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Title:

Genome-wide association study of 398,238 women unveils seven loci associated with high-grade serous ovarian cancer

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Genome-wide association study of 398,238 women unveils seven loci associated with high-grade serous ovarian cancer

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Nineteen genomic regions have been associated with high-grade serous ovarian cancer (HGSOC). We meta-analyzed >22 million variants for 398,238 women from the Ovarian Cancer Association Consortium (OCAC), UK Biobank (UKBB) and Consortium of Investigators of Modifiers of *BRCA1/BRCA2* (CIMBA) to identify novel HGSOC susceptibility loci. Eight novel variants were associated with HGSOC risk. An interesting discovery biologically was *TP53* 3'-UTR SNP rs78378222-T's association with HGSOC (per-T-allele relative risk (RR) = 1.44, 95% CI:1.28–1.62, $P = 1.76 \times 10^{-9}$). Polygenic scores (PGS) were developed using OCAC and CIMBA data and trained on FinnGen data. The optimal PGS included 64,518 variants and was associated with an odds ratio of 1.46 (95% CI:1.37–1.54) per standard deviation when validated in the UKBB. This study represents the largest HGSOC GWAS to date – demonstrating that improvements in imputation reference panels and increased sample sizes help to identify HGSOC associated variants that previously went undetected, ultimately improving PGS which can improve personalized HGSOC risk prediction.

Globally, epithelial ovarian cancer (EOC) is the seventh most common cancer diagnosed in women, with ~314,000 new cases diagnosed each year¹. It is the most lethal gynecological cancer, responsible for ~207,000 deaths annually¹. EOC is a collection of five major histotypes, namely high-grade serous (HGSOC), endometrioid, clear cell, low-grade serous (LGS) and mucinous, which are thought to have distinct etiology². HGSOC is the most prevalent accounting for 60–70% of EOC diagnoses^{2,3}, and accounting for most EOCs diagnosed in *BRCA1* and *BRCA2* pathogenic variant (PV) carriers^{4–11}. Furthermore, HGSOC accounts for the majority of EOC mortality^{12,13}.

To date, 40 genomic regions associated with EOC have been identified through genome-wide association studies (GWAS)^{14–28}. For 19 of these regions, HGSOC is the most strongly associated histotype^{14–22,26–28}. These studies have relied on imputation efforts that used the 1000 Genomes Project²⁹ and Haplotype Reference Consortium³⁰ reference panels, yielding up to ~11 million well-imputed genetic variants. The Trans-Omics for Precision Medicine (TOPMed) reference panel³¹ and imputation server³² have recently become publicly available. The TOPMed panel consists of ~308 million variants, yielding greater genomic coverage than previously available reference panels, with the added benefit of containing many more low-frequency and rare variants. This prompted

us to re-impute genetic variant data from the population-based Ovarian Cancer Association Consortium (OCAC)³³, and *BRCA1/2* carriers from the Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* (CIMBA)^{34,35} to assess whether the larger coverage of the genome from the TOPMed reference panel leads to detection of novel loci associated with HGSOC risk. We additionally made use of the UK Biobank (UKBB)^{36,37} to boost the sample size and power to detect associations. We combined these data with summary statistics from FinnGen^{38,39} and BioBank Japan^{40,41} to develop and validate polygenic models (PGM) and scores (PGS) for non-mucinous OC.

Results

The genome-wide association analyses for HGSOC were based on up to 398,238 women from OCAC ($N = 120,248$, 30.2%), UKBB ($N = 245,377$, 61.6%) and CIMBA ($N = 32,613$, 8.2%) (Table 1, Supplementary Tables 1, 2). A total of 19,883 (5.0%) women were classified as being diagnosed with HGSOC. The mean (standard deviation, SD) age at diagnosis for women in OCAC and UKBB were 60.2 (10.9) years and 63.5 (10.0) years, respectively. The mean (SD) censoring ages for *BRCA1* and *BRCA2* PV carriers were 43.7 (SD = 12.0) years and 46.2 (SD = 12.9) years, respectively.

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Table 1 | Summary of European ancestry samples and imputed variants used in individual variant association analyses

Population	Study/ consortium	Study design	Genotyping array	Imputation panel	N controls/ unaffected ^a	N cases/ affected ^b	N variants ^c
Population-based	OCAC	Case-control	GWAS panels ^d	TOPMed	9071	1745	142,163,775
			iCOGS	TOPMed	28,706	2661	142,163,775
			OncoArray	TOPMed	67,110	10,955	142,163,775
	UKBB	Nested case-control	UK BiLEVE Axiom Array and UK Biobank Axiom Array	UK10K and HRC	244,529	848	59,918,121
<i>BRCA1/2</i> carriers	CIMBA	Retrospective cohort	iCOGS	TOPMed	3947	632	80,292,260
			OncoArray	TOPMed	24,992	3042	104,435,671

OCAC Ovarian Cancer Association Consortium, UKBB UK Biobank, CIMBA Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2*.

^aNumber of controls for population-based studies. UKBB analyses considered prevalent and incident cases to maximise number of cases. Number of carriers censored as unaffected for *BRCA1/2* carriers.

^bNumber of EOC cases for population-based studies. Number of carriers censored as affected with EOC for *BRCA1/2* carriers.

^cNumber of genotyped and well-imputed (imputation accuracy $r^2 > 0.30$) genetic variants available for statistical analyses.

^dThe five GWAS panels were from the UK GWAS, US GWAS, Poland GWAS, Mayo Clinic Ovarian Cancer Study GWAS and the Brigham and Women's Hospital GWAS.

Re-examining previously identified associations with EOC

We looked up the associations for the lead variants previously reported as being associated with EOC in our newly generated results (Supplementary Table 3, Supplementary Figs. 1–41). Most lead variants previously reported to be associated specifically with HGSOC risk replicated in the present meta-analysis of OCAC, UKBB and *BRCA1/2* carriers at the significance threshold $P < 5 \times 10^{-8}$. Exceptions were chr2:111138666 (rs17041869)²⁶, chr2:113216387 (rs895412), chr11: 62126500 (rs7937840)²⁶ and chr22:28538325 (rs6005807)²² (Supplementary Table 3). However, the chr2:110525257..111658369 and chr2:112716387..113716387 regions contained other variants that were associated at the genome-wide significance level in the present analysis, whilst the chr11:61626500..62626500 and chr22:28038325..29038325 regions did not contain any variants associated with HGSOC at the genome-wide significance level. It should be noted, however, that the chr2:111138666 (rs17041869) and chr11:62126500 (rs7937840) variants were identified through a cross-cancer (breast, ovarian, and prostate) GWAS²⁶ and were not specifically identified as HGSOC associated variants.

Novel loci associated with HGSOC

Associations with a total of 5786 variants from 44 loci were significant at $P < 5 \times 10^{-8}$. We excluded 5778 variants at 37 loci from further consideration, as they were either near known associated regions (Supplementary Table 3), were not conditionally independent of the lead variant in a nearby known region, or were likely statistical artifacts arising from strata specific effects.

There were eight variants associated ($P < 5 \times 10^{-8}$) with HGSOC, at 5q11, 6p12, 8p21, 9p24-23, 16q22, 17p13 and 19q12 (Table 2, Fig. 1, Supplementary Tables 4, 5).

The associations at 5q11 (rs528577783-G; RR = 5.15, 95% CI:2.96–8.96), 6p12 (rs1013698558-T; RR = 2.35, 95% CI:1.76–3.14), 8p21 (rs540569242-A; RR = 25.60, 95% CI:9.32–70.31), and 9p24-p23 (rs768719522-T; RR = 10.04, 95% CI:4.38–22.99) were all single rare variants (MAF $\leq 0.15\%$) associated with large HGSOC effects. The single SNPs associated with HGSOC at 16q22 (rs6979-G; RR = 1.07, 95% CI:1.04–1.09) and 19q12 (rs62107113-A; RR = 1.08, 95% CI:1.05–1.11) were common and conferred modest effects on HGSOC risk. There were two moderately correlated (TOPMed European⁴² $r^2 = 0.46$, $D' = 0.89$) low-frequency (MAF: 1.2% and 2.1%) variants at the 17p13 locus. The *TNFS13/TNFSF12-TNFSF13* intronic variant rs143094271-G was associated with a per-allele RR = 1.28 (95% CI:1.18–1.39, $P = 7.61 \times 10^{-9}$); and rs78378222-T, a *TP53* 3'-UTR variant, with a per-allele RR = 1.44 (95% CI:1.28–1.62, $P = 1.76 \times 10^{-9}$). The association effect size estimates at 16q22, 19q12 and 17p13 were consistent between OCAC/UKBB and *BRCA1/2* PV carriers.

Bayesian false-discovery probabilities (BFDPs) indicated that six of these associations are likely to be true, although two rare variants, rs540569242 and rs768719522, had noticeably larger BFDPs (Table 2).

Under a model assuming 1:1,000 truly associated variants, the BFDPs were 3.2% for rs540569242 and 11% for rs768719522. The other variants all had BFDP $\leq 0.42\%$.

Credible causal variants (CCVs)

We defined 52 CCVs across the seven novel regions (Supplementary Table 6, Supplementary Figs. 42–48). Four regions (5q11, 6p12, 8p21, 9p24-23) had only the lead variant as a CCV, whilst the 16q22 ($N = 5$), 17p13 ($N = 3$) and 19q12 ($N = 40$) loci had several CCVs.

Association of the PGS with HGSOC

Of the 1102 PGMs developed using OCAC and CIMBA data, the PGM that performed best in the FinnGen data comprised of 64,518 variants (Supplementary Data 1), denoted PGS₆₄₅₁₈. In the UKBB validation, the OR per SD of PGS₆₄₅₁₈ was estimated to be 1.46 (95% CI:1.37–1.54), with discriminatory ability of AUROC = 0.607 (95% CI:0.590–0.623) (Table 3). The association of PGS₆₄₅₁₈ was strongly attenuated in the BBJ validation (East Asian ancestry women), where the OR per SD was 1.12 (95% CI:1.05–1.20).

When restricting the PGS to include only genotyped variants from the 64,518 genotyped and imputed variants, which may make their implementation easier, PGS with 5957 (all genotyped variants from the 64,518) and 400 variants had similar performance characteristics. Relative to the PGS₆₄₅₁₈, a PGS considering the 400 most strongly associated genotyped variants, denoted PGS₄₀₀, resulted in a small decrease in the AUROC to 0.603, and a marginally attenuated OR per SD (OR = 1.43, 95% CI:1.35–1.52) in the UKBB.

Predicted absolute risks for the general population and *BRCA1/2* pathogenic variant carriers

Absolute lifetime risks of developing EOC by age 80 years for a woman from the general population were calculated to be 0.9%, 1.6% and 3.0% at the 5th, 50th and 95th percentiles of the PGS₆₄₅₁₈ (Table 3, Fig. 2). The absolute lifetime risks (at age 80 years) for *BRCA1* PV carriers were predicted to be 25.9%, 42.8% and 64.7% at the 5th, 50th and 95th percentiles of the PGS₆₄₅₁₈ distribution, respectively (Table 3, Fig. 2). The corresponding risks for PGS₆₄₅₁₈ for *BRCA2* PV carriers at the same PGS percentiles were predicted to be 9.3%, 16.7% and 28.9%, respectively (Table 3, Fig. 2). The range of predicted percentile specific risks for the previously published 36 variant PGS⁴³ was narrower, with risks for the same percentiles of 27.7%, 43.0% and 62.3% for *BRCA1* PV carriers, respectively, and 10.1%, 16.9% and 27.5% for *BRCA2* PV carriers, respectively. The PGS₄₀₀ yielded absolute risks which were approximately at the midpoint of the 36 and 64,518 variant PGS absolute risks (*BRCA1* PV carriers: 26.7%, 42.9% and 63.6% at the 5th, 50th and 95th percentiles, respectively; *BRCA2* PV carriers: 9.7%, 16.8% and 28.3% at the 5th, 50th and 95th percentiles, respectively).

Table 2 | Eight independent genetic variants at seven loci associated with high-grade serous epithelial ovarian cancer from the OCAC, UK Biobank and BRCA1/2 carrier meta-analysis

Locus	Nearest gene (distance, kb)	SNP	Position ^a	Alleles ^b	Frequency ^c	Sample size ^d		RR (95% CI) ^e	P ^f	Bayes false discovery probability	
						Controls/unaffected	Cases/affected			BFDP ^g	BFDP _M ^h
5q11.2	<i>FST</i> (24.693)	rs528577783	53511827	C/G	0.00120	375,400	18,882	5.15 (2.96–8.96)	6.60 × 10 ⁻⁹	0.33	3.21
6p12.1	<i>GCLC</i> (9.681)	rs1013698558	53554782	A/T	0.00148	133,826	19,035	2.35 (1.76–3.14)	6.86 × 10 ⁻⁹	0.06	0.62
8p21.2	<i>CDCA2</i> (156.65)	rs540569242	25522083	G/A	0.00014	375,839	19,254	25.60 (9.32–70.31)	3.15 × 10 ⁻¹⁰	3.17	24.70
9p24.1-p23	<i>PTRFD</i> (intronic)	rs768719522	8333517	C/T	0.00012	377,247	19,285	10.04 (4.38–22.99)	4.92 × 10 ⁻⁸	11.30	56.00
16q22.1	<i>ACD</i> (intronic)	rs6979	67657765	A/G	0.47145	378,355	19,883	1.07 (1.04–1.09)	2.30 × 10 ⁻⁸	0.12	1.19
17p13.1	<i>TNFSF12-TNFSF13</i> (intronic)	rs143094271	7559785	A/G	0.97983	378,355	19,883	1.28 (1.18–1.39)	7.61 × 10 ⁻⁹	0.12	1.19
	<i>TP53</i> (3' UTR)	rs78378222	7668434	G/T	0.98786	378,355	19,883	1.44 (1.28–1.62)	1.76 × 10 ⁻⁹	0.42	4.04
19q12	<i>CCNE1</i> (14.855)	rs62107113	29797136	G/A	0.22147	378,355	19,883	1.08 (1.05–1.11)	1.22 × 10 ⁻⁸	0.37	3.56

Supplementary Table 4 presents associations separately by OCAC, UK Biobank and BRCA1/2 carriers.

CI confidence interval.

^aPositions are Genome Reference Consortium Human Build 38 (GRCh38/hg38).

^bAlleles = other/effect alleles.

^cFrequency = frequency of the effect allele in the combined sample of OCAC and UK Biobank controls, and unaffected BRCA1/2 carriers.

^dControls/unaffected = number of population-based controls from OCAC and UKBB, and the number of unaffected BRCA1/2 carriers. Cases/affected = number of population-based EOC cases from OCAC and UKBB, and the number of affected BRCA1/2 carriers.

^eRR = relative risk from the OCAC, UK Biobank and BRCA1/2 carrier meta-analysis, combining the odds ratio from the population-based data with the hazard ratio from the BRCA1 and BRCA2 carriers.

^fP-value for association from the OCAC, UK Biobank and BRCA1/2 carrier meta-analysis.

^gBFDP_M = Bayes false discovery probability under model assuming a prior probability that 1 in 10⁶ variants are truly associated (%).

There was a total reclassification of *BRCA2* PV carriers at the 10% risk threshold when considering PGS₄₀₀ and PGS₆₄₅₁₈ of 4.8% and 5.4%, respectively, compared to the 36 variant PGS (Supplementary Table 7).

Discussion

We conducted the largest GWAS to date for HGSOC, both in terms of the sample size and the number of genetic variants assessed. To do this, we made use of large international consortia (OCAC and CIMBA), and harnessed data from the UKBB to bolster the sample size. We also utilized recent advances in imputation reference panels, namely the TOPMed panel, which allowed us to investigate the largest number of genetic variants to date. We identified eight independent variants at seven loci to be genome-wide statistically significant for association with HGSOC risk, including four rare variants (MAF < 1%) and two low-frequency polymorphisms (MAF 1–5%), demonstrating that GWAS with greater genomic coverage for imputation can contribute to identify previously undiscovered rare variant associations. Based on these associations, we defined 52 CCVs that have the strongest statistical evidence for being the likely causal variant for each locus. We also developed a polygenic model that exhibited improved discriminatory ability compared to previously published models.

The four rare variants were associated with large effect sizes, with RR estimates ranging from 2.35 to 25.6. The large effect sizes seem implausible and may reflect a winner's curse effect with true effect sizes actually being lower than these estimates⁴⁴. Moreover, they may represent false positive associations, hence we estimated BFDPs⁴⁵ for the eight novel variants to determine the likelihood of this. Six variants had low BFDPs, indicating they are likely true associations. However, 8p21 rs540569242 and 9p24-p23 rs768719522 had noticeably larger BFDPs and are more likely to represent false positive associations.

Variant rs78378222, in the *TP53* 3'-UTR, with the major T-allele (AF 98.8%) is associated with an increased risk of HGSOC. The same allele has been associated with an increased risk of triple-negative breast cancer⁴⁶ with a per-allele relative risk of 1.45, similar to its association with HGSOC (RR = 1.44). In contrast, the minor (G) allele of rs78378222 is associated with increased risks of skin^{47–51}, brain^{51–55} and prostate cancers^{47,56}. One study also found rs78378222 to be associated with standing height, lean body mass and basal metabolic rate⁵¹. The minor allele has been shown to impede *TP53* 3'-end processing, resulting in downregulated p53 mRNA levels and protein levels, and decreased apoptosis⁵⁷. Furthermore, germline and somatic variations in *TP53* are well established factors in cancer development and progression through its role as a tumor suppressor^{58–61} and the *TP53* 3'-UTR germline variant has been shown to interact with tumor *TP53* mutation status⁶². A previous study by the OCAC found five SNPs in the *TP53* region, within ±21 kb of rs78378222, to be associated with invasive EOC⁶³. However, none of these SNPs are in LD with rs78378222.

rs528577783 is a rare intergenic variant between the *FST* and *NDUFS4* genes. *FST* encodes follistatin, a single-chain gonadal protein that specifically inhibits follicle-stimulating hormone release and is moderately expressed in human reproductive tissues (Supplementary Table 5)⁶⁴. A linkage study identified *FST* as a candidate gene for polycystic ovary syndrome (PCOS)⁶⁵. PCOS may be associated with an increased risk of borderline or postmenopausal ovarian cancer⁶⁶, although a recent Mendelian Randomization study found that genetically predicted PCOS was associated with decreased risk of ovarian cancer⁶⁷. A GWAS of African ancestry women found rs37792 near *FST* to be genome-wide statistically significantly associated with HGSOC in African ancestry women⁶⁸.

The 6p12 variant rs1013698558, located ~9.7 kb from the *GCLC* gene, was moderately associated with HGSOC. A study found a synthetic lethality relationship between *GCLC* and *ARID1A*-deficient OC cells⁶⁹, whilst another reports that *GCLC* inhibition causes apoptosis in *ARID1A*-deficient cancer cells⁷⁰. *ARID1A* has been implicated as a tumor suppressor gene⁷¹. It may be that the association we find for rs1013698558 with HGSOC is a result of the interplay between *GCLC* and *ARID1A*. The 8p21 variant rs540569242 is 156 kb from *CDCA2* and was associated with HGSOC with the largest RR that we report. *CDCA2* is involved in the cell division cycle

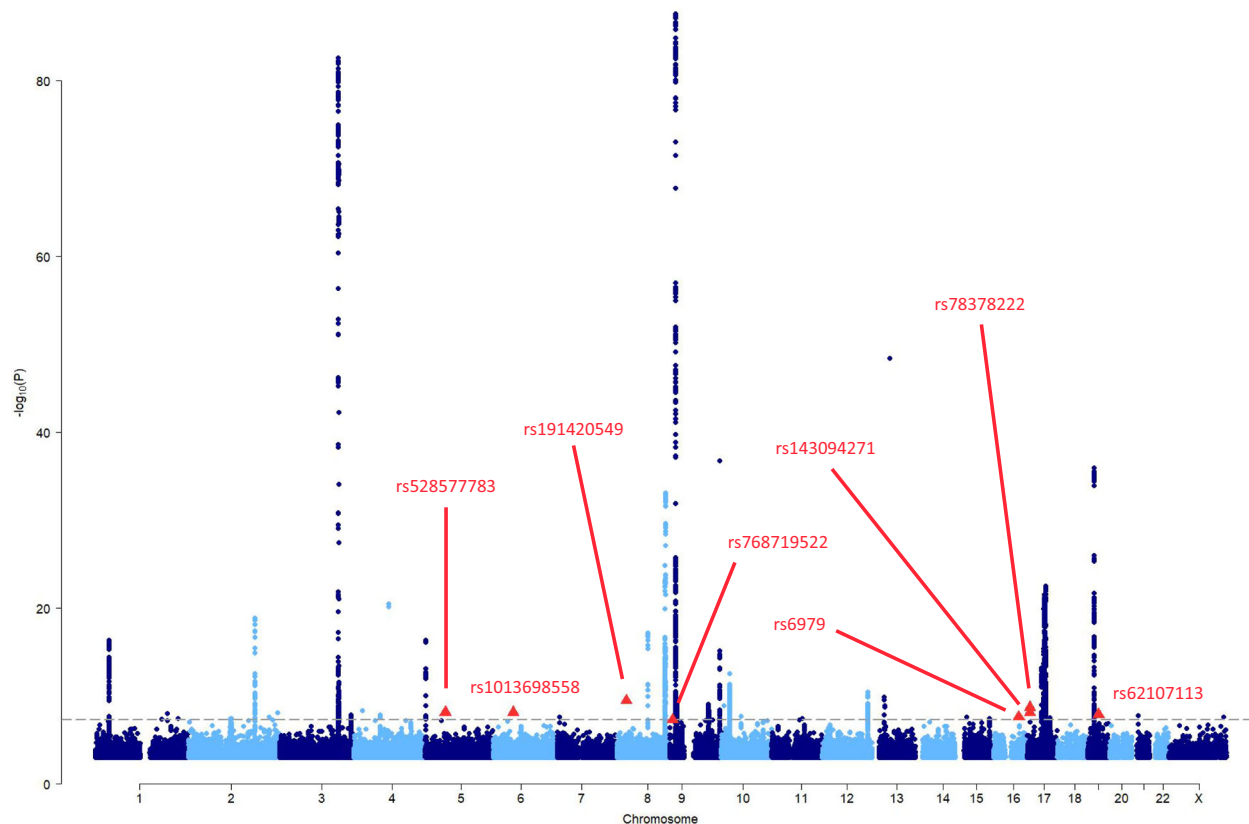


Fig. 1 | Manhattan plot showing the associations with HGSOE from the meta-analysis of OCAC, UKBB and CIMBA summary association data. The dashed line is the genome-wide statistical significance level ($P = 5 \times 10^{-8}$). The eight independent genome-wide statistically significant variants at seven novel loci are shown as red triangles.

Table 3 | Associations of polygenic scores (PGS) in UK Biobank and BioBank Japan

Nvariants	Selection ^a	Threshold ^b	UKBB associations ^c		BioBank Japan associations ^d	BRCA1 carrier lifetime risks at PGS percentiles (%) ^e			BRCA2 carrier lifetime risks at PGS percentiles (%) ^e		
			AUC	OR (95% CI)	OR (95% CI)	5 th centile	Median	95 th centile	5 th centile	Median	95 th centile
64,518	All	0.02	0.607	1.46 (1.37–1.54)	1.12 (1.05–1.20)	25.9	42.8	64.7	9.3	16.7	28.9
5957 ^f	All	0.02	0.603	1.45 (1.37–1.54)	1.14 (1.07–1.22)	26.2	42.8	64.4	9.4	16.7	28.7
3448 ^f	All	0.01	0.604	1.45 (1.37–1.54)	1.14 (1.06–1.22)	26.2	42.8	64.3	9.5	16.7	28.7
400 ^f	Filter	0.0005	0.603	1.43 (1.35–1.52)	1.13 (1.06–1.21)	26.7	42.9	63.6	9.7	16.8	28.3
36 ^g	All	Ad hoc	0.595	1.40 (1.32–1.48)	1.13 (1.06–1.21)	27.7	43.0	62.3	10.1	16.9	27.5

PGS polygenic score, UKBB UK Biobank, AUC area under the receiver operator classification (ROC) curve, OR odds ratio per standard deviation, CI confidence interval.

^aSet of variants considered for inclusion. “All” means that all imputed variants were considered. “Filter” means only non-indel variants genotyped on the OncoArray were considered.

^bThe P -value:LD- r^2 ratio used to select variants for inclusion in the PGM.

^cAssociation of the PGS estimated in 245,611 European ancestry women from UK Biobank (244,529 controls, 1082 cases).

^dAssociation of the PGS estimated in 61,457 East Asian ancestry women from BioBank Japan (60,614 controls, 843 cases).

^eLifetime risks of developing ovarian cancer (at age 80 years) at the 5th, 50th (median), and 95th percentiles of the PGS distribution for a BRCA1/2 pathogenic variant carrier. Calculations assume ovarian cancer incidence rates for BRCA1/2 pathogenic variant carriers from Kuchenbaecker et al.¹³⁰

^fSubset of the most predictive variants from the 64,518 variant PGS that were well genotyped on the OncoArray.

^g36 variant PGM developed by Dareng et al.⁴³

and response to DNA damage. One study found *CDCA2* expression is upregulated in ovarian tumor tissue compared with normal tissue⁷². This study also found that *CDCA2* and its 100 most co-expressed genes were primarily involved in cell cycle, oocyte meiosis, progesterone-mediated oocyte maturation, p53 signaling and pyruvate metabolism pathways. We found that the *PTPRD* intronic variant rs768719522 at the 9p24-p23 locus had a large association RR with HGSOE. *PTPRD* has been implicated as a tumor suppressor gene⁷³. This gene encodes a protein from the protein tyrosine phosphatase (PTP) family – PTPs are signaling molecules regulating processes such as cell growth, cell differentiation, the mitotic cycle and oncogenic transformation⁷⁴. The common *ACD* missense variant

rs6979 at 16q22 conferred a small per-allele RR to HGSOE risk. This gene encodes telomere protein TPP1, which is involved in maintenance of telomere length and protecting telomere ends. In addition to the 17p13 *TP53* 3'-UTR variant association, there was another independent variant associated with HGSOE risk at this locus. The rs143094271 variant is intronic in *TNFSF13/TNFSF12-TNFSF13*. These genes are members of the tumor necrosis factor family, which are involved in various cellular processes, including survival, proliferation, differentiation, and apoptosis. rs143094271-G has been associated with a decreased risk of having uterine fibroids (OR = 0.70)⁷⁵. Women with uterine fibroids have been found to be at increased risk of developing OC⁷⁶. However, despite rs143094271-G being

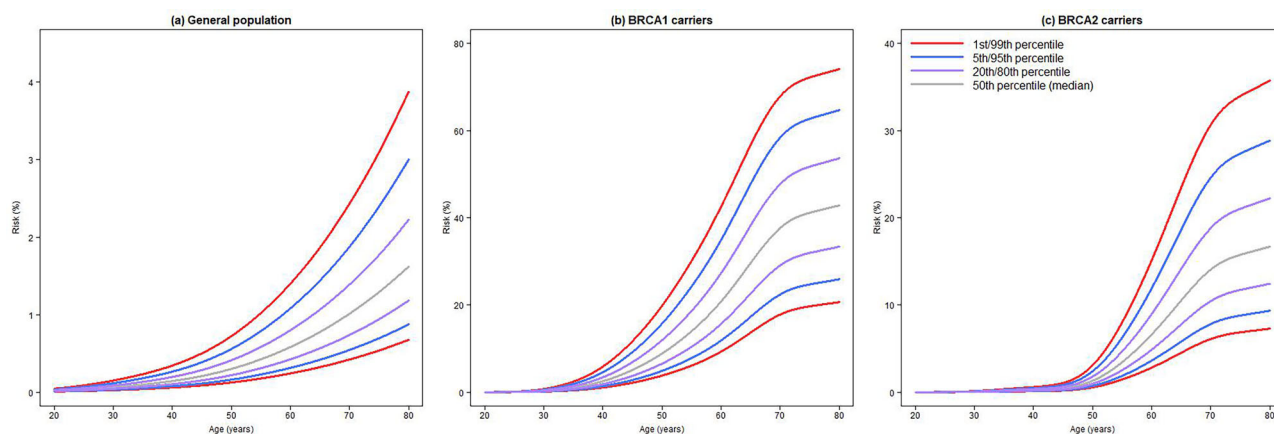


Fig. 2 | Predicted cumulative risks of developing EOC by PGS percentiles. Predicted cumulative risks of developing EOC based on the PGS₆₄₅₁₈ at various percentiles of the PGS distribution for: **a** the general population (0.7% for 1st percentile

to 3.9% for the 99th percentile), **b** *BRCA1* PV carriers (20.7% for 1st percentile to 74.1% for the 99th percentile), and **c** *BRCA2* PV carriers (7.3% for 1st percentile to 35.7% for the 99th percentile).

associated with women being less likely to have uterine fibroids, we found that rs143094271-G yielded an increased risk of developing HGSOE. The 19q12 common variant rs62107113 is located ~15 kb from the *CCNE1* gene and was associated with a modest increased risk of developing HGSOE. *CCNE1* encodes cyclin E1, which regulate cyclin-dependent kinases. Overexpression of *CCNE1* has been observed in genomically unstable tumors, notably HGSOE^{77–81} and triple-negative breast cancer^{78,82–84}. Moreover, it has been shown that replication stress in cells overexpressing *CCNE1* is likely a consequence of replication initiation, ultimately resulting in DNA damage and genomic instability⁸⁵. There is evidence indicating *CCNE1* amplification is mutually exclusive to *BRCA* inactivation⁷⁹. *CCNE1* is an exciting novel therapeutic target, Gallo et al. developed an orally bioavailable PKMYT1 inhibitor that activated CDK1 in *CCNE1* overexpressed cells, promoting early mitosis in cells undergoing DNA synthesis⁸⁶.

In addition to the 40 loci previously found to be associated with EOC^{14–27}, we have identified genetic variants at a further seven loci associated with HGSOE, taking the number of loci associated with EOC to 47, 26 specifically with HGSOE. The previous known loci (52 variants at 40 loci) explained 8.5% of the polygenic variance of OC, assuming a total polygenic variance of 2.004 from Lee et al.⁸⁷. The six variants that we report to be associated with HGSOE with low BFD explain an additional 2.8%, making the total variance explained by GWAS identified variants to be 11.3%.

For previously identified variants, the estimated associations from general population data (combined OCAC and UKBB) ORs were broadly consistent with the estimated HRs for *BRCA1* and *BRCA2* PV carriers (Supplementary Table 3). Furthermore, testing for heterogeneity of effects resulted in a small number of variants exhibiting differences in effect sizes between population-based ORs and carrier HRs. None of the eight novel associations exhibited any heterogeneous effects between population-based ORs and *BRCA1/2* PV carrier HRs (Supplementary Table 4).

Using the S4 method, we developed a 64,518 variant PGS, whose PGS was associated with a per SD OR of 1.46 (95% CI:1.37–1.54) and had discriminatory ability of AUROC = 0.607 (95% CI:0.590–0.623). There was a small improvement over the previous best performing PGM developed by Dareng et al.⁴³ (18,007 variants; OR per unit SD = 1.42; AUROC = 0.596) developed using similar methodology. The PGS₄₀₀ could be more practical to implement in a clinical setting, since it contains fewer variants, all of which are known to successfully genotype from the OncoArray experiment, compared to the best performing PGS₆₄₅₁₈ which requires imputation. We found that the PGS₄₀₀ had similar performance to the optimal PGS₆₄₅₁₈. This also suggests that most of the predictive ability of the PGS may derive from genotyped SNPs with the largest variance contributions.

When each of the PGS were tested in individuals of East Asian ancestry from BB, the PGS associations were strongly attenuated, each to a similar

degree. For women of East Asian ancestry, the PGS consisting of genotyped variants with 5957 and 3448 variants performed marginally better, with a slightly larger OR per PGS SD. The observed attenuations for East Asian women compared with European women are likely a result of the PGM derivation data being strongly weighted towards Europeans, as the majority of OCAC and CIMBA samples came from this ancestry group.

We calculated lifetime risks of developing EOC by PGS percentiles for the optimal 64,518 variant PGS for *BRCA1/2* carriers. The risks ranged from 25.9% to 64.7% for *BRCA1* carriers, and 9.3% to 28.9% for *BRCA2* carriers, at the 5th and 95th percentiles, respectively. The range of risks for the 36 variant PGS that is currently implemented in the CanRisk ovarian cancer risk prediction algorithm^{43,87} were narrower than those for the PGS₆₄₅₁₈. The lifetime risks based on the PGS₄₀₀ that used a subset of 400 reliably genotyped variants included in the PGS₆₄₅₁₈ at these percentiles sat approximately at the midpoints of the risks from the 64,518 and 36 variant PGS. We compared what risk reclassification (lower risk, <10%, or higher risk, ≥10% lifetime risk) would occur when using the PGS₆₄₅₁₈ or PGS₄₀₀ versus the 36 variant PGS for *BRCA2* PV carriers. We were unable to assess reclassification for *BRCA1* carriers as the lifetime absolute risks at the lowest percentiles of the PGS distributions were always above 10%. We found that the PGS₆₄₅₁₈ and PGS₄₀₀ led to total reclassification of risk groups of around 5% versus the 36 variant PGS. Most reclassification shifted women from lower risk (<10%) using the 36 variant PGS to higher risk (≥10%) using the alternative PGS₆₄₅₁₈ or PGS₄₀₀. Taken together, these estimated lifetime risks and risk reclassifications will help to more accurately determine a carriers' risk and inform clinical management of risk, such as the timing of risk reducing surgery or the initiation of cancer surveillance. In practice, PGS should be used in combination with pathogenic variants in ovarian cancer susceptibility genes and other risk lifestyle/hormonal factors in validated multifactorial cancer risk prediction models, such as CanRisk^{87–89}, to improve comprehensive risk assessment. The clinical implementation of PGMs is mainly in the context of risk management for women with a family history of ovarian cancer. The CanRisk breast/ovarian cancer risk prediction model^{87–89} currently incorporates polygenic scores for both breast and ovarian cancer, together with lifestyle risk factors, family history and moderate/high penetrance risk alleles. The familial risk used in the model is the risk after exclusion of the contribution of polygenic risk as the polygenic risk explains ~11.3% of the excess familial risk. A key assumption that underlies the model is that the effects of the various risk factors are multiplicative (log-additive). There is a large body of evidence supporting this assumption^{90–99}.

Strengths of this study include using the TOPMed imputation reference panel, enabling us to assess a larger number of low-frequency and rare variants than previous studies. A further strength was its power to detect low-frequency and rare variant associations, as well as previously

unidentified common variant associations. This was facilitated by additional genotyped samples included in both OCAC and CIMBA and using population-based data from UKBB, resulting in the largest sample size analyzed for assessing genetic variant associations with HGSOC risk.

Limitations include the fact that the GWAS discovery data available were primarily of European ancestry; the associations of these variants are likely to differ for women of non-European ancestries, as they are likely to have different frequencies and LD patterns. A limitation of the PGM was that the derivation data differed from the GWAS discovery data presented here. Ideally, all the discovery GWAS data would have been used for PGM development. However, it was essential to validate the PGM on independent data, hence the OCAC and CIMBA data were used for development, whilst the UKBB data were reserved for validation. Lastly, the PGM training data (FinnGen) did not have specific histotypes available, meaning we were only able to consider overall EOC in the PGM training. As we were investigating non-mucinous OC, we would ideally have had specific EOC histotypes available at each stage of the PGM development, training and validation. However, given that HGSOC is the most prevalent EOC histotype, it is unlikely to have a major impact on the PGM hyperparameter fine-tuning.

Future research may aim to fine-map the novel loci identified here, to refine the candidate causal variants associated with HGSOC risk; and in-silico analyses may identify candidate target genes or pathways for further experimental studies¹⁰⁰. Additionally, future research could aim to identify novel variants associated with other OC histotypes and to discover novel associations for other ancestries.

We have shown that improvements in imputation reference panels that have larger genomic coverage and increased sample sizes can assist in identification of novel HGSOC associated variants that previously went undetected, either from absence from genotyping or imputation reference panels, or from lack of power to detect associations. Furthermore, these associations can be used to develop PGM that outperform previous best efforts that can be incorporated into cancer risk prediction algorithms to improve personalized risk prediction for HGSOC.

Methods

Study samples

OCAC participants were enrolled in 65 studies from 16 countries and a large European multinational nested case-control study (Supplementary Table 1). OCAC individual participant data were used for GWAS discovery analyses and developing polygenic models (PGMs).

CIMBA study participants were enrolled in 64 studies from 28 countries (Supplementary Table 2). Eligibility was restricted to women aged at least 18 years at the time of recruitment who carried a PV in either *BRCA1* or *BRCA2*. Data collected included year of birth, PV description, age at recruitment, age at last follow-up, and age at breast and ovarian cancer (invasive, fallopian tube and peritoneal) diagnoses, and age or date of prophylactic surgeries (bilateral mastectomy and bilateral oophorectomy). Most participants were recruited through cancer genetics clinics and enrolled in regional/national research studies. CIMBA individual participant data were used in the GWAS discovery and in PGM development.

The UK Biobank (UKBB) is a large-scale biomedical research resource, with detailed genetic and health data on half a million UK participants^{36,37}. For the purposes of these analyses, data from 245,377 female participants of European ancestry were used. UKBB individual participant data were used in the GWAS discovery analyses and to independently validate PGS.

FinnGen is a large collection of newly recruited and legacy samples from Finnish biobanks, research institutes, universities, university hospitals, international pharmaceutical partners, the Finnish Blood Service, the Finnish Biobank Cooperative, and the Finnish Institute for Health and Welfare, utilizing Finnish longitudinal health register data collected on every resident of Finland since 1969^{38,39}. FinnGen summary statistics (data freeze 8) based on 150,658 women (149,394 controls, 1264 EOC cases of any histotype) were used to train PGM hyperparameters.

BioBank Japan (BBJ) is a large biobank resource containing clinical and genetic data on over 300,000 participants^{40,41}. BBJ summary statistics based

on 61,457 women (60,614 controls, 843 EOC cases) were used for assessing PGS associations for women of East Asian ancestry¹⁰¹.

Genotyping and re-imputation using the TOPMed reference panel

Genotyping of OCAC and CIMBA samples were performed on one of two custom single nucleotide polymorphism (SNP) genotyping arrays, the iCOGS^{23,102} array or OncoArray^{22,103,104}. The iCOGS array included ~210,000 SNPs that were selected for previous evidence of association with breast, ovarian and prostate cancer. The OncoArray is a custom genotyping chip consisting of ~533,000 SNPs, approximately half of which is a GWAS backbone that tags common SNPs. A standard quality control (QC) process was applied, including assessment of SNP call rate, allele frequency, genotyping intensity clustering, Hardy-Weinberg equilibrium, and SNP concordance from duplicated samples¹⁰⁴. OCAC had additional samples genotyped on GWAS arrays¹⁴⁻¹⁶. These data were imputed to the TOPMed reference panel (version R2 on GRCh38, with 97,256 samples)³¹ using the Michigan Imputation Server^{32,105}. Phasing was performed with Eagle2¹⁰⁶ and imputation with Minimac^{107,108}. Prior to imputation, variants were excluded from imputation genotype files if they: (1) were not in Hardy-Weinberg equilibrium ($P < 1 \times 10^{-7}$ in controls, or $P < 1 \times 10^{-12}$ in cases); (2) had poor cluster plots; or (3) had a call rate <95% (common variants), or a call rate <98% (rare variants, MAF < 1%). We used <https://www.well.ox.ac.uk/~wrayner/tools/> script HRC-1000G-check-bim-v4.3.0.pl to remove variants not on the TOPMed reference panel or align them to the correct strand. This tool excluded variants where the genotyped frequency differed from the panel by more than 0.20. Samples were randomized into batches of <25,000 to meet the maximum sample requirement of the imputation server^{31,32,105}. The same list of variants was included for each genotype batch. Details of the UKBB genotyping and imputation to a combined UK10K^{109,110} and HRC³⁰ reference panel have been described elsewhere^{36,37}. The OCAC, CIMBA and UKBB analyses were based on 142 million, 104 million and 60 million well-imputed (imputation $r^2 > 0.30$) variants, respectively (Table 1). Downstream meta-analyses were restricted to variants that had minor allele counts (MACs) of MAC > 5 and did not have heterogeneous effects (Cochran Q-statistic, $P_{\text{het}} > 1 \times 10^{-8}$) in the meta-analysis of OCAC studies. Variants were aligned to the Genome Reference Consortium Human Build 38 (GRCh38/hg38).

Analyses including FinnGen and BBJ data made use of summary statistic data only. Details of FinnGen and BBJ genotyping and imputation have been described elsewhere^{38-41,101}.

Statistical analyses of OCAC and UKBB data

We examined the associations between genotypes and HGSOC risk in the OCAC data using logistic regression (using custom software). Analyses were conducted separately for OncoArray, iCOGS, and five GWAS datasets^{14-16,111} and were combined by fixed-effects inverse-variance weighted meta-analysis (Fig. 3). We included project-specific principal components (PCs) as covariates in the model with the number of PCs based on the inflection point observed in a scree plot (Supplementary Fig. 49). PCs for OncoArray data were calculated using 33,661 uncorrelated ($r^2 < 0.10$) common (MAF > 0.05) variants. Calculations were performed using a custom program (PCAlcal), available at https://github.com/CCGE-Cambridge/OCAC_CIMBA_HGSOC. Details of PC calculations for the other genotype data has been previously described elsewhere^{19,23}. All women were of European ancestry and unrelated, determined using genetic data^{22,103}. Ancestry was evaluated using the FastPop software¹¹². Women with >80% European ancestry were retained for statistical analyses. Relatedness was checked by genetic concordance statistics. This process has been described previously²². Briefly, women with concordance statistics between 0.74 and 0.86 were considered to be related (values > 0.86 considered duplicates). In instances of case-control pairs, the case was retained for statistical analyses and the control was excluded. For instances of case-case and control-control pairs, the sample with the lower call rate was excluded.

The UKBB analysis was restricted to women with European ancestry, selected based on their PCs. EOC histotypes were classified using diagnostic

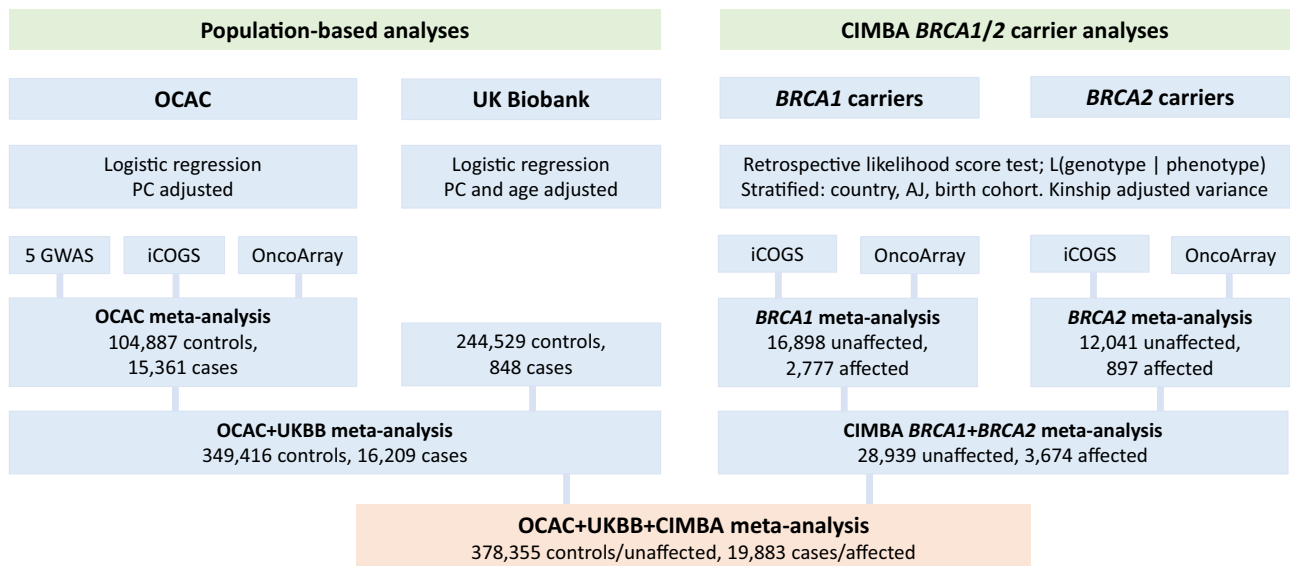


Fig. 3 | Schema describing the analytical process for the GWAS analyses from OCAC, UKBB and CIMBA, and subsequent meta-analyses.

codes provided by UKBB, with “serous”, “undifferentiated”, or “other” classified as HGSOc, a methodology similar to that used in OCAC²². Association analyses between genotypes and HGSOc risk were assessed by logistic regression (Fig. 3). We adjusted for the top four PCs and age at recruitment.

Statistical analyses of BRCA1 and BRCA2 pathogenic variant carriers

Analyses of CIMBA data were limited to carriers of European ancestry, determined by genetic data and multidimensional scaling^{22,103}. We used 33,661 common uncorrelated variants (the same set used to calculate PCs) to calculate kinship coefficients between all CIMBA participants and 267 HapMap samples (CHD, JPT, YRI and CEU ancestries). These kinship coefficients were converted to distances and then underwent multidimensional scaling. Using the top two PCs, the proportion of European ancestry for each participant was calculated. Women with >27% non-European ancestry were excluded, ensuring that women with Ashkenazi Jewish ancestry were retained for statistical analyses. Association analyses were performed separately by genotyping array (iCOGS or OncoArray), and separately for BRCA1 and BRCA2 PV carriers (Fig. 3). iCOGS and OncoArray associations were combined by fixed-effects inverse-variance weighted meta-analysis to estimate BRCA1 and BRCA2 PV carrier specific associations. The association analysis was carried out within a survival analysis framework, by modeling the retrospective likelihood of observing the genotypes conditional on the disease phenotypes to adjust for the non-random ascertainment with respect to disease phenotypes^{113,114}. The censoring process followed carriers from birth until the first occurrence of: EOC (including fallopian tube and peritoneal cancers) diagnosis, risk-reducing salpingo-oophorectomy, or study entry. Breast cancer diagnoses were not considered to be a censoring event and EOC was the endpoint of interest. Associations were then assessed using the score test statistic based on the retrospective likelihood^{113,114} assuming BRCA1 and BRCA2 PV carrier specific and age-cohort specific EOC incidences⁸⁸. Analyses were stratified by country and Ashkenazi Jewish ancestry, and to account for relatedness between individuals we calculated kinship adjusted variances¹¹⁵. Only variants that were available through OncoArray genotyping and imputation were considered, as the majority of samples were available from this genotyping platform (Table 1). As HGSOc is the predominant histotype for both BRCA1 and BRCA2 PV carriers, the associations were combined by fixed-effects and inverse variance weighted meta-analysis using the METAL software¹¹⁶.

Meta-analyses

We pooled the combined OCAC and UKBB summary association data (per-allele odds ratios, ORs) with the combined BRCA1 and BRCA2 PV carrier summary association data (per-allele hazard ratios, HRs) by fixed-effects inverse-variance weighted meta-analysis using METAL¹¹⁶ to give per-allele relative risks (RRs, a combination of population-based ORs and BRCA1/2 carrier HRs) (Fig. 3).

Eliminating likely statistical artifacts

The associations of all variants with genome-wide significant associations and falling outside known regions were re-evaluated to eliminate likely spurious associations potentially due to unstable effect estimates from strata with small numbers. For this purpose, the associations were re-analyzed, pooling individual level data from OCAC and UKBB, incorporating 29 PCs derived across all genotyping projects (PCs set to 0 for women not in specific studies/projects). The UKBB data were also adjusted for age (set to 0 for the OCAC samples). Any variant with imputation accuracy $r^2 < 0.30$ within a panel were considered missing for that particular panel. The associations for BRCA1/2 PV carriers were reassessed assuming all study participants came from a single stratum.

We also re-evaluated potentially novel associations with variants in regions proximal to known regions by performing approximate conditional analyses¹¹⁷. This approach utilized summary statistics from the combined OCAC, UKBB and BRCA1/2 PV carrier meta-analysis and the linkage disequilibrium (LD) structure from 111,304 women genotyped on the OncoArray from OCAC and CIMBA.

For variants passing these checks, we calculated Bayesian false-discovery probabilities (BFDPs)⁴⁵. BFDPs are approximate Bayes factors, statistical measures of the strength of evidence in favor of a given statistical model over another. They are akin to false-positive reporting probabilities, aiming to control the number of false positive associations whilst not dismissing too many associations that may merit scientific interest, by including Bayesian priors on an effect or association. BFDPs are especially useful in contexts where many statistical tests are performed, such as GWAS. We assumed prior probabilities of 1:1000 and 1:10,000 variants being truly associated. BFDPs were calculated using the BFDP function from the R gap package¹¹⁸.

Genomic database searches

Variants found to be associated with HGSOc at the genome-wide statistical significance level that also passed the additional checks detailed above, and the nearest genes to these variants, were looked up in genomic resource

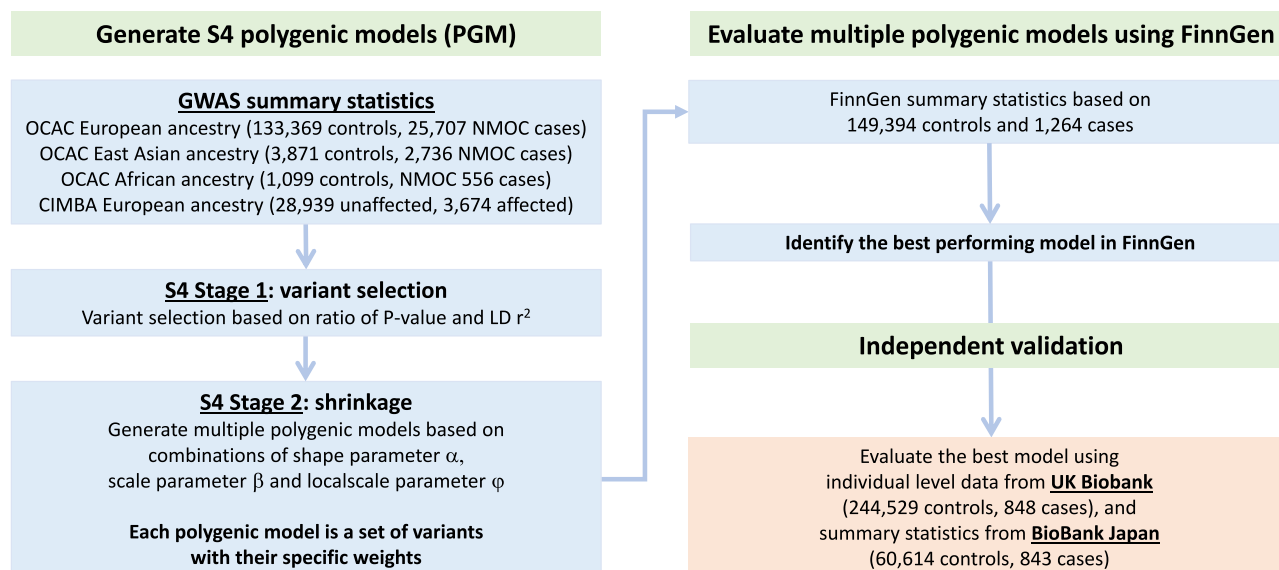


Fig. 4 | Schema describing the development of polygenic models, determining the optimal model, and validating the resultant polygenic score in European ancestry women from UKBB and East Asian ancestry women from BBJ. S4 select and

shrink using summary statistics, PGM polygenic model, NMOC non-mucinous ovarian cancer, LD linkage disequilibrium.

databases. We accessed dbSNP⁷⁴, Phenoscanner (version 2)^{119–121}, PheWeb (version 1.3.15)¹²², GTEX⁶⁴ and eQTLGen^{123,124} (accessed on 15th May 2023).

Defining credible causal variants

The lead variant (variant with the smallest *P*-value) at each novel region may not be causal. Therefore, we identified lists of credible causal variants (CCVs) that are likely to contain the genetic variant responsible for altering HGSOC risk defined as the set of variants within ±500 kb of the lead variant whose *P*-value was within two orders of magnitude of the lead variant’s *P*-value¹²⁵.

Development of polygenic risk models

Previous analyses of PGMs specific to HGS, LGS, and mucinous histotypes showed that all histotypes, except mucinous, were associated with either the HGSOC PGS or LGSOC PGS²⁸. Genetic correlations between mucinous ovarian cancer and other ovarian cancer histotypes have been estimated to be 0.24, 0.21, 0.23 and −0.21 with high-grade serous ovarian cancer, low-grade serous ovarian cancer, endometrioid ovarian cancer and clear cell, respectively²⁸. Whereas the genetic correlations are stronger for pairs of the other non-mucinous histotypes²⁸. Thus, the non-mucinous histotypes were combined here¹²⁶. The PGMs were developed on summary statistics using associations obtained from a meta-analysis of the OCAC and CIMBA data (Fig. 4). To maximize sample size and genetic diversity, the OCAC summary statistics came from a meta-analysis of European (133,369 controls, 25,707 cases), East Asian (3871 controls, 2736 cases) and African (1099 controls, 556 cases) ancestry women, considering the associations with non-mucinous OC. Hence, these OCAC summary statistics differed from those obtained from the analyses described in ‘Statistical analyses of OCAC and UKBB data’, as a result of analyzing additional cases from non-mucinous histotypes (and further controls from studies previously excluded because they had no HGSOC cases), and additional women of East Asian and African ancestry. The CIMBA summary statistics were identical to those generated in the analyses described in ‘Statistical analyses of *BRCA1* and *BRCA2* pathogenic variant carriers’.

We developed 1102 PGMs (sets of variants and their weights) for non-mucinous OC using the Select and Shrink with Summary Statistics (S4) method^{43,126}. We used two *P*-value to LD *r*² ratios to select variants: (i) *P*:*r*² < 0.02 that resulted in ~64k variants (562 PGMs tested) and (ii)

P:*r*² < 0.15 resulting in ~394k variants (540 models tested). The LD structure was weighted to reflect the average effects from each ancestry based on a subset of OCAC OncoArray data. Each model had different combinations of model hyperparameters (shrinkage parameters controlling small and large variant effect sizes, and an overall shrinkage parameter) that were trained using summary statistics based on 150,658 women (149,394 controls, 1264 EOC cases) from FinnGen (data freeze 8)^{38,39}. EOC histotype data was not available for FinnGen, hence we used the associations with overall EOC for PGM training.

Polygenic scores (PGS) are PGMs applied to observed or imputed genotypes. We used the resultant PGM to calculate PGS on individual-level data in the UKBB^{36,37} to test its association with HGSOC and calculated its discriminatory ability for HGSOC by estimating the area under the ROC (AUROC) curve. AUROCs were calculated using the R pROC package auc function¹²⁷.

We assessed the performance of the PGS for women of East Asian ancestry using BBJ data. As individual-level data were unavailable, we used association summary statistics from BBJ¹⁰¹ and assessed the PGS performance using a previously described method for evaluating PGS on summary statistic data¹²⁶. The reference panel used consisted of individuals of East Asian ancestry from the 1000 Genomes Project²⁹.

We also created candidate PGMs consisting of genotyped variants that could be more easily applied in clinical settings by selecting variants known to reliably genotype from the OncoArray¹⁰³, many of which had been chosen for their relevance to ovarian cancer. We selected a subset of genotyped variants, based on “relative importance”, where the importance of each variant is approximately proportional to *p**(1-*p*)*β², where β is the log-RR and *p* is the minor allele frequency for that variant. We ranked each variant based on relative importance and selected the top *N* desired variants.

Absolute risks of EOC by PGS percentile

We calculated predicted lifetime risks (to age 80 years) of developing EOC for women in the general population (unselected for PV status), *BRCA1* and *BRCA2* PV carriers at the 1st, 5th, 20th, 50th (median), 80th, 95th and 99th percentiles of the various PGS distributions, following previously published methodologies¹²⁸. To ensure consistency with known EOC risks for the general population, *BRCA1* and *BRCA2* PV carriers, average age-specific EOC incidence rates were constrained over PGS percentiles to agree with

external EOC incidence rates for the general population¹²⁹ and *BRCA1/2* carriers¹³⁰.

We examined the number of *BRCA2* PV carriers genotyped on the OncoArray that would transition between risk groups (low (<10%) or high (≥10%) lifetime risk) of developing EOC, based on their observed PGS percentile. These risk reclassification analyses were limited to *BRCA2* carriers as their lifetime risks transition over the 10% lifetime risk threshold, whereas a *BRCA1* carrier is already at substantially increased lifetime risk.

Ethics statement

All study participants provided written informed consent and participated in research studies at the host institute under ethically approved protocols. This study was conducted in accordance with the Declaration of Helsinki.

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: Australian site of the Breast Cancer Family Registry (BCFR-AU) - The University of Melbourne Health Sciences Human Ethics Sub-Committee; Northern California site of the Breast Cancer Family Registry (BCFR-NC) - Northern California Cancer Center Institutional Review Board; New York site of the Breast Cancer Family Registry (BCFR-NY) - Columbia University Medical Center Institutional Review Board; Ontario site of the Breast Cancer Family Registry (BCFR-ON) - Mount Sinai Hospital Research Ethics Board; Philadelphia site of the Breast Cancer Family Registry (BCFR-PA) - Institutional Review Board Fox Chase Cancer Center; Utah site of the Breast Cancer Family Registry (BCFR-UT) - Institutional Review Board University of Utah; Baltic Familial Breast and Ovarian Cancer Consortium (BFBOCC) - Centrālā medicīnas ētikas Komiteja; Lietuvos Bioetikos Komitetas; BRCA-gene mutations and breast cancer in South African women (BMBSA) - University of Pretoria and Pretoria Academic Hospitals Ethics Committee; Beckman Research Institute of the City of Hope (BRICOH) - City of Hope Medical Center Institutional Review Board; Copenhagen Breast Cancer Study (CBCS) - De Videnskabetiske Komiteer I Region Hovedstaden; Spanish National Cancer Centre (CNIO) - Instituto de Salud Carlos III Comité de Bioética y Bienestar Animal; City of Hope Cancer Center (COH) - City of Hope Institutional Review Board; Consorzio Studi Italiani sui Tumori Ereditari Alla Mammella (CONSIT TEAM) - Comitato Etico Indipendente della Fondazione IRCCS "Istituto Nazionale dei Tumori"; National Centre for Scientific Research Demokritos (DEMOKRITOS) - Bioethics committee of NCSR "Demokritos", 240/EHA/11.3; National Centre for Scientific Research Demokritos (DEMOKRITOS) - Papageorgiou Hospital Ethics Committee; Dana Farber Cancer Institute (DFCI) - Dana Farber Cancer Institute Institutional Review Board; Deutsches Krebsforschungszentrum (DKFZ) - Ethik-Kommission des Klinikums der Universität; Deutsches Krebsforschungszentrum (DKFZ) - Hospital Universitario de San Ignacio Comité de Investigaciones y Etica; Deutsches Krebsforschungszentrum (DKFZ) - Shaikat Khanum Memorial Cancer Hospital and Research Centre Institutional Review Board; Epidemiological study of BRCA1 and BRCA2 mutation carriers (EMBRACE) - Anglia & Oxford MREC; Fox Chase Cancer Center (FCCC) - Institutional Review Board Fox Chase Cancer Center; Fundación Pública Galega de Medicina Xenómica - Comité Autonómico de Etica da Investigación de Galicia; German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) - Ethik-Kommission der Medizinischen Fakultät der Universität zu Köln; Genetic Modifiers of cancer risk in BRCA1/2 mutation carriers (GEMO) - Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé; Georgetown University (GEORGETOWN) - MedStar Research Institute - Georgetown University Oncology Institutional Review Board; Ghent University Hospital (G-FAST) - Universitair Ziekenhuis Gent - Ethics Committee; Hospital Clinico San Carlos (HCSC) - Comité Ético de Investigación Clínica Hospital Clínico San Carlos; Helsinki Breast Cancer Study (HEBCS) - Helsingin ja uudenmaan sairaanhoitopiiri (Helsinki University Central Hospital ethics committee); Hereditary Breast and Ovarian study Netherlands (HEBON) - Protocol Toetsingscommissie van het Nederlands Kanker Instituut/Antoni van

Leeuwenhoek Ziekenhuis; Molecular Genetic Studies of Breast- and Ovarian Cancer in Hungary (HUNBOCS) - Institutional Review Board of the Hungarian National Institute of Oncology; University Hospital Vall d'Hebron (HVH) - The Hospital Universitario Vall d'Hebron Clinical Research Ethics Committee; Institut Català d'Oncologia (ICO) - Catalan Institute of Oncology Institutional Review Board; International Hereditary Cancer Centre (IHCC) - Komisji Bioetycznej Pomorskiej Akademii Medycznej (Pomeranian Medical University Bioethics Committee); Iceland Landspítali - University Hospital (ILUH) - Vísindasáðanefnd National Bioethics Committee; Interdisciplinary Health Research International Team Breast Cancer Susceptibility (INHERIT) - Comité d'éthique de la recherche du Centre Hospitalier Universitaire de Québec; Istituto Oncologico Veneto Hereditary Breast and Ovarian Cancer Study (IOVHBOCS) - Centro Oncologico Regionale Azienda Ospedale Di Padova Comitato Etico; Portuguese Oncology Institute-Porto Breast Cancer Study - COMISSÃO DE ÉTICA PARA A SAÚDE (CES); Kathleen Cuninghame Foundation Consortium for Research into Familial Breast Cancer (KCONFAB) - Queensland Institute of Medical Research - Human Research Ethics Committee; Kathleen Cuninghame Foundation Consortium for Research into Familial Breast Cancer (KCONFAB) - Peter MacCallum Cancer Centre Ethics Committee; University of Kansas Medical Center (KUMC) - The University of Kansas Medical Center Human Research Protection Program; Mayo Clinic (MAYO) - Mayo Clinic Institutional Review Boards; McGill University (MCGILL) - McGill Faculty of Medicine Institutional Review Board; Modifier Study of Quantitative Effects on Disease (MOD-SQUAD) - Mayo Clinic Institutional Review Boards; Memorial Sloane Kettering Cancer Center (MSKCC) - Human Biospecimen Utilization Committee; Memorial Sloan Kettering Cancer Center (MSKCC) - Memorial Sloan-Kettering Cancer Center IRB; General Hospital Vienna (MUV) - Ethikkommission der Medizinischen Universität Wien; Women's College Research Institute Hereditary Breast and Ovarian Cancer Study - University of Toronto Health Sciences Review Ethics Board; National Cancer Institute (NCI) - NIH Ethics Office; National Israeli Cancer Control Center (NICCC) - Carmel Medical Center Institutional Review Board (Helsinki Committee); N.N. Petrov Institute of Oncology (NNPIO) - N.N. Petrov Institutional Ethical Committee; NorthShore University HealthSystem (NORTHSHORE) - Institutional Review Board of NorthShore University HealthSystem; NRG Oncology (NRG_ONCOLOGY) - Cancer Prevention and Control Protocol Review Committee; Ontario Cancer Genetics Network (OCGN) - University Health Network Research Ethics Board; The Ohio State University Comprehensive Cancer Center (MACBRCA) - The Ohio State University Cancer Institutional Review Board; Odense University Hospital (OUH) - Den Videnskabetiske Komité for Region Syddanmark; Pisa Breast Cancer Study (PBCS) - Azienda Ospedaliera Pisana Comitato Etico per lo studio del farmaco sull'uomo; Sheba Medical Centre - Chaim Sheba Medical Center IRB; Swedish Breast Cancer Study (SWE-BRCA) - Regionala Etikprövningsnämnden Stockholm; University of Chicago (UCHICAGO) - The University of Chicago Biological Sciences Division. Institutional Review Board (BSD IRB); University of California Los Angeles (UCLA) - UCLA Institutional Review Board (UCLA IRB); University of California San Francisco (UCSF) - Human Research Protection Program Institutional Review Board (IRB); UK and Gilda Radner Familial Ovarian Cancer Registries (UKGRFOCR) - Roswell Park Cancer Institute IRB; UK and Gilda Radner Familial Ovarian Cancer Registries (UKGRFOCR) - Cambridge Local Research Ethics Committee; University of Pennsylvania (UPENN) - University of Pennsylvania Institutional Review Board; Cancer Family Registry University of Pittsburgh (UPITT) - University of Pittsburgh Institutional Review Board; University of Texas MD Anderson Cancer Center (UTMDACC) - University of Texas MD Anderson Cancer Center Office of Protocol Research Institutional Review Board; Victorian Familial Cancer Trials Group (VFCTG) - Peter MacCallum Cancer Centre Ethics Committee; Women's Cancer Program at Cedars-Sinai Medical Center (WCP) - (Cedars-Sinai Medical Center) CSMC Institutional Review Board. GynBiobank (WMH) - Western Sydney Local Health District Human Research Ethics Committee.

Data availability

GWAS summary statistics from OCAC and CIMBA are publicly available from the GWAS Catalog under study accession identifiers GCST90455658 (OCAC), GCST90455659 (CIMBA BRCA1 PV carriers), GCST90455660 (CIMBA BRCA2 PV carriers). The summary statistics from the meta-analysis of OCAC, UKBB and CIMBA associations are also available under study accession identifier GCST90455661. Variants included in the polygenic scores and their corresponding weights are publicly available from the PGS Catalog under identifiers PGS005086 (PGS₆₄₅₁₈), PGS005087 (PGS₅₉₅₇), PGS005088 (PGS₃₄₄₈) and PGS005089 (PGS₄₀₀). The FinnGen summary statistics used were from data freeze 8. The summary statistics across all data freezes are available at https://www.finnngen.fi/en/access_results and the data freeze 8 summary statistics are available at <https://r8.finnngen.fi/>. The Biobank Japan summary statistics used were from Sakaue et al.¹⁰¹. The summary statistic data for all traits are available at <https://pheweb.jp/> and the ovarian cancer summary statistic data can be accessed here <https://pheweb.jp/pheno/OvC>.

Code availability

Code and software used to implement analyses is publicly available at https://github.com/CCGE-Cambridge/OCAC_CIMBA_HGSOC.

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References

- Sung, H. et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **71**, 209–249 (2021).
- Prat, J. New insights into ovarian cancer pathology. *Ann. Oncol.* **23**, x111–x117 (2012).
- Peres, L. C. et al. Invasive epithelial ovarian cancer survival by histotype and disease stage. *J. Natl Cancer Inst.* **111**, 60–68 (2019).
- Risch, H. A. et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. *J. Natl Cancer Inst.* **98**, 1694–1706 (2006).
- Risch, H. A. et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *Am. J. Hum. Genet.* **68**, 700–710 (2001).
- Shaw, P. A. et al. Histopathologic features of genetically determined ovarian cancer. *Int. J. Gynecol. Pathol.* **21**, 407–411 (2002).
- Zhang, S. et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. *Gynecol. Oncol.* **121**, 353–357 (2011).
- Schrader, K. A. et al. Germline BRCA1 and BRCA2 mutations in ovarian cancer: utility of a histology-based referral strategy. *Obstet. Gynecol.* **120**, 235–240 (2012).
- Wang, Y. K. et al. Genomic consequences of aberrant DNA repair mechanisms stratify ovarian cancer histotypes. *Nat. Genet.* **49**, 856–865 (2017).
- Lakhani, S. R. et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. *Clin. Cancer Res.* **10**, 2473–2481 (2004).
- O’Mahony, D. G. et al. Ovarian cancer pathology characteristics as predictors of variant pathogenicity in BRCA1 and BRCA2. *Br. J. Cancer* **128**, 2283–2294 (2023).
- Singh, N., McCluggage, W. G. & Gilks, C. B. High-grade serous carcinoma of tubo-ovarian origin: recent developments. *Histopathology* **71**, 339–356 (2017).
- Kobel, M. et al. Differences in tumor type in low-stage versus high-stage ovarian carcinomas. *Int. J. Gynecol. Pathol.* **29**, 203–211 (2010).
- Song, H. et al. A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2. *Nat. Genet.* **41**, 996–1000 (2009).
- Bolton, K. L. et al. Common variants at 19p13 are associated with susceptibility to ovarian cancer. *Nat. Genet.* **42**, 880–884 (2010).
- Goode, E. L. et al. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. *Nat. Genet.* **42**, 874–879 (2010).
- Bojesen, S. E. et al. Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. *Nat. Genet.* **45**, 371–384 (2013).
- Permeth-Wey, J. et al. Identification and molecular characterization of a new ovarian cancer susceptibility locus at 17q21.31. *Nat. Commun.* **4**, 1627 (2013).
- Pharoah, P. D. et al. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. *Nat. Genet.* **45**, 362–370 (2013).
- Shen, H. et al. Epigenetic analysis leads to identification of HNF1B as a subtype-specific susceptibility gene for ovarian cancer. *Nat. Commun.* **4**, 1628 (2013).
- Kuchenbaecker, K. B. et al. Identification of six new susceptibility loci for invasive epithelial ovarian cancer. *Nat. Genet.* **47**, 164–171 (2015).
- Phelan, C. M. et al. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. *Nat. Genet.* **49**, 680–691 (2017).
- Couch, F. J. et al. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. *PLoS Genet.* **9**, e1003212 (2013).
- Chen, K. et al. Genome-wide association study identifies new susceptibility loci for epithelial ovarian cancer in Han Chinese women. *Nat. Commun.* **5**, 4682 (2014).
- Kelemen, L. E. et al. Genome-wide significant risk associations for mucinous ovarian carcinoma. *Nat. Genet.* **47**, 888–897 (2015).
- Kar, S. P. et al. Genome-wide meta-analyses of breast, ovarian, and prostate cancer association studies identify multiple new susceptibility loci shared by at least two cancer types. *Cancer Discov.* **6**, 1052–1067 (2016).
- Lawrenson, K. et al. Functional mechanisms underlying pleiotropic risk alleles at the 19p13.1 breast-ovarian cancer susceptibility locus. *Nat. Commun.* **7**, 12675 (2016).
- Dareng, E. O. et al. Integrative multi-omics analyses to identify the genetic and functional mechanisms underlying ovarian cancer risk regions. *Am. J. Hum. Genet.* **111**, 1061–1083 (2024).
- Genomes Project Consortium et al. A global reference for human genetic variation. *Nature* **526**, 68–74 (2015).
- McCarthy, S. et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.* **48**, 1279–1283 (2016).
- Taliun, D. et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. *Nature* **590**, 290–299 (2021).
- Das, S. et al. Next-generation genotype imputation service and methods. *Nat. Genet.* **48**, 1284–1287 (2016).
- OCAC. Ovarian Cancer Association Consortium, <https://ocac.ccgemedschl.cam.ac.uk/> (2023).
- Chenevix-Trench, G. et al. An international initiative to identify genetic modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: the Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA). *Breast Cancer Res.* **9**, 104 (2007).
- CIMBA. Consortium of Investigators of Modifiers of BRCA1 & BRCA2, <https://cimba.ccgemedschl.cam.ac.uk/> (2023).
- Bycroft, C. et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203–209 (2018).
- Biobank, U. UK Biobank, <https://www.ukbiobank.ac.uk/> (2023).
- Kurki, M. I. et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature* **613**, 508–518 (2023).
- FinnGen. FinnGen, <https://www.finnngen.fi/en> (2023).
- Nagai, A. et al. Overview of the BioBank Japan project: study design and profile. *J. Epidemiol.* **27**, S2–S8 (2017).

41. Japan, B. *BioBank Japan*, <https://biobankjp.org/en/> (2023).
42. Huang, L. et al. TOP-LD: a tool to explore linkage disequilibrium with TOPMed whole-genome sequence data. *Am. J. Hum. Genet.* **109**, 1175–1181 (2022).
43. Dareng, E. O. et al. Polygenic risk modeling for prediction of epithelial ovarian cancer risk. *Eur. J. Hum. Genet.* **30**, 349–362 (2022).
44. Xiao, R. & Boehnke, M. Quantifying and correcting for the winner’s curse in genetic association studies. *Genet. Epidemiol.* **33**, 453–462 (2009).
45. Wakefield, J. A Bayesian measure of the probability of false discovery in genetic epidemiology studies. *Am. J. Hum. Genet.* **81**, 208–227 (2007).
46. Zhang, H. et al. Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses. *Nat. Genet.* **52**, 572–581 (2020).
47. Stacey, S. N. et al. A germline variant in the TP53 polyadenylation signal confers cancer susceptibility. *Nat. Genet.* **43**, 1098–1103 (2011).
48. Stacey, S. N. et al. Germline sequence variants in TGM3 and RGS22 confer risk of basal cell carcinoma. *Hum. Mol. Genet.* **23**, 3045–3053 (2014).
49. Stacey, S. N. et al. New basal cell carcinoma susceptibility loci. *Nat. Commun.* **6**, 6825 (2015).
50. Chahal, H. S. et al. Genome-wide association study identifies 14 novel risk alleles associated with basal cell carcinoma. *Nat. Commun.* **7**, 12510 (2016).
51. Di Giovannantonio, M. et al. Heritable genetic variants in key cancer genes link cancer risk with anthropometric traits. *J. Med. Genet.* **58**, 392–399 (2021).
52. Melin, B. S. et al. Genome-wide association study of glioma subtypes identifies specific differences in genetic susceptibility to glioblastoma and non-glioblastoma tumors. *Nat. Genet.* **49**, 789–794 (2017).
53. Egan, K. M. et al. Rare TP53 genetic variant associated with glioma risk and outcome. *J. Med. Genet.* **49**, 420–421 (2012).
54. Enciso-Mora, V. et al. Low penetrance susceptibility to glioma is caused by the TP53 variant rs78378222. *Br. J. Cancer* **108**, 2178–2185 (2013).
55. Wang, Z. et al. Further confirmation of germline glioma risk variant rs78378222 in TP53 and its implication in tumor tissues via integrative analysis of TCGA data. *Hum. Mutat.* **36**, 684–688 (2015).
56. Conti, D. V. et al. Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction. *Nat. Genet.* **53**, 65–75 (2021).
57. Li, Y. et al. Single nucleotide variation in the TP53 3’ untranslated region in diffuse large B-cell lymphoma treated with rituximab-CHOP: a report from the International DLBCL Rituximab-CHOP Consortium Program. *Blood* **121**, 4529–4540 (2013).
58. Bode, A. M. & Dong, Z. Post-translational modification of p53 in tumorigenesis. *Nat. Rev. Cancer* **4**, 793–805 (2004).
59. Olivier, M., Hussain, S. P., Caron de Fromental, C., Hainaut, P. & Harris, C. C. *TP53 Mutation Spectra and Load: A Tool for Generating Hypotheses on the Etiology of Cancer*, 247–270 (IARC Science Publication, 2004).
60. Levine, A. J. p53, the cellular gatekeeper for growth and division. *Cell* **88**, 323–331 (1997).
61. Vogelstein, B., Lane, D. & Levine, A. J. Surfing the p53 network. *Nature* **408**, 307–310 (2000).
62. Zhang, P. et al. Germline and somatic genetic variants in the p53 pathway interact to affect cancer risk, progression, and drug response. *Cancer Res.* **81**, 1667–1680 (2021).
63. Schildkraut, J. M. et al. Single nucleotide polymorphisms in the TP53 region and susceptibility to invasive epithelial ovarian cancer. *Cancer Res.* **69**, 2349–2357 (2009).
64. GTEx. *Genotype-Tissue Expression project*, <https://gtexportal.org/home/> (2023).
65. Urbanek, M. et al. Thirty-seven candidate genes for polycystic ovary syndrome: strongest evidence for linkage is with follistatin. *Proc. Natl Acad. Sci. USA* **96**, 8573–8578 (1999).
66. Frandsen, C. L. B. et al. Risk of epithelial ovarian tumors among women with polycystic ovary syndrome: a nationwide population-based cohort study. *Int. J. Cancer* **153**, 958–968 (2023).
67. Harris, H. R. et al. Association between genetically predicted polycystic ovary syndrome and ovarian cancer: a Mendelian randomization study. *Int. J. Epidemiol.* **48**, 822–830 (2019).
68. Manichaikul, A. et al. Identification of novel epithelial ovarian cancer loci in women of African ancestry. *Int. J. Cancer* **146**, 2987–2998 (2020).
69. Lin, C. H. et al. Glutamate-cysteine ligase catalytic subunit as a therapeutic target in acute myeloid leukemia and solid tumors. *Am. J. Cancer Res.* **11**, 2911–2927 (2021).
70. Ogiwara, H. et al. Targeting the vulnerability of glutathione metabolism in ARID1A-deficient cancers. *Cancer Cell* **35**, 177–190.e178 (2019).
71. Wu, R. C., Wang, T. L. & Shih Ie, M. The emerging roles of ARID1A in tumor suppression. *Cancer Biol. Ther.* **15**, 655–664 (2014).
72. Li, W. et al. A pan-cancer analysis reveals the diagnostic and prognostic role of CDCA2 in low-grade glioma. *PLOS ONE* **18**, e0291024 (2023).
73. Veeriah, S. et al. The tyrosine phosphatase PTPRD is a tumor suppressor that is frequently inactivated and mutated in glioblastoma and other human cancers. *Proc. Natl Acad. Sci. USA* **106**, 9435–9440 (2009).
74. Sherry, S. T., Ward, M. & Sirotkin, K. dbSNP-database for single nucleotide polymorphisms and other classes of minor genetic variation. *Genome Res.* **9**, 677–679 (1999).
75. Rafnar, T. et al. Variants associating with uterine leiomyoma highlight genetic background shared by various cancers and hormone-related traits. *Nat. Commun.* **9**, 3636 (2018).
76. Harris, H. R. et al. Racial differences in the association of endometriosis and uterine leiomyomas with the risk of ovarian cancer. *Obstet. Gynecol.* **141**, 1124–1138 (2023).
77. Broggin, M. et al. Cell cycle-related phosphatases CDC25A and B expression correlates with survival in ovarian cancer patients. *Anticancer Res.* **20**, 4835–4840 (2000).
78. Schraml, P. et al. Cyclin E overexpression and amplification in human tumours. *J. Pathol.* **200**, 375–382 (2003).
79. Cancer Genome Atlas Research, N Integrated genomic analyses of ovarian carcinoma. *Nature* **474**, 609–615 (2011).
80. Goundiam, O. et al. Histo-genomic stratification reveals the frequent amplification/overexpression of CCNE1 and BRD4 genes in non-BRCAness high grade ovarian carcinoma. *Int. J. Cancer* **137**, 1890–1900 (2015).
81. Kang, E. Y. et al. CCNE1 and survival of patients with tubo-ovarian high-grade serous carcinoma: an Ovarian Tumor Tissue Analysis consortium study. *Cancer* **129**, 697–713 (2023).
82. Cancer Genome Atlas, N Comprehensive molecular portraits of human breast tumours. *Nature* **490**, 61–70 (2012).
83. Curtis, C. et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature* **486**, 346–352 (2012).
84. Jiang, Y. Z. et al. Genomic and transcriptomic landscape of triple-negative breast cancers: subtypes and treatment strategies. *Cancer Cell* **35**, 428–440.e425 (2019).
85. Jones, R. M. et al. Increased replication initiation and conflicts with transcription underlie Cyclin E-induced replication stress. *Oncogene* **32**, 3744–3753 (2013).
86. Gallo, D. et al. CCNE1 amplification is synthetic lethal with PKMYT1 kinase inhibition. *Nature* **604**, 749–756 (2022).
87. Lee, A. et al. Comprehensive epithelial tubo-ovarian cancer risk prediction model incorporating genetic and epidemiological risk factors. *J. Med. Genet.* **59**, 632–643 (2022).

88. Lee, A. et al. Enhancing the BOADICEA cancer risk prediction model to incorporate new data on RAD51C, RAD51D, BARD1 updates to tumour pathology and cancer incidence. *J. Med. Genet.* **59**, 1206–1218 (2022).
89. Yang, X. et al. Validation of the BOADICEA model for epithelial tubo-ovarian cancer risk prediction in UK Biobank. *Br J Cancer* **131**, 1473–1479 (2024).
90. Milne, R. L. et al. Assessing interactions between the associations of common genetic susceptibility variants, reproductive history and body mass index with breast cancer risk in the breast cancer association consortium: a combined case-control study. *Breast Cancer Res.* **12**, R110 (2010).
91. Nickels, S. et al. Evidence of gene-environment interactions between common breast cancer susceptibility loci and established environmental risk factors. *PLoS Genet.* **9**, e1003284 (2013).
92. Rudolph, A. et al. Investigation of gene-environment interactions between 47 newly identified breast cancer susceptibility loci and environmental risk factors. *Int. J. Cancer* **136**, E685–E696 (2015).
93. Clyde, M. A. et al. Risk prediction for epithelial ovarian cancer in 11 United States-based case-control studies: incorporation of epidemiologic risk factors and 17 confirmed genetic loci. *Am. J. Epidemiol.* **184**, 579–589 (2016).
94. Rudolph, A. et al. Joint associations of a polygenic risk score and environmental risk factors for breast cancer in the Breast Cancer Association Consortium. *Int. J. Epidemiol.* **47**, 526–536 (2018).
95. Vachon, C. M. et al. Joint association of mammographic density adjusted for age and body mass index and polygenic risk score with breast cancer risk. *Breast Cancer Res.* **21**, 68 (2019).
96. Kachuri, L. et al. Pan-cancer analysis demonstrates that integrating polygenic risk scores with modifiable risk factors improves risk prediction. *Nat. Commun.* **11**, 6084 (2020).
97. Kapoor, P. M. et al. Assessment of interactions between 205 breast cancer susceptibility loci and 13 established risk factors in relation to breast cancer risk, in the Breast Cancer Association Consortium. *Int. J. Epidemiol.* **49**, 216–232 (2020).
98. Archambault, A. N. et al. Risk stratification for early-onset colorectal cancer using a combination of genetic and environmental risk scores: an international multi-center study. *J. Natl Cancer Inst.* **114**, 528–539 (2022).
99. Wang, X. et al. Genome-wide interaction analysis of menopausal hormone therapy use and breast cancer risk among 62,370 women. *Sci. Rep.* **12**, 6199 (2022).
100. Brnich, S. E. et al. Recommendations for application of the functional evidence PS3/BS3 criterion using the ACMG/AMP sequence variant interpretation framework. *Genome Med.* **12**, 3 (2019).
101. Sakaue, S. et al. A cross-population atlas of genetic associations for 220 human phenotypes. *Nat. Genet.* **53**, 1415–1424 (2021).
102. Gaudet, M. M. et al. Identification of a BRCA2-specific modifier locus at 6p24 related to breast cancer risk. *PLoS Genet.* **9**, e1003173 (2013).
103. Amos, C. I. et al. The OncoArray Consortium: a network for understanding the genetic architecture of common cancers. *Cancer Epidemiol. Biomark. Prev.* **26**, 126–135 (2017).
104. Milne, R. L. et al. Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. *Nat. Genet.* **49**, 1767–1778 (2017).
105. TOPMed. *TOPMed Imputation Server*, <https://imputation.biodatacatalyst.nih.gov/> (2023).
106. Loh, P. R. et al. Reference-based phasing using the Haplotype Reference Consortium panel. *Nat. Genet.* **48**, 1443–1448 (2016).
107. Howie, B., Fuchsberger, C., Stephens, M., Marchini, J. & Abecasis, G. R. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nat. Genet.* **44**, 955–959 (2012).
108. Fuchsberger, C., Abecasis, G. R. & Hinds, D. A. minimac2: faster genotype imputation. *Bioinformatics* **31**, 782–784 (2015).
109. Consortium, U. K. et al. The UK10K project identifies rare variants in health and disease. *Nature* **526**, 82–90 (2015).
110. UK10K. *UK10K Project*, <https://www.uk10k.org/> (2014).
111. Permuth-Wey, J. et al. LIN28B polymorphisms influence susceptibility to epithelial ovarian cancer. *Cancer Res* **71**, 3896–3903 (2011).
112. Li, Y. et al. FastPop: a rapid principal component derived method to infer intercontinental ancestry using genetic data. *BMC Bioinforma.* **17**, 122 (2016).
113. Antoniou, A. C. et al. RAD51 135G->C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies. *Am. J. Hum. Genet.* **81**, 1186–1200 (2007).
114. Barnes, D. R. et al. Evaluation of association methods for analysing modifiers of disease risk in carriers of high-risk mutations. *Genet. Epidemiol.* **36**, 274–291 (2012).
115. Antoniou, A. C. et al. A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. *Nat. Genet.* **42**, 885–892 (2010).
116. Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**, 2190–2191 (2010).
117. Yang, J. et al. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat. Genet.* **44**, 369–375 (2012).
118. Zhao, J. H. gap: genetic analysis package. *J. Stat. Softw.* **23**, 1–18 (2007).
119. Staley, J. R. et al. PhenoScanner: a database of human genotype-phenotype associations. *Bioinformatics* **32**, 3207–3209 (2016).
120. Kamat, M. A. et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. *Bioinformatics* **35**, 4851–4853 (2019).
121. PhenoScanner. *PhenoScanner V2: A database of human genotype-phenotype associations*, <http://www.phenoscanter.medschl.cam.ac.uk/> (2023).
122. PheWeb. *PheWeb*, <https://pheweb.org/UKB-TOPMed/> (2023).
123. Vosa, U. et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. *Nat. Genet.* **53**, 1300–1310 (2021).
124. eQTLGen. *eQTLGen*, <https://www.eqtngen.org/> (2023).
125. Udler, M. S., Tyrer, J. & Easton, D. F. Evaluating the power to discriminate between highly correlated SNPs in genetic association studies. *Genet Epidemiol.* **34**, 463–468 (2010).
126. Tyrer, J. P. et al. Improving on polygenic scores across complex traits using select and shrink with summary statistics (S4) and LDpred2. *BMC Genomics.* **25**, 878 (2024).
127. Robin, X. et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinforma.* **12**, 77 (2011).
128. Antoniou, A. C. et al. Common breast cancer susceptibility alleles and the risk of breast cancer for BRCA1 and BRCA2 mutation carriers: implications for risk prediction. *Cancer Res.* **70**, 9742–9754 (2010).
129. UK, C. R. *Cancer Research UK: Ovarian Cancer incidence by age*, <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/incidence#heading-One> (2024).
130. Kuchenbaecker, K. B. et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA* **317**, 2402–2416 (2017).

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Competing interests

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Additional information

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