometrioid, clear cell and mucinous histotype. The mucinous histotype is the least common and its origin is the most controversial with up to 60% of diagnosed cases of mucinous ovarian cancer often being misdiagnosed metastasis from non-ovarian sites (11). Therefore, in this study, we performed PRS modelling and association testing for all cases of invasive, non-mucinous EOC. We used genotype data from 23,564 invasive non-mucinous EOC cases and 40,138 controls with >80% European ancestries from 63 case-control studies included in the Ovarian Cancer Association Consortium (OCAC) for model development. The distribution of cases by histotype was high-grade serous (13,609), low-grade serous (2,749), endometrioid (2,877), clear cell (1,427), and others (2,902). Sample collection, genotyping and quality control have been previously described (12). Genotype data were imputed to the Haplotype Reference Consortium reference panel using 470,825 SNPs that passed quality control. Of the 32 million SNPs imputed, 10 million had imputation $r^2 > 0.3$ and were included in this analysis.

Model Validation Study Populations

We validated the best-fitting PRS models developed in the OCAC data in 657 prevalent and incident cases of invasive, non-mucinous EOC and 198,101 female controls of European ancestries from the UK Biobank. Samples were genotyped using either the Affymetrix UK BiLEVE Axiom Array or Affymetrix UK Biobank Axiom Array (which share 95% marker content), and then imputed to a combination of the Haplotype Reference Consortium, the 1000Genomes phase 3 and the UK10K reference panels (13). We restricted analysis to genetically confirmed females of European ancestries. We excluded individuals if they were outliers for heterozygosity, had low genotyping call rate <95%, had sex chromosome aneuploidy, or if they were duplicates (cryptic or intended) (12). All SNPs selected in the model development phase were available in the UK Biobank.

We investigated transferability of the best-fitting PRS models to populations of non-European ancestries using genotype data from females of East Asian and African ancestries genotyped as part of the OCAC OncoArray Project (14,15). Women of East Asian ancestries - 2,841 non-mucinous invasive EOC and 4,828 controls - were identified using a criterion of >80% Asian ancestries. This included samples collected from studies in China, Japan, Korea and Malaysia and samples from studies conducted in the US, Europe and Australia (14). Similarly, women of African ancestries - 368 cases of non-mucinous invasive EOC and 704 controls - mainly from studies conducted in the US, were identified using a criterion of >80% African ancestries as described previously (15).

We also assessed the performance of the best-fitting PRS models in women of European ancestries (>80% European ancestries) with the pathogenic *BRCA1* and *BRCA2* variants from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA). We used genotype data from 18,915 *BRCA1* (2,053 invasive EOC cases) and 12,337 *BRCA2* (717 invasive EOC cases) pathogenic variant carriers from 63 studies contributing to CIMBA (16). Genotyping, data quality control measures, intercontinental ancestries assessment and imputation to the HRC reference panel are as described for the OCAC study population.

Statistical Analysis

Polygenic Risk Models

For all PRS models, we created scores as linear functions of the allele dosage in the general form $PRS_i = \sum_j^p x_{ij}\beta_j$ where genotypes are denoted as x (taking on the minor allele dosages of 0, 1 and 2), with x_{ij} representing the ith individual for the jth SNP (out of p SNPs) on an additive log scale and β_j represents the weight - the log of the odds ratio - of the jth SNP. We used different approaches to select and derive the optimal weights, β_j, in models as described below.

Penalized logistic regression models

A penalized logistic regression model for a set of SNPs aims to identify a set of regression coefficients that minimize the regularized loss function given by

$$plr(x;\lambda,\kappa) = \begin{cases} x - \lambda sign(x)/(1-\kappa) & if|x| < \lambda/\kappa \; and \; |(x)| > \lambda \\ x \; if|x| \geq \dfrac{\lambda}{\kappa} \\ 0 \; if|(x)| < \lambda \end{cases}$$

where x is the effect estimate of a SNP, λ is the tuning parameter and κ is the threshold (penalty) for different regularization paths. λ and κ are parameters that need to be chosen during model development to optimize performance. The lasso, elastic net, minimax concave penalty (MCP), and p-value thresholds are instances of the function with different κ values. We minimized the winner's curse effect on inflated effect estimates for rare SNPs by penalizing rarer SNPs more heavily than common SNPs. Details are provided in the Supplementary Methods.

We used a two-stage approach to reduce computational burden without a corresponding loss in predictive power. The first stage was a SNP selection stage using a sliding windows approach, with 5.5Mb data blocks and a 500kb overlap between blocks. SNP selection was performed for each block and selected SNPs were collated. Single SNP association analyses were then run, and all SNPs with a χ^2 test statistic of less than 2.25 were excluded. The 2.25 cutoff was arbitrary and selected to maximise computational efficiency without loss in predictive power. Penalized regression models were applied to the remaining SNPs using λ values of 3.0 and κ values of 0.0, 0.2, 0.4, 0.6, 0.8 and 1.0. SNPs selected in any of these models were included in subsequent analyses. In the second stage, we fit penalized regression models to the training dataset with λ values ranging from 3.0 to 5.5 in increments of 0.1 iterated over κ values from -3.0 to 1 in increments of 0.1. The lasso model ($\kappa = 0$) for each value of λ was fitted first, to obtain a unique maximum. From the fitted maximum the κ value was changed, and the model refitted.

We applied this two-stage approach with five-fold cross-validation (**Figure 1**). In each iteration, the data set was split into five, with one part constituting the the test data and the other four constituting the training data. The variants and their weights from the two-stage penalized logistic regression modelling in the training data were used to calculate the area under the receiver operating characteristic curve (AUC) in the test data in each iteration. AUC estimates for each combination of λ and κ were obtained. We repeated this process for each cross-validation iteration to obtain a mean AUC for each combination of λ and κ. Finally, we selected the tuning and threshold parameters from the lasso, elastic net and minimax concave penalty models with the maximum mean cross-validated AUC and fitted penalized logistic regression models with these parameters to the entire OCAC dataset to obtain SNP weights for PRS scores.

Stepwise logistic regression with variable P-value threshold

This model is a general PLR model with κ=1. As with the other PLR models, we investigated various values for λ values (corresponding to a variable P-value threshold for including a SNP in the model). However, we observed that the implementation of this model on individual level data was more difficult than for other κ values because the model would sometimes converge to a local optimum rather than the global optimum. Therefore, we applied an approximate conditional and joint association analysis using summary level statistics correcting for estimated LD between SNPs, using a reference panel of 5,000 individual level genotype OCAC data as described in Yang et.al. (17). Details are provided in the Supplementary Methods.

LDPred

LDPred is a Bayesian approach that shrinks the posterior mean effect size of each marker based on a point-normal prior and LD information from an external reference panel. We derived seven candidate polygenic risk scores assuming the fractions of associated variants

were 0.001, 0.003, 0.01, 0.03, 0.1, 0.3 and 1.0 respectively using the default parameters as detailed in Vilhjálmsson et.al. (18) using an LD reference panel of 503 samples of European ancestries from the 1000 Genomes phase 3 release and effect estimates from the OCAC model development data.

Select and shrink using summary statistics (S4)

The S4 algorithm is similar to the PRS-CS algorithm (19) - a Bayesian method that uses summary statistics and between-SNP correlation data from a reference panel to generate the PRS scores by placing a continuous shrinkage prior on effect sizes. We adapted this method with penalization of rarer SNPs by correcting for the standard deviation resulting in the selection of fewer SNPs. We varied three parameters, *a, b,* φ, which control the degree of shrinkage of effect estimates. Φ, the overall shrinkage parameter, is influenced by values of *a* which controls shrinkage of effect estimates around 0 and *b* which control shrinkage of larger effect estimates. We generated summary statistics for each cross-validation training set and selected the parameters that gave the best results on average from the cross-validation and applied these to the set of summary statistics for the complete OCAC data set to obtain the final set of weights.

PRS based on meta-analysis of OCAC-CIMBA summary statistics

We conducted a meta-analysis of the EOC associations in *BRCA1* variant carriers, *BRCA2* variant carriers and the participants participating in OCAC (see Supplementary Methods) and constructed two PRS models. An S4 PRS was generated by applying the *a, b* and φ parameters from the S4 model described above. A stepwise PRS was generated by selecting all SNPs that were genome-wide significant ($p < 5 \times 10^{-8}$) in the meta-analysis, along with any independent signals in the same region with $p < 10^{-5}$ from the histotype specific analyses for low-grade serous, high-grade serous, endometrioid, clear cell ovarian cancer and non-mucinous invasive EOC.

Polygenic risk score performance

The best lasso, elastic net, stepwise and S4 models from the model development stage were validated using two independent data sources: the UK Biobank data and *BRCA1/BRCA2* pathogenic variant carriers from the CIMBA. In the UK Biobank data, we evaluated discriminatory performance of the models using the AUC and examined the association between standardized PRS and risk of non-mucinous EOC using logistic regression analysis. For the CIMBA data, we assessed associations for each version of the PRS and invasive non-mucinous EOC risk using weighted Cox regression methods (20). PRSs in the CIMBA data were scaled to the same PRS standard deviations as the OCAC data, meaning that per standard deviation hazard ratios estimated on CIMBA data are comparable to PRS associations in the OCAC and UK Biobank data. The regression models were adjusted for birth cohort (<1920, 1920-1929, 1930-1939, 1940-1949, ≥1950) and the first four ancestries informative principal components (calculated separately by iCOGS/OncoArray genotyping array) and stratified by Ashkenazi Jewish ancestries and country. Absolute risks by PRS percentiles adjusting for competing risks of mortality from other causes were calculated as described in the Supplementary Material.

Transferability of PRS scores to non-European Ancestries

We implemented two straightforward approaches to disentangle the role of ancestries on polygenic risk scoring. We selected homogenous ancestral samples by using a high cut-off criterion of 80% ancestries and we standardized the polygenic risk scores by mean-centering within each population. These approaches led to a more uniform distribution of polygenic risk scores within each ancestral population. Further adjustments using principal components of ancestries did not attenuate risk estimates.

RESULTS

Model development

The results for the models based on individual level genotype data are shown in **Table 1**. The elastic net model had the best predictive accuracy (AUC=0.586). The optimal value of λ obtained from regularization paths for the MCP model was 3.3 meaning the best MCP model was equivalent to the lasso model. The best-fitting model based on summary statistics was the S4 (AUC=0.593) and the LDPred model had the poorest performance of the methods tested (AUC=0.552. It was not considered for further validation in other datasets. All SNPs selected and the associated weights for each model are provided in **Supplementary Tables 1 – 6**.

Model validation in women of European ancestries

Overall the PLR models performed slightly better in the UK Biobank data than the model development data (**Table 2**). Of the models developed using the OCAC model development data, the association was strongest with the S4 PRS. In *BRCA1* and *BRCA2* variant carriers, prediction accuracy was generally higher among *BRCA2* carriers than *BRCA1* carriers. Consistent with results from the general population in the UK Biobank, the S4 PRS model also had the strongest association and predictive accuracy for invasive EOC risk in both *BRCA1* and *BRCA2* carriers. Sensitivity analyses were conducted in which the unadjusted models for *BRCA1* and *BRCA2* carriers were progressively adjusted for birth cohort and 6 principal components. There was little difference in HR estimates and association P-values going from the unadjusted model to the model adjusting for six principal components (Supplementary Table 7). The PRS models developed using the OCAC-CIMBA meta-analysis results had better discriminative ability in the UK Biobank than the PRS models developed using only OCAC data. Compared with the S4 PRS using only OCAC data, the S4 PRS model derived from the meta-analysis had fewer SNPs, a stronger association with invasive EOC risk and better predictive accuracy. Similarly, the stepwise model from the OCAC-CIMBA meta-

analysis performed better than the stepwise model from only OCAC data, but included more SNPs.

The observed distribution of the OR estimates within centiles of the PRS distribution were consistent with ORs from predicted values under the assumption that all SNPs interact multiplicatively (**Figure 3**), with all 95% confidence intervals intersecting with the theoretical estimates for women of European ancestries. Compared with women in the middle quintile, women in the top 95th percentile of the lasso derived PRS model had a 2.23-fold increased odds of non-mucinous EOC (**Table 3**).

Absolute Risk of Developing Ovarian Cancer by PRS percentiles

We estimated cumulative risk of EOC within PRS percentiles for women in the general population (**Figure 2**), by applying the odds ratio from the PRS models to age-specific population incidence and mortality data for England in 2016. For *BRCA1* and *BRCA2* pathogenic variant carriers, we applied the estimated hazard ratios from PRS models to age-specific incidence rates obtained from Kuchenbaecker et al. (21). For women in the general population, the estimated cumulative risks of EOC by age 80 for women at the 99th centile of the PRS distribution were 2.24%, 2.18%, 2.54% and 2.81% for the lasso, elastic net, stepwise and S4 models, respectively. In comparison, the absolute risks of EOC by age 80 for women at the 1st centile were 0.76%, 0.78%, 0.64% and 0.56% for the lasso, elastic net, stepwise and S4 models, respectively.

The absolute risks of developing EOC in *BRCA1* and *BRCA2* pathogenic variant carriers were considerably higher than for women in the general population (Figures S1 and S2). The estimated absolute risk of developing ovarian cancer by age 80 for *BRCA1* carriers at the 99th PRS centiles were 63.2%, 66.3%, 59.0% and 68.4% for the lasso, elastic net, stepwise and S4 models, respectively. The corresponding absolute risks for women at the 1st PRS centile were 27.7%, 25.6%, 30.8% and 24.2%. For *BRCA2* carriers the absolute risks for women at the

714 99th centile were 36.3%, 36.3%, 33.0% and 36.9%; and 7.10%, 7.12%, 8.24% and 6.92% at the
715 1st centile for the lasso, elastic net, stepwise and S4 models, respectively.

716 ***PRS distribution and ancestries***

717 To investigate the transferability of the PRS to other populations, we applied the scores
718 to women of African (N=1,072) and Asian (N=7,669) ancestries genotyped as part of the
719 OncoArray project. In general, the distributions of the raw PRS were dependent on both the
720 statistical methods used in SNP selection and ancestral group. PRS models that included more
721 variants had less dispersion, such that the elastic net models had the least between individual
722 variation in all ancestral groups (standard deviation=0.15, 0.19 and 0.22 for individuals of
723 Asian, African and European ancestries respectively), while the distributions from the stepwise
724 models were the most dispersed (standard deviation = 0.23, 0.27 and 0.30 for individuals of
725 Asian, African and European ancestries respectively). As expected, given the variation in
726 variant frequencies by population, the distribution of polygenic scores was significantly
727 different across the three ancestral groups, with the least dispersion among women of Asian
728 ancestries and the most variation in women of European ancestries. The difference in polygenic
729 risk score distribution was minimized after correction for ancestry by standardizing the PRS to
730 have unit standard deviation using the control subjects for each ancestral group.

731 High PRSs were significantly associated with risk of non-mucinous EOC in both Asian
732 and African ancestries (**Table 4**), although the effects were weaker than in women of European
733 ancestries. For example, with the lasso model, the odds ratio per unit standard deviation
734 increment in polygenic score was 1.16 (1.11–1.22) in women of East Asian ancestries, 1.28
735 (1.13–1.45) in women of African ancestries and 1.37 (1.27–1.48) in women of European
736 ancestries (p for heterogeneity < 0.0001). Variability in effect sizes among ancestral groups
737 was highest for the stepwise model (I^2 = 92%) versus 84% and 83% for elastic net and lasso
738 derived polygenic scores respectively. The best discriminative model among women of East

Asian and African ancestries were the elastic net PRS (AUC=0.543) and the S4 PRS derived from OCAC-CIMBA meta-analysis (AUC=0.596). Women of African ancestries in the top 5% of the PRS had about two-fold increased risk compared to women in the middle quintile (lasso OR:1.64,95%CI: 0.90–3.00; elastic net OR:1.64,95%CI:0.90–3.00; stepwise OR:2.15, 95%CI:1.17–3.95; S4 OR:1.80, 95%CI:0.99–3.31). Effect estimates were smaller in women of East Asian ancestries with women in the top 5% of the PRS, having about a 1.5 fold increased risk compared to women in the middle quintile (lasso OR:1.40, 95%CI:1.12–1.76; elastic net OR:1.60, 95% CI:1.28–2.01; stepwise OR:1.32, 95%CI:1.04–1.65; S4 OR:1.32, 95%CI:1.05–1.66).

DISCUSSION

Genetic risk profiling with polygenic risk scores has led to actionable outcomes for cancers such as breast and prostate (22,23). Previous PRS scores for invasive EOC risk in the general population and *BRCA1/BRCA2* pathogenic variant carriers have been based on genetic variants for which an association with EOC risk had been established at nominal genome-wide significance (20,24,25). Here, we explored the predictive performance of computationally-efficient, penalized, regression methods in modelling joint SNP effects for EOC risk prediction in diverse populations and compared them with common approaches. By leveraging the correlation between SNPs which do not reach nominal genome-wide thresholds and including them in PRS models, the polygenic risk scores derived from penalized regression models provide stronger evidence of association with risk of non-mucinous EOC than previously published PRSs in both the general population and in *BRCA1/BRCA2* pathogenic variant carriers.

Recently, Barnes et. al derived a PRS score using 22 SNPs that were significantly associated with high-grade serous EOC risk (PRS_{HGS}) to predict EOC risk in *BRCA1/BRCA2* pathogenic variant carriers (20). To make effect estimates obtained in this analysis comparable

764 to the effect estimates obtained from the PRS_{HGS}, we standardized all PRSs using the standard
765 deviation from unaffected *BRCA1/BRCA2* carriers and provide estimates which are directly
766 comparable to the PRS_{HGS} in Supplementary Table 9. All PRS models in this analysis except
767 the Stepwise (OCAC only) had higher effect estimates (20). The AUC estimates from the
768 adjusted PLR methods implemented in this analysis, are higher than the corresponding PRS_{HGS}
769 estimates for *BRCA1* carriers (0.604). In *BRCA2* carriers, the AUC estimates for the lasso and
770 S4 models did slightly better than the PRS_{HGS} AUC estimate (0.667), while the stepwise did
771 slightly worse and the elastic net estimate was comparable. The AUC estimates for women in
772 the general population, as estimated from the UK Biobank, are slightly higher than estimates
773 from previously published PRS models for overall EOC risk by Jia et al (AUC=0.57) and Yang
774 et al (AUC=0.58) (25,26).

775 The level of risk for women above the 95th percentile of the PRS is similar to that
776 conferred by pathogenic variants in moderate penetrance genes such as *FANCM* (RR=2.1,
777 95%CI=1.1–3.9) and *PALB2* (RR=2.91 95%CI=1.40–6.04) (27,28). The inclusion of other risk
778 factors such as family history of ovarian cancer, presence of rare pathogenic variants, age at
779 menarche, oral contraceptive use, hormone replacement therapy, parity, and endometriosis in
780 combination with the PRS could potentially improve risk stratification as implemented in the
781 CanRisk tool (www.canrisk.org), which currently uses a 36-SNP PRS with the potential to use
782 other PRS models (29,30).

783 We found that the discrimination of the PRS varied by ancestry with greater
784 discrimination in women of European ancestries than in women of African and East Asian
785 ancestries. The better performance in African than East Asian populations is in contrast to what
786 one would expect given human demographic history, and the performance of PRS for other
787 phenotypes in African populations. This may simply be the play of chance given the small
788 number of samples of African ancestries. Alternatively it reflects the fact that the allele

789 frequencies of the PRS SNPs were more similar between the African and European populations
790 than they were with the East Asian population (Supplementary Tables 10-14).

791 Further optimization of the models could be achieved by varying the penalization
792 function based on prior knowledge. For example, varying the penalty function to select more
793 SNPs from genomic regions with know susceptibility variants given that susceptibility variants
794 tend to cluster together. Alternatively, the penalty functions could be modified to incorporate
795 information about functionally active regions of the genome such a promoters, enhancers and
796 transcription factor binding sites. However, incorporating functional annotation has resulted in
797 limited gains in prediction accuracy for complex traits such as breast cancer, celiac disease,
798 type 2 diabetes and rheumatoid arthritis (31).

799 Machine/deep learning approaches are alternative ways to constructing PRS, but
800 methods such as the neural net, support vector machine and random forest have been shown to
801 be computationally prohibitive or produce inferior results to other approaches (32,33).Other
802 machine learning methods, such as those based on gradient boosting do not perform well in
803 genomic regions where strong genetic interactions are present, for which alternative
804 approaches such as the LDPred may perform better (18). Our approach has several benefits
805 over alternative machine learning methods, including its simplicity, and intrinsic robustness to
806 minor misspecification of LD or association strength.

807 In conclusion, our results indicate that using the lasso model for individual level
808 genotype data and the S4 model for summary level data in polygenic risk score construction
809 provide an improvement in risk prediction for non-mucinous EOC over more common
810 approaches. Our approach overcomes the computational limitations in the use of penalized
811 methods for large scale genetic data, particularly in the presence of highly-correlated SNPs and
812 the use of cross-validation for parameter estimation is preferred. In practical terms, the
813 polygenic risk score provides sufficient discrimination, particularly for women of European

ancestries, to be considered for inclusion in risk prediction and prevention approaches for EOC in the future. Further studies are required to optimize these polygenic risk scores in ancestrally diverse populations and to validate their performance with the inclusion of other genetic and lifestyle risk factors.

Data Availability

OncoArray germline genotype data for the OCAC studies have been deposited at the European Genome-phenome Archive (EGA; https://ega-archive.org/), which is hosted by the EBI and the CRG, under accession EGAS00001002305. Summary statisitics for the Ovarian Cancer Association Consortium are available in the NHGRI-EBI GWAS catalogue (https://www/ebi.ac.uk/gwas/home) under the accession number GCST90016665. A subset of the OncoArray germline genotype data for the CIMBA studies are publically available through the database of Genotypes and Phenotypes (dbGaP) under accession phs001321.v1.p1. The complete data set will not be made publically available because of restraints imposed by the ethics committees of individual studies; requests for further data can be made to the Data Access Coordination Committee (http://cimba.ccge.medschl.cam.ac.uk/)

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See Supplementary Material

Conflicts of Interest

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Ethics Statement

All study participants provided written informed consent and participated in research or clinical studies at the host institute under ethically approved protocols. The studies and their approving institutes are listed in the Supplementary Material (Ethics Statement)

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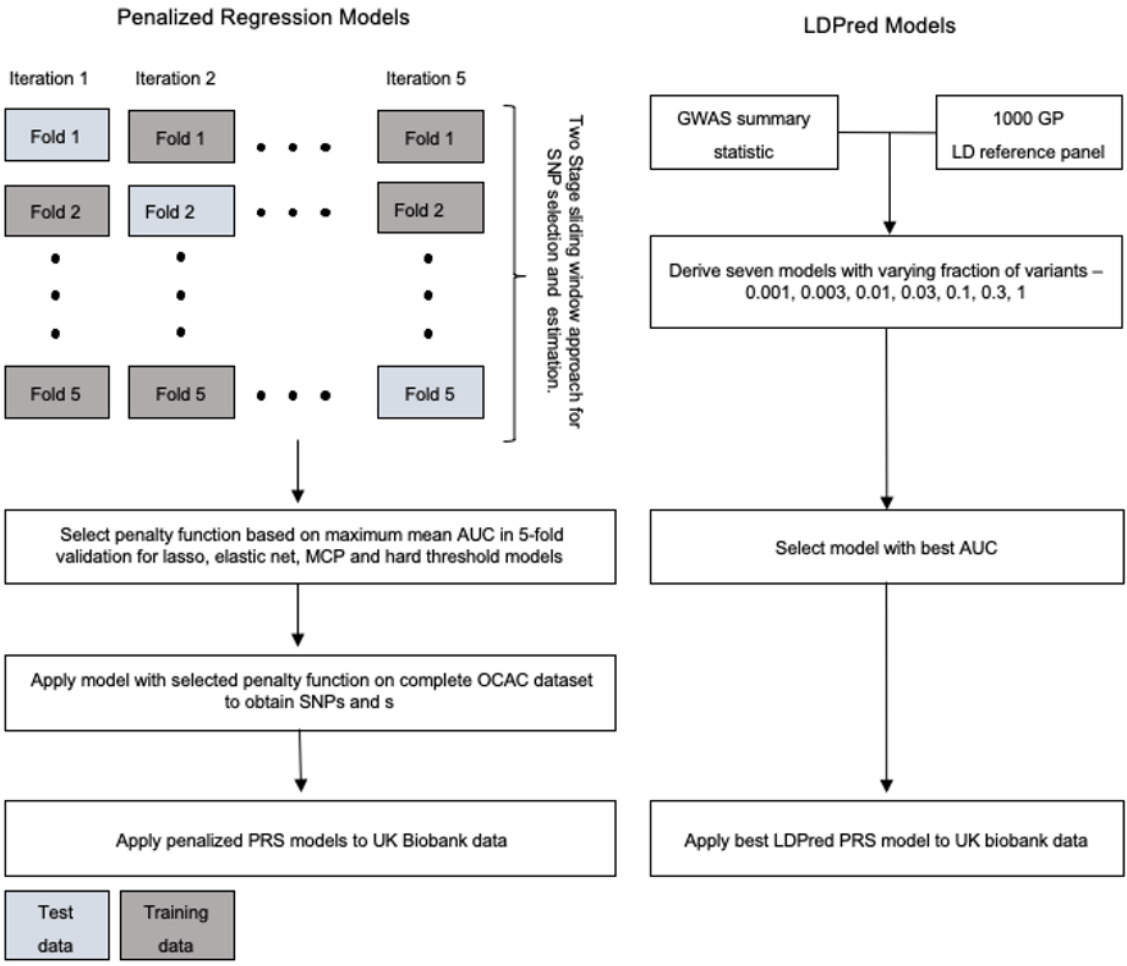
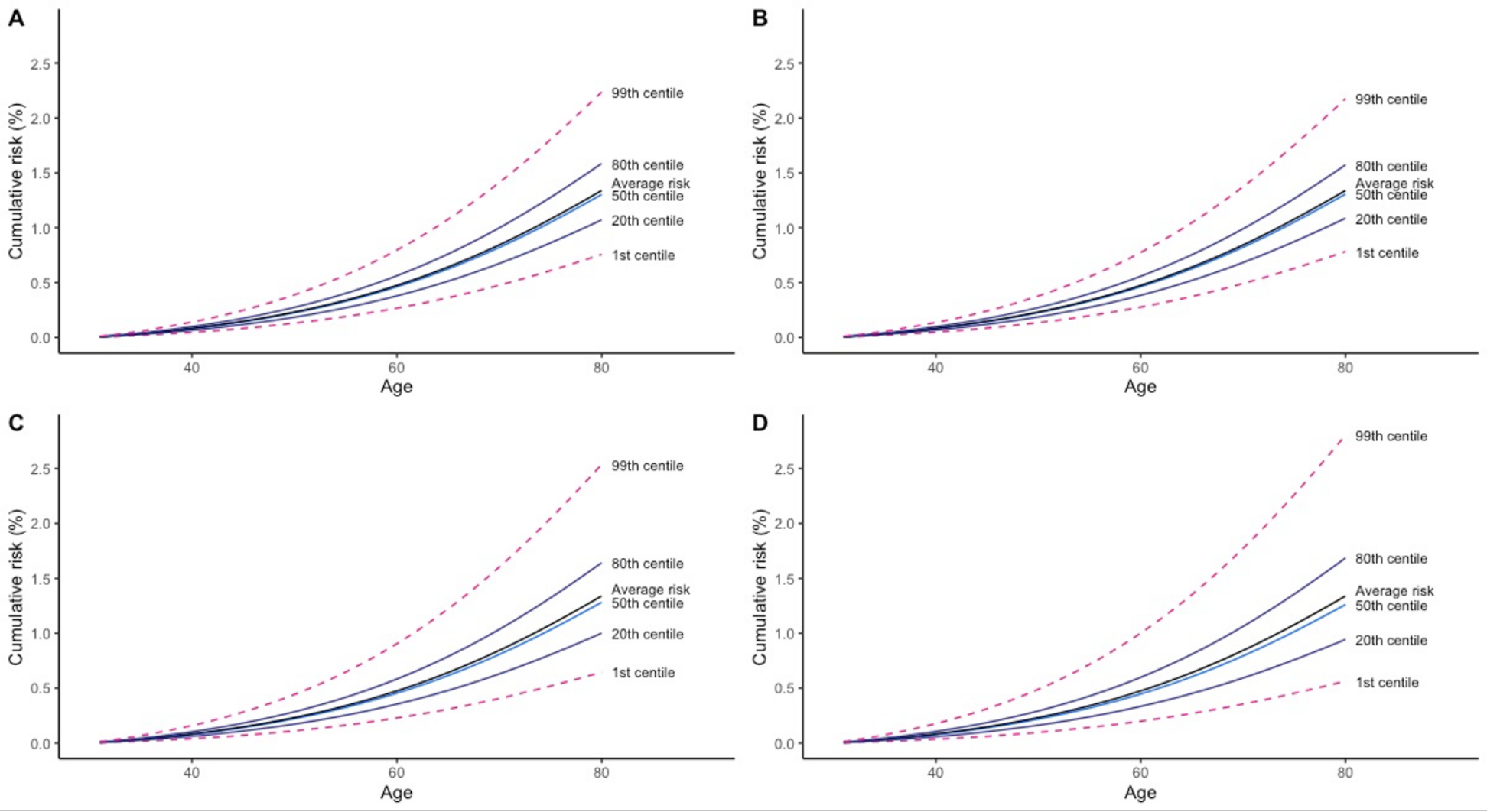
Figure captions

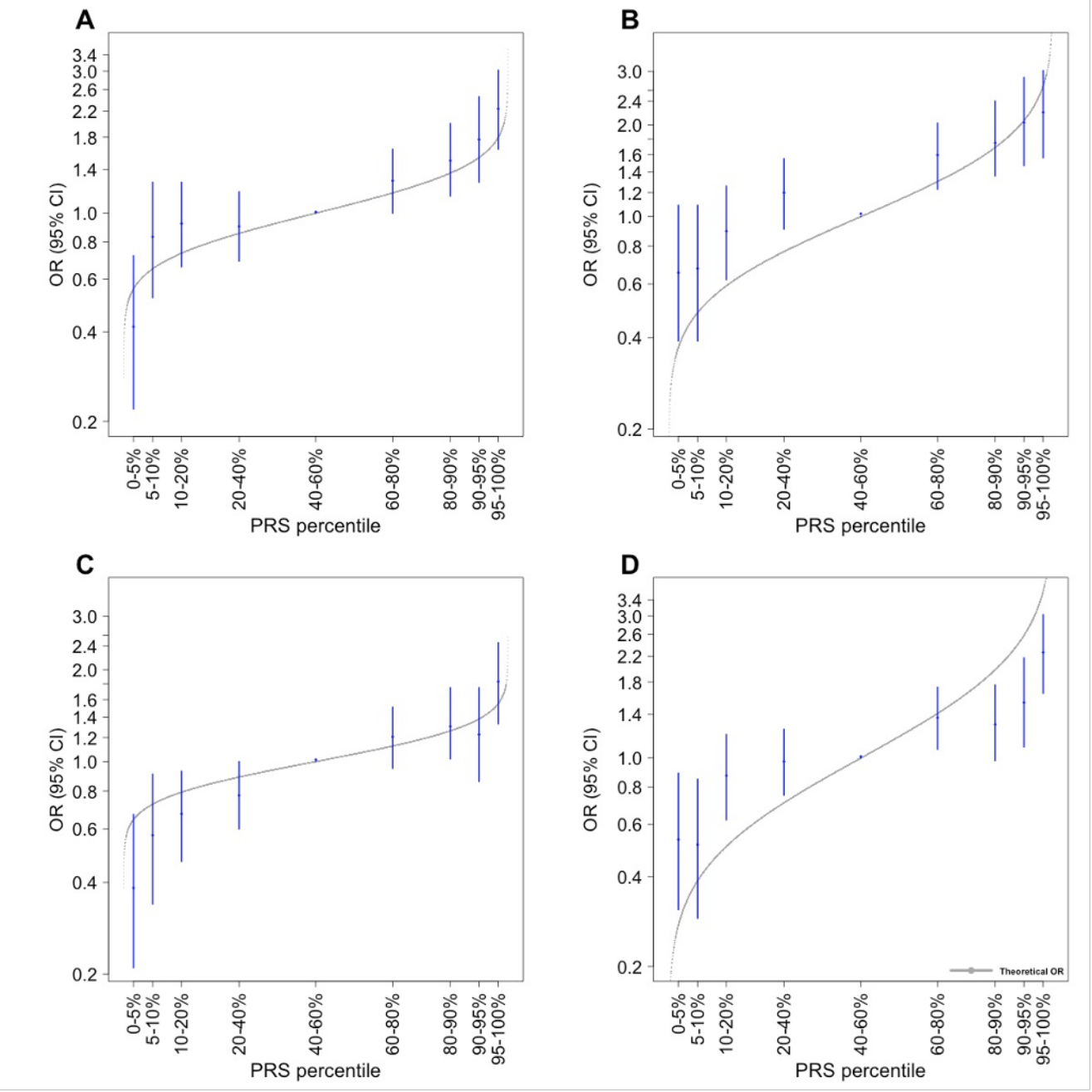
Figure 1: PRS model development using penalized regression and LDPred Bayesian approach

Figure 2: Cumulative risk of ovarian cancer between birth and age 80 by PRS percentiles and PRS models. Shown are the cumulative risk of ovarian cancer risk in UK women by polygenic risk score percentiles. The lasso (A) and elastic net (B) penalized regression models were applied to individual level genotype data, while the stepwise (C) and S4 (D) models were applied to summary level statistics**.** Note that the median and the mean risk differ because the distribution of the relative risk in the population is left-skewed (the log relative risk is a Normal distribution)

Figure 3: Association between the PLR PRS models and non-mucinous ovarian cancer by PRS percentiles. Shown are estimated odds ratios (OR) and confidence intervals for women of European ancestries by percentiles of polygenic risk scores derived from lasso (A), elastic net (B), stepwise (C) and S4 (D) models relative to the middle quintile.


Penalized Regression Models
Iteration 1
Iteration 2
Iteration 5
Fold 1
Fold 2
Fold 5
Two Stage sliding window approach for SNP selection and estimation.
Select penalty function based on maximum mean AUC in 5-fold validation for lasso, elastic net, MCP and hard threshold models
Apply model with selected penalty function on complete OCAC dataset to obtain SNPs and s
Apply penalized PRS models to UK Biobank data
Test data
Training data
LDPred Models
GWAS summary statistic
1000 GP LD reference panel
Derive seven models with varying fraction of variants – 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1
Select model with best AUC
Apply best LDPred PRS model to UK biobank data


A
B
C
D
Cumulative risk (%)
0.0
0.5
1.0
1.5
2.0
2.5
40
60
80
Age
99th centile
80th centile
Average risk
50th centile
20th centile
1st centile


A
B
C
D
OR (95% CI)
PRS percentile
0-5%
5-10%
10-20%
20-40%
40-60%
60-80%
80-90%
90-95%
95-100%
Theoretical OR

SUPPLEMENTARY MATERIAL

Supplementary Method

Penalized logistic regression models: the lasso, elastic net and minimax concave penalty.

A penalized logistic regression model for a set of SNPs aims to identify a set of regression coefficients that minimize the regularized loss function. The aim is to correct the effect estimates towards zero in order to account for prior likelihood. The regularized loss function is given by

$$plr(x;\lambda,\kappa) = \begin{cases} x - \lambda sign(x)/(1-\kappa) & if|x| < \lambda/\kappa \; and \; |(x)| > \lambda \\ x \; if|x| \geq \dfrac{\lambda}{\kappa} \\ 0 \; if|(x)| < \lambda \end{cases}$$

where x is the estimate of SNP effect, λ is the tuning parameter and κ is the threshold (penalty) for different regularization paths. λ and κ are parameters that need to be chosen during model development to optimize performance. The lasso, elastic net, minimax concave penalty (MCP), and p-value thresholds are instances of the function with different κ values. At $\kappa = 0$, the function is a lasso regularization path and several regression coefficients are shrunk to zero. When $\kappa < 0$, the function is an elastic-net solution. The MCP model is obtained when $0 \leq \kappa \leq 1$. When $\kappa = 1$, the function is equivalent to a P-value threshold model.

As the winner's curse effect can result in inflated estimates for rarer SNPs, it is desirable to penalize rarer SNPs more heavily than common SNPs. We therefore rescaled and normalized the imputed SNP genotypes (coded as number of alternate alleles carried) as follows:

The alternate allele dose, d_i, is first rescaled so that the mean value is zero

$$d_i^{rescaled} = d_i - mean(d)$$

The rescaled alternate allele dose is then normalized:

$$d_i^{normalized} = \frac{d_i^{rescaled}}{\sqrt{(\sum_i p_i(1-p_i))(var(d)+0.008)/var(d)}}$$

where p_i is the estimated probability of individual i being a case based on a simple logistic regression model. This conversion penalizes rarer SNPs and also means that the tuning parameter, λ, used in a penalized logistic regression model corresponds closely to a threshold for including a SNP if the SNP z-score for association is greater than λ.

There are two general problems with fitting penalized models to high dimensional genetic data: the large number of SNPs which need to be fitted into memory and the correlation between SNPs. We used a two-stage approach to reduce computational burden without a corresponding loss in predictive power. The first stage was a selection stage to reduce the set of SNPs to a manageable number by excluding those unlikely to be included in a final model. We used a sliding windows approach and split the data into 5.5Mb blocks with a 500kb overlap between blocks. The SNP selection analysis was carried out for each block and the selected SNPs collated. Single SNP association analyses were run, and all SNPs with a X^2 test statistic of less than 2.25 were excluded. Lasso regression models were then run on the remaining SNPs using lambda values of 3.0 and kappa values (penalty score) of 0.0, 0.2, 0.4, 0.6, 0.8 and 1.0. SNPs selected in any of these models were included in subsequent analyses. In the second stage, we fit penalized regression models to the training dataset with λ values from 3.0 to 5.5 in increments of 0.1 iterated over κ values from -3.0 to 1 in increments of 0.1. The lasso model ($\kappa = 0$) for each value of lambda was fitted first, which has a unique maximum. From the fitted maximum the kappa value is changed, and the model fitted again. This helps to ensure that the final fitted model is close to the global maximum for non-zero

values of kappa. For small lambda values the larger kappa values were not analysed as these would not fit the data well and require significant computational resources and time.

We applied this two-stage approach with five-fold cross-validation by splitting the dataset into five groups, and randomly assigning each individual to one of the five groups. We restricted to OCAC studies with at least five controls and five cases, so that each group in the cross-validation analyses would have cases and controls from all studies in the OCAC data (**Figure 1**). In each iteration, four-groups were used as the training set and the fifth group used as the test set. The variants and their weights from the two-stage penalized logistic regression modelling in the training data were used to calculate the area under the receiver operating characteristic curve (AUC) in the test data. We repeated this process for each cross-validation iteration to obtain a mean AUC for each combination of λ and κ.

Finally, we selected the tuning and threshold parameters from the lasso, elastic net and minimax concave penalty models with the maximum mean cross-validated AUC and fitted penalized logistic regression models with these parameters to the entire OCAC dataset to obtain SNP weights for PRS scores. Details of the workflow are provided in Figure 1.
We developed a custom program written in C++ to implement the penalized logistic regression PLR models using individual level genotype data. This used the coordinate descent algorithm where the loss of function for each variable is optimized using a univariable Newton step while keeping other variables constant to obtain the optimum penalized likelihood function (36).

Stepwise logistic regression with variable P-value threshold

This model is a general PLR model with $\kappa = 1$. As with the other PLR models, we investigated various values for λ values (corresponding to a variable P-value threshold for including a SNP in the model). However, we observed that the implementation of this model on individual level data was more difficult than for other κ values because the model would sometimes converge to a local optimum rather than the global optimum. Therefore, we applied an approximate conditional and joint association analysis using summary level statistics correcting for estimated LD between SNPs using a reference panel of 5,000 individual level genotype OCAC data as described in Yang et.al (37). In brief, to initiate the model, we identified the most significant SNP at a specified λ value threshold, and subsequently investigated all other SNPs across the genome conditional on the SNP already selected. If a new SNP being jointly tested had correlation $r^2 > 0.9$, it was left out of the analysis. The SNP with the minimum conditional SNP lower than the cut-off threshold was selected. This process was repeated until no new SNPs could be selected. All selected SNPs were jointly fitted in the model and SNPs with the largest p-value greater than the cut-off threshold were dropped. This process was repeated until no new SNPs were selected or dropped using the training data. As with the PLR models, we investigated several λ values. We used the same cross-validated sets as were used by the PLR methods. The lambda coefficient that gave the best average likelihood increase in the cross-validation test set was applied to the full OCAC data set to obtain the final set of weights.

Meta-analysis of OCAC-CIMBA summary statistics

We conducted a meta-analysis of the EOC associations in *BRCA1* pathogenic variant carriers, *BRCA2* pathogenic variant carriers and the participants participating in OCAC using previously described methodological approaches (3). In brief, the primary analyses of SNPs

and EOC risk in *BRCA1/BRCA2* pathogenic variant carriers included samples genotyped on the iCOGS and OncoArray genotyping chips (with a preference for data from the OncoArray chip when samples were genotyped on both platforms), excluded all overlapping OCAC samples (148 *BRCA1* and 51 *BRCA2*) and SNPs not included in the OncoArray chip. Association analyses were carried out separately for *BRCA1* pathogenic variant carriers and *BRCA2* pathogenic variant carriers, within a survival analysis framework, with time to ovarian cancer diagnosis as the end point. Hazards ratios (HRs) from BRCA1 and BRCA2 pathogenic variants carriers were pooled to give an overall *BRCA1+BRCA2* effect estimate. SNPs exhibiting evidence of heterogeneity ($P_{het}<1x10^{-4}$) were not considered for downstream analyses. Per-allele HR estimates from *BRCA1+BRCA2* pathogenic variant carriers were combined with per allele odds ratios from OCAC to provide an overall relative risk invasive EOC. SNPs with allele frequencies <0.5% were excluded from consideration. All meta-analyses were fixed-effects inverse-variance weighted and implemented using the METAL software (39).

Absolute risk calculations

We calculated the absolute risk of EOC by PRS percentiles adjusting for competing risks of mortality from other causes. We obtained incidence rates of EOC associated with an average risk profile and mortality estimates from 2016 population-based registries in the UK. The absolute risk of EOC in PRS percentiles at a given age (AR_{prs} (t)) is calculated as

$$AR_{PRS}(t) = \sum_{u=0}^{t} I_{PRS}(u).S_{PRS}(u).S_m(u)$$

Where $I_{PRS}(u)$ is the EOC incidence associated with the PRS at age t, $S_{PRS}(t)$ is the PRS-percentile specific probability of being free of ovarian cancer up to age t and $S_m(t)$ is the probability of surviving to age t, *i.e.,* not dying from a cause other than EOC

SUPPLEMENTARY TABLES

Table S1: Effect estimates (weights) of SNPs selected for lasso PRS model.

Table S2: Effect estimates (weights) of SNPs selected for elastic net PRS model.

Table S3: Effect estimates (weights) of SNPs selected for Stepwise (OCAC) PRS model.

Table S4: Effect estimates (weights) of SNPs selected for Select and Shrink (OCAC) PRS model.

Table S5: Effect estimates (weights) of SNPs selected for Stepwise (OCAC-CIMBA) PRS model.

Table S6: Effect estimates (weights) of SNPs selected for Slect and Shrink (OCAC-CIMBA) PRS model.

SUPPLEMENTARY FIGURES

Figure S1: Cumulative risk of ovarian cancer risk in *BRCA1* carriers by polygenic risk score percentiles. The lasso (A) and elastic net (B) penalized regression models were applied to individual level genotype data, while the stepwise (C) and S4 (D) models were applied to summary level statistics.

Figure S2: Cumulative risk of ovarian cancer risk in *BRCA2* carriers by polygenic risk score percentiles. The lasso (A) and elastic net (B) penalized regression models were applied to individual level genotype data, while the stepwise (C) and S4 (D) models were applied to summary level statistics.

ETHICS STATEMENT

All study participants provided written informed consent and participated in research studies at the host institute under ethically approved protocols.

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Ethics Statement

CIMBA Ethics Statement

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