

SUPPLEMENTARY MATERIALS

Supplementary Methods

Study Population: CIMBA Consortium

The Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) is an international collaboration developed to assess clinical and genetic risk factors in BRCA1/2 carriers and their respective associations with the development of breast and ovarian cancer [1, 2]. Investigators from 33 countries including 55 centers and multicenter consortia submitted de-identified data to a central database. The selection criteria for participants are as follows: 1) female carriers of verified disease-causing mutation in either *BRCA1* or *BRCA2* (participants were excluded if they carried mutations in both genes, N = 84) and 2), who were 18 years of age or older, with sufficient clinical data to assess risk which could include demographic/clinical characteristics, specific cancer diagnosis, ascertainment and follow-up dates, and history of prophylactic surgeries. At each center, carriers underwent interview and clinical testing or participated in a research study, after providing written informed consent in accordance with the local institutional review board. A family identifier was applied to indicate related individuals. Race/ethnicity were obtained via questionnaires in pre-defined categories or open-ended questions. Participants with self-reported non-European ancestry were excluded from the present analysis.

Genotyping and Imputation

The genotyping for the current analysis was conducted using the Collaborative Oncological Gene-Environment Study (iCOGS) custom array [3-5]. This array was part of a multi-consortia collaboration, including the Breast Cancer Association Consortium (BCAC), Ovarian Cancer Association Consortium (OCAC), and the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL), to identify and replicate common and rare genetic variants associated with the development of breast, ovarian, and prostate cancers. Development of the array was divided among the consortium in the following distribution: 25% was allotted to each of BCAC, OCAC, and PRACTICAL, 17.5% to CIMBA, and the remaining 7.5% were designed to be from common pathways that have been previously researched. Ultimately, the iCOGs array comprised of 220,123 SNPs, of which 211,155 were successfully manufactured for genotyping.

Genotyping for *BRCA1* carriers was conducted at the Mayo Clinic (USA) and for *BRCA2* carriers at McGill University and Génome Québec Innovation Centre (both in Canada). Genotypes identified through the iCOGs array were called using the Illumina GenCall algorithm [3, 4]. A total of 270 samples from Hapmap2 were used to generate a cluster file for the initial file. For the final call, 3,018 individuals were selected, which included samples from each of the study centers, consortia, and ethnicities from the iCOGs collaboration. Plates at this stage that have a consistently high call rate were used. A different cluster file was generated using 380 genotyped samples from the 1000 Genomes project and Hapmap including European, African, and Asian ethnicity along with 160 positive control samples for rare variants for the iCOGs array. This file was used to call the remaining genotype samples. Subsequently, additional exclusion criteria for quality assurance were applied: 1) single nucleotide polymorphisms (SNPs) located on the Y chromosome, 2) monomorphic SNPs, 3) SNPs that deviated significantly from Hardy-Weinberg equilibrium ($P < 10^{-7}$), 4) SNPs with call rates $< 95\%$, or 5) SNPs demonstrating extreme heterozygosity [3, 5]. After applying these quality control measures to the original 211,155 SNPs from the iCOGs array, we included data on 200,720 SNPs in *BRCA1* mutation carriers and 200,908 SNPs in *BRCA2* mutation carriers. For SNPs not genotyped on the iCOGS custom array, imputation was performed using the IMPUTE2 software based on the January 2012 version of the 1,000 Genomes haplotype [6]. SNPs were excluded from the analysis if they had imputation quality $r^2 < 0.30$. After applying these quality control and exclusion criteria, the current analysis included genotype data from 14,676 *BRCA1* carriers (7,360 of them developed breast cancer) and 7,912 *BRCA2* carriers (4,091 of them developed breast cancer).

Principal components analysis was conducted using 33,661 autosomal SNPs ($MAF > 0.05$) that were weakly correlated with one another (pairwise $r^2 < 0.1$) with 267 HapMap samples (ancestries represented included CHB, JPT, YRI, and CEU) [3]. The first 15 principal components were available for analysis in the present study.

Two-stage Residual Inclusion Regression

In the main instrumental variable (IV) analysis of the data, we have constructed the literature-reported per-allele associations between BMI and SNPs to build a genetic score (GS) for BMI using the formula: $BMI - GS = \sum_{i=1}^{93} \beta_{XGi} SNP_i$. Then we used $BMI - GS$ in the Cox regression of ovarian cancer risk. This method and the inverse variance-weighted meta-analysis

method can both be considered as two-stage predictor substitution (2SPS) method, while the predictor is from the external genome-wide association of BMI in the literature. For non-linear models, the 2SPS methods may give biased estimates in theory [7]. An alternative method of the two-stage instrumental variable analysis is the two-stage residual inclusion (2SRI) method, which can give consistent estimates [7, 8]. For the present study, we described the 2SRI regression using BMI as an example. In the first stage, we fit a linear model of observed BMI as below:

$$BMI = \alpha_0 + \beta_{xg}GS + \alpha_2\mathbf{birthcohort} + \alpha_3\mathbf{country}_j + \alpha_4mutation + \alpha_4\mathbf{PC} + e$$

where β_{xg} is the estimated effect of genetic score in the current BRCA1/2 study sample, ***birthcohort***, ***country***, ***PC*** (*principal components*) are vectors of the dummy variables the three factors, and e is the residual of the regression. Under the assumptions of instrumental variable analysis, e can represent the unobserved confounders. so if it is adjusted for, then the confounding effect for BMI would cease to exist.

In the second stage, we fit a stratified Cox model of ovarian cancer including both observed BMI and the residual e as below:

$$\log\left(\frac{h_j(t)}{h_j(0)}\right) = \beta_{yx}BMI + \beta_1e + \beta_2\mathbf{birthcohort} + \beta_3mutation + \beta_4\mathbf{PC}$$

where β_{yx} is the IV estimate of interest, and j indicates category of study country for stratified Cox model. In both stage 1 and 2 of the model, we used the robust sandwich estimator of variance to account for non-independence among multiple carriers per family, but there is no easy close-form formula to calculate variance for the simultaneous two equation model. Therefore, we applied the bootstrapping method to estimate variance. In brief, we generated 10,000 randomly selected datasets with replacement, run the 2SRI 10,000 times, and the variation in β_{yx} estimates was used to calculate its 95% confidence interval.

Although the 2SRI method is preferred for non-linear IV regression in theory, its estimator β_{yx} is less stable than the 2SPS estimator β_{YX} because the 2SPS method utilized β_{XGi} directly and data from all study participants even if BMI was missing. Therefore, we considered the 2SRI method as a sensitivity analysis.

References

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The institutional committees that approved individual studies

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Columbia University Medical Center Institutional Review Board

Mount Sinai Hospital Research Ethics Board

Institutional Review Board Fox Chase Cancer Center

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Comissão de Ética para a Saúde do Instituto Português de Oncologia do Porto

Notes:

[1] Imputation quality of 1 indicates genotyped SNPs.

[2] Effect estimate after height standardization.

[3] *P*-values were calculated using student's *t*-test. All *P*-values are two-sided.

[4] Association with ovarian cancer were estimated using weighted Cox models that adjusted for principal components, birth cohort, menopausal status, country of enrollment and mutation status.

[5] *P*-values were calculated using chi-squared test. All *P*-values are two-sided.

Supplementary Table 2. List of 93 BMI-associated genetic variants and their associations with BMI in prior published GWAS and in CIMBA, along with effect on ovarian cancer risk in CIMBA

Rsid #	Chromosome	Position	Nearest gene	Reference allele	Effect allele	Effect allele frequency in published GWAS	Effect allele frequency in CIMBA	Imputation quality ¹	Published association with BMI			Association with BMI in CIMBA			Association with ovarian cancer in CIMBA			Association with ovarian cancer in BRCA1 carriers			Association with ovarian cancer in BRCA2 carriers		
									Beta ²	SE	<i>P</i> -value ³	Beta, Kg/m ²	SE	<i>P</i> -value ³	Log Hazard Ratio ⁴	SE	<i>P</i> -value ⁵	Log Hazard Ratio ⁴	SE	<i>P</i> -value ⁵	Log Hazard Ratio ⁴	SE	<i>P</i> -value ⁵
rs977747	1	47684677	<i>TAL1</i>	T	G	0.61	0.61	0.97	-0.017	0.003	8.7E-08	-0.164	0.085	0.0544	0.005	0.033	0.8834	0.000	0.036	0.9948	0.036	0.071	0.6140
rs657452	1	49589847	<i>AGBL4</i>	A	G	0.61	0.62	0.93	-0.023	0.003	5.5E-13	-0.108	0.087	0.214	-0.047	0.033	0.1596	-0.046	0.037	0.2092	-0.053	0.073	0.4694
rs11583200	1	50559820	<i>ELAVL4</i>	C	T	0.60	0.61	0.88	-0.018	0.003	1.5E-08	-0.167	0.090	0.0622	-0.024	0.035	0.4898	-0.005	0.039	0.9060	-0.162	0.074	0.0275
rs3101336	1	72751185	<i>NEGR1</i>	T	C	0.61	0.64	1.00	0.033	0.003	3.3E-26	0.141	0.085	0.0972	-0.025	0.033	0.4576	-0.042	0.037	0.2464	0.100	0.077	0.1982
rs12566985	1	75002193	<i>FPGT</i>	G	A	0.55	0.57	0.99	-0.024	0.003	1.2E-15	-0.272	0.082	0.0009	-0.053	0.032	0.0946	-0.075	0.035	0.0329	0.085	0.067	0.2055
rs12401738	1	78446761	<i>FUBP1</i>	G	A	0.35	0.33	0.81	0.021	0.003	2.1E-10	0.106	0.096	0.2704	0.038	0.039	0.3234	0.060	0.042	0.1597	-0.115	0.089	0.1964
rs11165643	1	96924097	<i>PTBP2</i>	C	T	0.58	0.59	0.68	0.022	0.003	8.7E-12	0.172	0.101	0.0905	0.004	0.040	0.9221	0.021	0.044	0.6390	-0.106	0.083	0.2023

rs17024393	1	110154688	<i>GNAT2</i>	T	C	0.04	0.03	0.98	0.066	0.009	7.0E-14	0.456	0.253	0.0714	-0.146	0.093	0.1181	-0.171	0.101	0.0914	0.048	0.229	0.8323
rs543874	1	177889480	<i>SEC16B</i>	A	G	0.19	0.18	1.00	0.048	0.004	2.6E-35	0.286	0.104	0.006	0.046	0.042	0.2717	0.050	0.046	0.2810	0.028	0.089	0.7563
rs2820292	1	201784287	<i>NAVI</i>	A	C	0.56	0.54	0.94	0.020	0.003	1.8E-10	0.281	0.086	0.001	-0.017	0.033	0.6073	-0.015	0.036	0.6704	-0.027	0.075	0.7189
rs13021737	2	632348	<i>TMEM18</i>	A	G	0.83	0.81	0.99	0.060	0.004	1.1E-50	0.479	0.106	<0.0001	0.020	0.042	0.6332	0.026	0.046	0.5688	-0.027	0.091	0.7695
rs10182181	2	25150296	<i>ADCY3</i>	A	G	0.46	0.45	0.64	0.031	0.003	8.8E-24	0.191	0.104	0.067	0.013	0.041	0.7565	0.031	0.046	0.4987	-0.105	0.094	0.2669
rs11126666	2	26928811	<i>KCNK3</i>	G	A	0.28	0.25	0.54	0.021	0.003	1.3E-09	-0.033	0.130	0.8018	-0.001	0.050	0.9775	-0.004	0.056	0.9366	0.014	0.111	0.9001
rs1016287	2	59305625	<i>LINC011</i>	T	C	0.71	0.70	0.93	-0.023	0.003	1.9E-11	-0.105	0.092	0.2527	0.028	0.037	0.4436	0.033	0.040	0.4134	-0.010	0.081	0.9066
rs11688816	2	63053048	<i>EHBP1</i>	G	A	0.48	0.50	1.00	-0.017	0.003	2.3E-08	0.040	0.082	0.6282	0.009	0.033	0.7753	0.011	0.036	0.7513	-0.008	0.072	0.9121
rs2121279	2	143043285	<i>LRPIB</i>	C	T	0.15	0.12	0.83	0.024	0.004	9.0E-08	-0.102	0.137	0.4584	-0.018	0.053	0.7381	-0.029	0.059	0.6225	0.051	0.115	0.6543
rs1460676	2	164567689	<i>FIGN</i>	T	C	0.17	0.17	1.00	0.020	0.004	1.2E-07	0.018	0.112	0.8689	0.080	0.041	0.0502	0.104	0.045	0.0201	-0.092	0.097	0.3433
rs1528435	2	181550962	<i>UBE2E3</i>	C	T	0.63	0.62	0.88	0.018	0.003	8.2E-08	0.111	0.089	0.2112	0.030	0.036	0.4070	0.021	0.040	0.5925	0.083	0.074	0.2658
rs17203016	2	208255518	<i>CREB1</i>	A	G	0.20	0.18	0.90	0.021	0.004	1.2E-08	-0.236	0.112	0.0352	0.064	0.044	0.1464	0.070	0.048	0.1450	0.014	0.096	0.8874
rs7599312	2	213413231	<i>ERBB4</i>	G	A	0.28	0.27	0.88	-0.022	0.003	4.2E-10	0.092	0.098	0.3483	0.052	0.039	0.1736	0.048	0.042	0.2630	0.078	0.085	0.3558
rs492400	2	219349752	<i>USP37</i>	C	T	0.58	0.59	0.86	-0.016	0.003	6.1E-07	-0.216	0.090	0.0168	-0.004	0.036	0.9139	0.000	0.039	0.9940	-0.035	0.082	0.6667
rs2176040	2	227092802	<i>LOC6467</i>	A	G	0.63	0.64	1.00	-0.014	0.003	2.5E-06	0.003	0.086	0.9706	0.024	0.034	0.4749	0.025	0.037	0.5054	0.023	0.076	0.7617
rs6804842	3	25106437	<i>RARB</i>	A	G	0.57	0.58	0.58	0.019	0.003	1.6E-09	-0.050	0.109	0.6453	0.087	0.044	0.0461	0.099	0.048	0.0398	0.004	0.090	0.9627
rs2365389	3	61236462	<i>FHIT</i>	C	T	0.42	0.41	0.96	-0.020	0.003	2.6E-10	-0.101	0.085	0.2358	0.022	0.033	0.5041	0.015	0.037	0.6915	0.076	0.072	0.2916
rs3849570	3	81792112	<i>GBE1</i>	C	A	0.36	0.30	0.84	0.019	0.003	1.7E-08	0.117	0.097	0.2271	-0.039	0.038	0.3032	-0.060	0.042	0.1533	0.109	0.086	0.2055
rs13078960	3	85807590	<i>CADM2</i>	T	G	0.20	0.20	0.91	0.030	0.004	3.6E-14	0.071	0.107	0.5102	-0.079	0.042	0.0585	-0.069	0.046	0.1302	-0.136	0.096	0.1552
rs16851483	3	141275436	<i>RASA2</i>	G	T	0.07	0.07	1.00	0.048	0.008	1.9E-10	-0.141	0.163	0.3871	-0.203	0.068	0.0030	-0.204	0.075	0.0068	-0.188	0.148	0.2033
rs1516725	3	185824004	<i>ETV5</i>	T	C	0.87	0.86	0.88	0.045	0.005	3.2E-22	-0.071	0.127	0.5764	0.043	0.050	0.3829	0.053	0.055	0.3376	-0.020	0.108	0.8511
rs10938397	4	45182527	<i>GNPDA2</i>	A	G	0.43	0.43	1.00	0.040	0.003	7.8E-38	0.302	0.083	0.0003	0.004	0.033	0.8913	0.016	0.036	0.6491	-0.076	0.073	0.2982
rs17001654	4	77129568	<i>SCARB2</i>	C	G	0.15	0.17	0.75	0.031	0.005	1.8E-09	0.044	0.128	0.7285	0.019	0.048	0.6883	0.021	0.053	0.6881	0.006	0.106	0.9567
rs13107325	4	103188709	<i>SLC39A8</i>	C	T	0.07	0.09	0.76	0.048	0.007	2.6E-12	0.163	0.171	0.3384	0.035	0.067	0.6061	0.031	0.074	0.6751	0.056	0.150	0.7092
rs11727676	4	145659064	<i>HHIP</i>	T	C	0.09	0.09	0.68	-0.036	0.006	6.2E-08	-0.055	0.172	0.751	0.060	0.064	0.3526	0.059	0.070	0.4042	0.066	0.159	0.6756
rs2112347	5	75015242	<i>POC5</i>	T	G	0.37	0.37	0.99	-0.026	0.003	1.7E-17	-0.239	0.085	0.0052	-0.008	0.033	0.8196	0.013	0.037	0.7139	-0.158	0.076	0.0369
rs7715256	5	153537893	<i>GALNT10</i>	G	T	0.58	0.56	0.99	-0.016	0.003	7.0E-07	-0.167	0.083	0.0449	-0.049	0.033	0.1373	-0.049	0.036	0.1770	-0.051	0.071	0.4782

rs205262	6	34563164	<i>C6orf10</i>	A	G	0.27	0.28	1.00	0.022	0.004	1.8E-10	0.185	0.091	0.0419	-0.015	0.036	0.6817	-0.017	0.039	0.6608	0.003	0.078	0.9739
rs2033529	6	40348653	<i>TDRG1</i>	A	G	0.29	0.30	0.63	0.019	0.003	1.4E-08	-0.015	0.113	0.8912	-0.040	0.045	0.3724	-0.034	0.049	0.4949	-0.077	0.098	0.4344
rs2207139	6	50845490	<i>TFAP2B</i>	A	G	0.18	0.16	0.99	0.045	0.004	4.1E-29	0.170	0.110	0.1224	0.120	0.043	0.0050	0.146	0.047	0.0019	-0.057	0.094	0.5439
rs9400239	6	108977663	<i>FOXO3</i>	T	C	0.69	0.70	0.97	0.019	0.003	1.6E-08	0.105	0.091	0.2458	0.016	0.035	0.6492	0.024	0.039	0.5304	-0.036	0.075	0.6292
rs9374842	6	120185665	<i>LOC2857</i>	C	T	0.75	0.77	0.89	0.019	0.004	9.7E-08	0.055	0.105	0.6025	0.021	0.040	0.5949	0.018	0.044	0.6728	0.040	0.089	0.6523
rs13191362	6	163033350	<i>PARK2</i>	A	G	0.12	0.12	0.91	-0.028	0.005	6.3E-09	-0.026	0.131	0.8453	0.022	0.052	0.6650	0.054	0.057	0.3383	-0.192	0.117	0.1001
rs1167827	7	75163169	<i>HIP1</i>	A	G	0.55	0.58	1.00	0.020	0.003	5.0E-10	-0.077	0.084	0.3553	-0.010	0.032	0.7688	0.006	0.036	0.8681	-0.110	0.072	0.1268
rs9641123	7	93197732	<i>CALCR</i>	G	C	0.43	0.41	1.00	0.019	0.004	2.3E-07	0.266	0.084	0.0016	0.014	0.031	0.6584	0.003	0.035	0.9228	0.082	0.069	0.2323
rs6465468	7	95169514	<i>ASB4</i>	G	T	0.30	0.26	0.65	0.017	0.004	2.1E-06	0.031	0.117	0.7881	-0.074	0.046	0.1082	-0.076	0.051	0.1339	-0.056	0.099	0.5758
rs17405819	8	76806584	<i>HNF4G</i>	T	C	0.30	0.31	0.97	-0.022	0.003	1.3E-11	-0.203	0.089	0.023	-0.010	0.035	0.7822	-0.020	0.039	0.6132	0.054	0.074	0.4689
rs16907751	8	81375457	<i>ZBTB10</i>	C	T	0.08	0.12	0.79	-0.035	0.007	4.9E-07	-0.187	0.145	0.1977	-0.027	0.056	0.6278	-0.052	0.063	0.4017	0.131	0.118	0.2670
rs2033732	8	85079709	<i>RALYL</i>	T	C	0.75	0.75	0.72	0.019	0.004	4.6E-08	0.068	0.112	0.5437	-0.088	0.042	0.0369	-0.047	0.047	0.3162	-0.345	0.088	<.0001
rs4740619	9	15634326	<i>C9orf93</i>	T	C	0.46	0.46	0.97	-0.018	0.003	6.6E-09	-0.065	0.083	0.4323	0.034	0.034	0.3128	0.032	0.037	0.3994	0.051	0.072	0.4843
rs10968576	9	28414339	<i>LINGO2</i>	A	G	0.32	0.30	0.99	0.025	0.003	2.7E-14	0.098	0.089	0.2701	0.048	0.035	0.1739	0.056	0.039	0.1475	-0.004	0.080	0.9639
rs6477694	9	111932342	<i>EPB41L4</i>	C	T	0.63	0.67	0.97	-0.017	0.003	7.9E-08	-0.152	0.088	0.0851	-0.042	0.034	0.2077	-0.042	0.037	0.2565	-0.045	0.071	0.5226
rs1928295	9	120378483	<i>TLR4</i>	T	C	0.45	0.45	0.91	-0.019	0.003	1.8E-10	-0.139	0.087	0.1099	-0.047	0.034	0.1612	-0.041	0.037	0.2647	-0.084	0.077	0.2744
rs10733682	9	129460914	<i>LMX1B</i>	A	G	0.52	0.51	0.83	-0.017	0.003	3.0E-08	-0.070	0.091	0.4389	0.026	0.036	0.4748	0.029	0.039	0.4533	0.002	0.080	0.9764
rs7899106	10	87410904	<i>GRID1</i>	A	G	0.05	0.05	0.95	0.040	0.007	5.9E-08	0.084	0.191	0.6602	0.097	0.075	0.1964	0.126	0.081	0.1228	-0.132	0.176	0.4525
rs17094222	10	102395440	<i>HIFIAN</i>	T	C	0.21	0.22	0.74	0.025	0.004	8.5E-11	0.140	0.114	0.219	-0.019	0.044	0.6750	-0.020	0.049	0.6898	-0.012	0.097	0.8987
rs11191560	10	104869038	<i>NT5C2</i>	T	C	0.09	0.09	0.86	0.031	0.005	1.1E-09	0.029	0.160	0.8581	-0.113	0.061	0.0636	-0.123	0.067	0.0655	-0.051	0.136	0.7070
rs7903146	10	114758349	<i>TCF7L2</i>	C	T	0.29	0.30	1.00	-0.023	0.003	2.9E-11	-0.151	0.089	0.0896	-0.061	0.034	0.0746	-0.061	0.038	0.1055	-0.061	0.074	0.4080
rs4256980	11	8673939	<i>TRIM66</i>	C	G	0.65	0.64	1.00	0.021	0.003	5.6E-11	0.093	0.086	0.2804	-0.041	0.033	0.2173	-0.038	0.036	0.2930	-0.060	0.074	0.4214
rs11030104	11	27684517	<i>BDNF</i>	A	G	0.21	0.23	0.99	-0.041	0.004	3.0E-28	-0.369	0.098	0.0002	0.039	0.039	0.3073	0.068	0.042	0.1101	-0.147	0.085	0.0850
rs2176598	11	43864278	<i>HSD17B1</i>	T	C	0.75	0.74	0.98	-0.020	0.004	5.2E-08	0.049	0.095	0.6044	0.013	0.037	0.7153	0.028	0.041	0.4975	-0.081	0.075	0.2791
rs3817334	11	47650993	<i>MTCH2</i>	C	T	0.41	0.43	0.75	0.026	0.003	1.3E-17	0.170	0.097	0.0781	0.034	0.037	0.3547	0.036	0.040	0.3671	0.019	0.084	0.8219
rs12286929	11	115022404	<i>CADM1</i>	A	G	0.52	0.51	0.72	0.022	0.003	8.2E-12	-0.001	0.097	0.9879	-0.056	0.038	0.1402	-0.055	0.042	0.1948	-0.069	0.081	0.3895
rs7138803	12	50247468	<i>BCDIN3D</i>	G	A	0.38	0.39	0.95	0.032	0.003	2.4	0.079	0.086	0.3581	0.027	0.033	0.4177	0.036	0.037	0.3301	-0.028	0.073	0.7044

rs11057405	12	122781897	<i>CLIP1</i>	G	A	0.10	0.10	0.69	-0.031	0.006	2.0E-08	-0.283	0.160	0.0765	0.084	0.068	0.2179	0.086	0.075	0.2522	0.076	0.148	0.6088
rs12429545	13	54102206	<i>OLFM4</i>	G	A	0.13	0.14	0.52	0.033	0.005	1.1E-12	0.282	0.161	0.0794	0.084	0.064	0.1902	0.077	0.071	0.2794	0.134	0.144	0.3488
rs9540493	13	66205704	<i>MIR548X</i>	A	G	0.54	0.55	0.62	-0.017	0.003	1.4E-07	0.029	0.104	0.7778	-0.045	0.041	0.2635	-0.058	0.045	0.1951	0.046	0.085	0.5824
rs1441264	13	79580919	<i>MIR548A</i>	G	A	0.61	0.64	0.55	0.018	0.003	6.0E-08	0.114	0.115	0.3219	0.001	0.044	0.9736	0.006	0.049	0.9034	-0.030	0.093	0.7455
rs10132280	14	25928179	<i>STXBP6</i>	C	A	0.32	0.32	0.88	-0.023	0.003	1.1E-11	-0.262	0.095	0.0058	-0.051	0.037	0.1726	-0.066	0.041	0.1104	0.049	0.080	0.5403
rs12885454	14	29736838	<i>PRKD1</i>	C	A	0.36	0.34	0.99	-0.021	0.003	1.2E-10	-0.129	0.086	0.1356	-0.043	0.034	0.1983	-0.055	0.037	0.1390	0.039	0.076	0.6033
rs7141420	14	79899454	<i>NRXN3</i>	C	T	0.53	0.50	0.64	0.023	0.003	7.4E-14	-0.014	0.102	0.8951	0.006	0.040	0.8734	0.004	0.044	0.9332	0.029	0.095	0.7596
rs3736485	15	51748610	<i>DMXL2</i>	A	G	0.55	0.51	0.89	-0.018	0.003	1.9E-09	-0.092	0.087	0.2915	0.009	0.035	0.7923	0.004	0.039	0.9190	0.043	0.072	0.5526
rs16951275	15	68077168	<i>MAP2K5</i>	T	C	0.22	0.24	1.00	-0.031	0.004	6.8E-17	-0.265	0.096	0.0055	0.013	0.037	0.7218	0.032	0.040	0.4236	-0.130	0.084	0.1245
rs7164727	15	73093991	<i>LOC1002</i>	C	T	0.69	0.67	0.91	0.018	0.003	7.5E-08	-0.004	0.092	0.9632	0.033	0.035	0.3578	0.008	0.039	0.8384	0.198	0.079	0.0121
rs758747	16	3627358	<i>NLRC3</i>	C	T	0.27	0.29	1.00	0.023	0.004	1.5E-10	0.041	0.090	0.645	0.005	0.035	0.8935	0.002	0.038	0.9688	0.032	0.072	0.6600
rs12446632	16	19935389	<i>GPRC5B</i>	G	A	0.13	0.14	0.98	-0.040	0.005	1.9E-18	-0.254	0.116	0.0282	0.007	0.046	0.8845	0.005	0.050	0.9145	0.008	0.109	0.9402
rs2650492	16	28333411	<i>SBK1</i>	G	A	0.30	0.23	0.61	0.021	0.004	3.1E-09	0.235	0.126	0.0623	-0.053	0.050	0.2954	-0.055	0.055	0.3215	-0.028	0.109	0.7970
rs3888190	16	28889486	<i>ATP2A1</i>	C	A	0.40	0.36	1.00	0.031	0.003	2.2E-23	0.160	0.085	0.0604	-0.025	0.034	0.4748	-0.022	0.038	0.5647	-0.042	0.077	0.5839
rs4787491	16	30015337	<i>INO80E</i>	A	G	0.51	0.54	0.92	0.016	0.003	8.1E-06	0.212	0.086	0.0134	-0.022	0.035	0.5247	-0.025	0.039	0.5115	-0.004	0.075	0.9608
rs9925964	16	31129895	<i>KAT8</i>	A	G	0.38	0.39	0.99	-0.019	0.003	6.6E-10	-0.238	0.084	0.0047	0.034	0.033	0.2994	0.035	0.036	0.3384	0.029	0.070	0.6797
rs2080454	16	49062590	<i>CBLN1</i>	C	A	0.59	0.59	0.72	-0.017	0.003	7.5E-08	-0.011	0.097	0.9114	0.073	0.038	0.0568	0.074	0.042	0.0794	0.060	0.085	0.4771
rs1558902	16	53803574	<i>FTO</i>	T	A	0.42	0.42	1.00	0.082	0.003	9.0E-153	0.492	0.083	<.0001	0.059	0.031	0.0613	0.070	0.035	0.0422	-0.021	0.070	0.7598
rs9914578	17	2005136	<i>SMG6</i>	C	G	0.21	0.19	0.98	0.020	0.004	1.3E-08	0.136	0.104	0.1915	0.021	0.040	0.5872	0.008	0.044	0.8612	0.113	0.088	0.1993
rs1000940	17	5283252	<i>RABEP1</i>	A	G	0.32	0.31	0.99	0.019	0.003	2.5E-08	0.074	0.088	0.3998	-0.018	0.036	0.6137	-0.010	0.039	0.7912	-0.076	0.079	0.3371
rs12940622	17	78615571	<i>RPTOR</i>	G	A	0.43	0.42	0.73	-0.018	0.003	4.2E-09	-0.040	0.097	0.6779	-0.012	0.037	0.7392	-0.010	0.041	0.8039	-0.027	0.082	0.7445
rs1808579	18	21104888	<i>C18orf8</i>	C	T	0.47	0.44	0.91	-0.017	0.003	1.6E-08	-0.086	0.087	0.3217	0.026	0.034	0.4414	0.040	0.037	0.2856	-0.068	0.075	0.3650
rs7239883	18	40147671	<i>LOC2842</i>	G	A	0.61	0.60	0.85	-0.016	0.003	3.9E-07	-0.098	0.091	0.284	-0.005	0.036	0.9002	-0.029	0.040	0.4699	0.163	0.081	0.0450
rs7243357	18	56883319	<i>GRP</i>	T	G	0.19	0.18	0.94	-0.022	0.004	3.9E-08	-0.025	0.111	0.8186	0.016	0.043	0.7074	0.009	0.047	0.8532	0.067	0.091	0.4640
rs6567160	18	57829135	<i>MC4R</i>	T	C	0.24	0.23	0.99	0.056	0.004	3.4E-053	0.408	0.097	<.0001	-0.038	0.040	0.3315	-0.054	0.044	0.2159	0.057	0.082	0.4855
rs17724992	19	18454825	<i>PGPEP1</i>	A	G	0.25	0.26	1.00	-0.019	0.004	2.4E-08	-0.090	0.093	0.333	-0.057	0.036	0.1124	-0.060	0.040	0.1308	-0.042	0.078	0.5941
rs29941	19	34309532	<i>KCTD15</i>	A	G	0.67	0.69	1.00	0.018	0.003	2.0E-08	0.118	0.089	0.1833	-0.006	0.034	0.8581	-0.002	0.037	0.9613	-0.031	0.074	0.6744

rs2075650	19	45395619	<i>TOMM40</i>	A	G	0.15	0.14	0.75	-0.026	0.005	1.3E-08	-0.080	0.135	0.5536	0.057	0.053	0.2845	0.053	0.058	0.3618	0.071	0.118	0.5470
rs2287019	19	46202172	<i>QPCTL</i>	C	T	0.20	0.21	0.67	-0.036	0.004	4.6E-18	-0.093	0.122	0.4445	-0.004	0.050	0.9289	-0.029	0.055	0.6052	0.172	0.103	0.0935
rs3810291	19	47569003	<i>ZC3H4</i>	G	A	0.67	0.67	1.00	0.028	0.004	4.8E-15	0.075	0.087	0.3908	-0.013	0.034	0.7063	-0.018	0.038	0.6384	0.017	0.073	0.8201
rs6091540	20	51087862	<i>ZFP64</i>	C	T	0.28	0.28	0.64	-0.019	0.004	8.0E-08	0.051	0.114	0.6513	0.022	0.044	0.6153	0.024	0.048	0.6182	0.016	0.098	0.8716
rs2836754	21	40291740	<i>ETS2</i>	T	C	0.61	0.62	1.00	0.016	0.003	4.2E-07	0.051	0.084	0.542	-0.051	0.033	0.1204	-0.054	0.036	0.1355	-0.032	0.071	0.6574

CIMBA: The Consortium of Investigators of Modifiers of *BRCA1/2*; GWAS: genome-wide association studies

Notes:

[1] Imputation quality of 1 indicates genotyped SNPs.

[2] Effect estimate after BMI standardization.

[3] *P*-values were calculated using student's *t*-test. All *P*-values are two-sided.

[4] Association with ovarian cancer were estimated using weighted Cox models that adjusted for principal components, birth cohort, menopausal status, country of enrollment and mutation status.

[5] *P*-values were calculated using chi-squared test. All *P*-values are two-sided.

Supplementary Table 3. Associations of the height genetic score (height-GS) with height and ovarian cancer risk factors

	Number of participants	Summary effect	Standard error	P-value	% variation explained
Measured height, cm					
All participants	7,657	0.993	0.029	7.00E-241	13.4
<i>BRCA1</i> carriers	4,502	1.004	0.037	3.84E-149	14.0
<i>BRCA2</i> carriers	3,155	0.980	0.046	2.48E-94	12.6
Case participants	784	0.939	0.087	1.20E-25	13.1
Control participants	6,873	1.000	0.031	2.31E-218	13.5
Traditional risk factors					
BMI, kg/m ²	7,516	-0.010	0.024	0.66	
Weight, kg	7,569	0.798	0.064	2.73E-35	
Age at baseline, y	22,588	-0.128	0.032	4.52E-05	
Age at menarche, y	7,459	0.028	0.007	7.25E-05	
Parous, yes vs no	8,394	-0.010	0.011	0.35	
Age at first live birth, y	6,290	-0.013	0.025	0.58	
Menopausal status, pre vs post	8,445	0.012	0.009	0.18	
Age at menopause, y	4,336	-0.080	0.036	0.03	

Notes:

Regression coefficient is presented for continuous variables and natural log-scale odds ratio for binary variables, per unit increase of the weighted height genetic score. P-values were calculated from linear regression models for all variables except for parity and menopausal status (logistic regression models).

Supplementary Table 4. Associations of the body mass index genetic score (BMI-GS) with BMI and ovarian cancer risk factors

	Number of participants	Summary effect	Standard error	P-value	% variation explained
Observed BMI at date of questionnaire, kg/m ²					
All participants	7,516	0.966	0.069	2.79E-44	2.6
<i>BRCA1</i> carrier	4,401	0.912	0.088	8.05E-25	2.4
<i>BRCA2</i> carrier	3,115	1.048	0.110	2.10E-21	2.9
Case participants	772	0.671	0.215	1.88E-03	1.3
Control participants	6,744	1.000	0.073	1.11E-42	2.7
Premenopausal control participants	3,253	0.949	0.101	1.09E-20	2.6
Postmenopausal control participants	3,152	1.052	0.109	8.10E-22	2.9
Observed BMI in young adulthood, kg/m ²					
All participants	5,417	0.971	0.102	2.31E-21	1.7
<i>BRCA1</i> carrier	3,134	0.942	0.132	1.24E-12	1.6
<i>BRCA2</i> carrier	2,283	1.015	0.160	2.76E-10	1.7
Case participants	536	0.734	0.285	1.04E-02	1.2
Control participants	4,881	1.000	0.109	5.69E-20	1.7
Premenopausal control participants	2,180	1.171	0.168	4.18E-12	2.2
Postmenopausal control participants	2,365	0.872	0.153	1.27E-08	1.4
Traditional risk factors					
Height	7,657	0.371	0.092	5.40E-05	
Age at baseline, y	22,588	-0.165	0.085	0.79	
Age at menarche, y	7,459	-0.104	0.020	3.30E-07	
Parous, yes vs no	8,394	0.028	0.031	0.38	
Age at first live birth, y	6,290	-0.131	0.073	0.07	
Menopausal status, pre vs post	8,445	-0.027	0.026	0.28	
Age at menopause, y	4,336	-0.200	0.108	0.06	

Notes:

Regression coefficient is presented for continuous variables and natural log-scale odds ratio for binary variables, per unit increase of the weighted BMI genetic score. *P*-values were calculated from linear regression models for all variables except for parity and menopausal status (logistic regression models).