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Author/s:

Qian, F;Rookus, MA;Leslie, G;Risch, HA;Greene, MH;Aalfs, CM;Adank, MA;Adlard, J;Agnarsson, BA;Ahmed, M;Aittomäki, K;Andrulis, IL;Arnold, N;Arun, BK;Ausems, MGEM;Azzollini, J;Barrowdale, D;Barwell, J;Benitez, J;Białkowska, K;Bonadona, V;Borde, J;Borg, A;Bradbury, AR;Brunet, J;Buys, SS;Caldés, T;Caligo, MA;Campbell, I;Carter, J;Chiquette, J;Chung, WK;Claes, KBM;Collée, JM;Collonge-Rame, MA;Couch, FJ;Daly, MB;Delnatte, C;Diez, O;Domchek, SM;Dorfling, CM;Eason, J;Easton, DF;Eeles, R;Engel, C;Evans, DG;Faivre, L;Feliubadaló, L;Foretova, L;Friedman, E;Frost, D;Ganz, PA;Garber, J;Garcia-Barberan, V;Gehrig, A;Glendon, G;Godwin, AK;Gómez Garcia, EB;Hamann, U;Hauke, J;Hopper, JL;Hulick, PJ;Imyanitov, EN;Isaacs, C;Izatt, L;Jakubowska, A;Janavicius, R;John, EM;Karlan, BY;Kets, CM;Laitman, Y;Lázaro, C;Leroux, D;Lester, J;Lesueur, F;Loud, JT;Lubiński, J;Łukomska, A;McGuffog, L;Mebirouk, N;Meijers-Heijboer, HEJ;Meindl, A;Miller, A;Montagna, M;Mooij, TM;Mouret-Fourme, E;Nathanson, KL;Nehoray, B;Neuhausen, SL;Nevanlinna, H;Nielsen, FC;Offit, K;Olah, E;Ong, KR;Oosterwijk, JC;Ottini, L;Parsons, MT;Peterlongo, P;Pfeiler, G;Pradhan, N

Title:

Mendelian randomisation study of height and body mass index as modifiers of ovarian cancer risk in 22,588 BRCA1 and BRCA2 mutation carriers

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ARTICLE

Epidemiology

Mendelian randomisation study of height and body mass index as modifiers of ovarian cancer risk in 22,588 *BRCA1* and *BRCA2* mutation carriers

Frank Qian et al.

BACKGROUND: Height and body mass index (BMI) are associated with higher ovarian cancer risk in the general population, but whether such associations exist among *BRCA1/2* mutation carriers is unknown.

METHODS: We applied a Mendelian randomisation approach to examine height/BMI with ovarian cancer risk using the Consortium of Investigators for the Modifiers of *BRCA1/2* (CIMBA) data set, comprising 14,676 *BRCA1* and 7912 *BRCA2* mutation carriers, with 2923 ovarian cancer cases. We created a height genetic score (height-GS) using 586 height-associated variants and a BMI genetic score (BMI-GS) using 93 BMI-associated variants. Associations were assessed using weighted Cox models.

RESULTS: Observed height was not associated with ovarian cancer risk (hazard ratio [HR]: 1.07 per 10-cm increase in height, 95% confidence interval [CI]: 0.94–1.23). Height-GS showed similar results (HR = 1.02, 95% CI: 0.85–1.23). Higher BMI was significantly associated with increased risk in premenopausal women with HR = 1.25 (95% CI: 1.06–1.48) and HR = 1.59 (95% CI: 1.08–2.33) per 5-kg/m² increase in observed and genetically determined BMI, respectively. No association was found for postmenopausal women. Interaction between menopausal status and BMI was significant ($P_{\text{interaction}} < 0.05$).

CONCLUSION: Our observation of a positive association between BMI and ovarian cancer risk in premenopausal *BRCA1/2* mutation carriers is consistent with findings in the general population.

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BACKGROUND

Ovarian cancer is the fifth leading cause of cancer deaths in US women, due to its typically advanced stage at presentation.^{1,2} Furthermore, unlike breast or colorectal cancer, there is no proven screening method for ovarian cancer to identify early disease and initiate treatment to improve survival.^{3,4} Family history, oral contraceptive use, parity, body mass index (BMI), and genetic variants are potentially useful in estimating lifetime risk.¹ In particular, inherited *BRCA1* and *BRCA2* mutations are associated with increased lifetime risk of ovarian cancer and account for ~10–15% of overall disease incidence.^{5–7} However, among mutation carriers, age at diagnosis is variable. Penetrance of *BRCA1/2* mutations is likely modified by other genetic variants and lifestyle or reproductive factors.^{8,9} Investigation of these factors could aid in implementation of strategies to reduce ovarian cancer risk among mutation carriers.

Both height and BMI are quantitative traits with substantial genetic bases. In recent genome-wide association studies (GWAS), numerous genetic variants were found to be associated with these traits.^{10,11} In the general population, both height and BMI appear to be positively but inconsistently associated with risk of ovarian cancer.^{12–14} Previous studies also showed that the association between BMI and ovarian cancer was stronger in premenopausal women.^{12,15,16} Because of differences in age at onset and tumour histology/grade, risk factors for ovarian cancer might be different

for *BRCA1/2* mutation carriers than women in the general population.¹⁷ Only one case–control study, with 469 ovarian cancer cases, has examined anthropometric measurements in *BRCA1/2* mutation carriers and found that neither height nor BMI were related to ovarian cancer risk.¹⁸ Larger, adequately powered studies are needed to assess whether a relationship between either height or BMI and ovarian cancer risk exists for *BRCA1/2* mutation carriers, and whether the direction of association is concordant with that in the general population.

Mendelian randomisation (MR) methods use genetic markers associated with a trait as an instrumental variable (IV) to assess their potential relationship with a disease outcome.^{19–21} Compared to traditional epidemiologic approaches, MR can reduce biases such as reverse causation and residual confounding, which can interfere with causal interpretations. However, the MR approach requires that the genetic variants are associated with the exposure, the variants are not or only weakly associated with confounding factors in the causal pathway, and the variants only affect disease risk through the exposure (i.e. absence of pleiotropic effects).^{20,21} To the degree that these assumptions are met, the MR approach can strengthen the evidence for a causal relationship between exposure and disease.

Herein, using traditional epidemiologic and MR methods, we conducted analyses of height and BMI and their association with ovarian cancer risk in the Consortium of Investigators for the

Correspondence: Dezheng Huo (dhuo@health.bsd.uchicago.edu)

Extended author information available on the last page of the article

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Modifiers of *BRCA1/2* (CIMBA) with 22,588 participants. We examined heterogeneity of these associations with respect to the mutation carried (*BRCA1* vs *BRCA2*), menopausal status, tumour histology, and tumour grade.

METHODS

Characteristics of the CIMBA consortium and information on specific genotyping protocols are provided in Supplementary Methods and were described previously.^{22–24}

Selection of genetic variants

From the latest publications of the Genetic Investigation of Anthropometric Traits, we identified single-nucleotide polymorphisms (SNPs) associated with height or BMI at genome-wide significance level ($P < 5 \times 10^{-8}$).^{11,25} SNPs with low imputation quality (<0.5) were excluded, leaving 586 SNPs for height and 93 for BMI. Supplementary Tables 1 and 2 provide additional details on these SNPs.

Statistical analysis

Calculation of the height and BMI genetic scores (GS) was described in detail previously.²⁴ Briefly, we calculated the weighted sums of all of the height- and BMI-associated variants under additive models, which do not include interactions between variants. Namely, we used the formulas: Height – GS = $\sum_{i=1}^{586} \beta_{XGi} \text{SNP}_i$ and BMI – GS = $\sum_{i=1}^{93} \beta_{XGi} \text{SNP}_i$, where β_{XGi} is the literature-reported per-allele magnitude of association of the *i*th SNP for height and BMI, respectively. A scaling factor was calculated by regressing each GS against its respective trait among non-case carriers. The corresponding regression coefficients were β_0 (intercept = 165.455) and β_1 (slope = 5.217) for height and β_0 (22.607) and β_1 (5.523) for BMI. In the present study, BMI-GS was scaled to BMI at the date of questionnaire, rather than BMI at age 18 years, as previous GWAS were based on BMI measurements in middle-aged adults.

We subsequently modelled each scaled GS against ovarian cancer risk using weighted Cox models. Our primary outcome of interest was ovarian cancer diagnosis, with individuals censored for breast cancer diagnosis, risk-reducing bilateral salpingo-oophorectomy, death, or end of follow-up, whichever occurred first. Owing to the study design of CIMBA, weights in the model were applied for cases and non-cases based on previously observed incidence of ovarian cancer in *BRCA1/2* carriers.^{26,27} We applied a robust sandwich variance-estimation approach to the risk estimates to account for non-independence among multiple carriers per family. In addition, we performed subgroup analyses by *BRCA1/2* mutations and menopausal status. Menopausal status was defined as a time-varying covariate, coded as premenopausal from birth until age at natural menopause or bilateral salpingo-oophorectomy. For individuals with missing age at menopause, we imputed the age as 50 years. Imputing missing age at menopause as 46 years did not materially change the results. The mean and median ages at natural menopause in this population were 46 and 48 years, respectively. All analyses were adjusted for the first eight principal components (to account for ethnicity and population stratification), birth cohort, and country of enrolment. Additional analyses assessed the associations of height and BMI with ovarian cancer subgroups by histological type (serous vs. non-serous) and by tumour grade (well or moderately differentiated tumours vs. poorly or undifferentiated).

In addition, phenotype associations with each individual height and BMI variant were assessed and pooled using inverse variance-weighted meta-analysis. The individual associations were obtained by first extracting β_{XGi} for each SNP *i*, which represents the per-allele magnitude of association with height or BMI from previous GWAS. Next, we calculated β_{YGi} and $SE(\beta_{YGi})$ using multivariate-adjusted weighted Cox models for each SNP using the CIMBA

data, where ovarian cancer risk is predicted by genotype *G* (with $G = 0, 1, 2$ for the allele corresponding to greater height or BMI), principal components, birth cohort, *BRCA* mutation, and country of enrolment. The overall causal association (β_{YX}) is calculated using inverse-variance weighted estimate of each variant's effect:

$$\beta_{YX} = \frac{\sum_i \beta_{XGi} \beta_{YGi} SE(\beta_{YGi})^{-2}}{\sum_i \beta_{XGi}^2 SE(\beta_{YGi})^{-2}}$$
. Standard error was estimated as $SE_{YX} = \frac{1}{\sqrt{\sum_i \beta_{XGi}^2 SE(\beta_{YGi})^{-2}}}$ using the Burgess's method.^{19,28} Egger's test was used to assess for possible pleiotropic effects of the variants (i.e. whether variants influence the outcome through other pathways), to ensure that this assumption held.²⁹

Finally, in participants with available data on height and BMI, we conducted a formal IV analysis using the method of two-stage residual inclusion regression.³⁰ In stage one, observed height or BMI was regressed against the corresponding GS, principal components, birth cohort, country, and mutation status. In the second stage, we used a Cox model to fit ovarian cancer risk against height or BMI, birth cohort, country, mutation status, and residuals from stage one. Variance estimates were obtained through 10,000 boot-straps (see details in Supplementary Methods). In these individuals, we also analysed the association between observed measurements of height or BMI and ovarian cancer risk using weighted Cox models, adjusted for established ovarian cancer risk factors, including birth cohort, menopausal status, age at menarche (years), and parity (continuous). The BMI values used were obtained at the date of questionnaire, usually close to the date of genetic testing and recalled for BMI at age 18 years.

In models with menopausal status as time-varying variable, the test for heterogeneity by menopausal status was essentially a test of the proportional hazards assumption. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and Stata 14.0 (StataCorp, College Station, TX). A two-sided *P*-value < 0.05 was considered statistically significant unless stated otherwise.

RESULTS

Demographic and clinical characteristics

Characteristics for the 22,588 individuals in the CIMBA consortium, comprising 14,676 *BRCA1* and 7912 *BRCA2* mutation carriers, are shown in Table 1. We documented 2923 women with ovarian cancer (*BRCA1*: 2319; *BRCA2*: 604). Compared with non-cases, participants who developed ovarian cancer were more often parous women, were younger at first live birth, and were from earlier birth cohorts. At the date of questionnaire/interview, height measurement was available for 7657 participants and BMI measurement for 7516 participants. Most tumours for *BRCA1/2* mutation carriers were invasive, of serous, poorly, or undifferentiated grade, and stages 3 or 4 at diagnosis, characteristics which are consistent with prior reports.³¹

Observed and predicted height on risk of ovarian cancer

In the survival modelling of ovarian cancer risk, age was used as the underlying timescale and the numbers of individuals retained in the analysis were 20535, 14647, 7375, and 2832 at ages 30, 40, 50, and 60 years, respectively, suggesting that statistical power for the late age is limited. After adjustment for birth cohort, country of enrolment, mutation, menopausal status, and principal components, a nonsignificant association was found for observed height and ovarian cancer risk (hazard ratio (HR) = 1.07 per 10-cm increase, 95% confidence interval (CI): 0.94–1.23, $P = 0.31$) (Table 2). We found broadly consistent associations of height in both *BRCA1* and *BRCA2* mutation carriers by menopausal status and by tumour histological type and grade.

The height GS was significantly associated with height in all participants, in ovarian cancer cases, and in non-case participants (all $P < 10^{-24}$) (Supplementary Table 3). Overall, approximately

Table 1. Baseline characteristics of participants in the CIMBA consortium with genotype information

Variable	Ovarian cancer cases, <i>N</i> = 2923	Non-cases, <i>N</i> = 19,665	<i>P</i> value ^b
Mutation carrier status			<0.0001
<i>BRCA1</i>	2319 (79.3)	12,357 (62.8)	
<i>BRCA2</i>	604 (20.7)	7308 (37.2)	
Year of birth, median (IQR)	1948 (1940, 1955)	1960 (1951, 1969)	<0.0001
Age at diagnosis or censoring, years (mean ± SD)	52.5 ± 9.8	44.7 ± 12.4	<0.0001
Ethnicity, <i>n</i> (%)			0.07
Caucasian, not otherwise specified	2060 (89.7)	13,613 (88.4)	
Ashkenazi Jewish	237 (10.3)	1780 (11.6)	
Height in cm, <i>n</i>	784	6873	
Mean ± SD	163.2 ± 6.5	164.8 ± 6.9	<0.0001
Weight at baseline ^a in kg, <i>n</i>	780	6789	
Mean ± SD	69.0 ± 14.6	68.5 ± 14.1	0.32
Body mass index at baseline ^a in kg/m ² , <i>n</i>	772	6744	
Mean ± SD	25.9 ± 5.3	25.2 ± 5.1	0.0002
Weight in early adulthood in kg, <i>n</i>	536	4,912	
Mean ± SD	56.5 ± 8.3	57.9 ± 9.5	0.0007
Body mass index in early adulthood in kg/m ² , <i>n</i>	536	4881	
Mean ± SD	21.2 ± 3.0	21.3 ± 3.3	0.43
Age at menarche in years, <i>n</i>	771	6688	
Mean ± SD	13.0 ± 1.5	13.0 ± 1.5	0.90
Parous, <i>n</i> (%)			<0.0001
Yes	805 (88.3)	5790 (77.4)	
No	107 (11.7)	1692 (22.6)	
Age at first live birth in years, <i>n</i>	735	5555	
Mean ± SD	24.4 ± 4.5	25.4 ± 4.9	<0.0001
Menopausal status, <i>n</i> (%)			<0.0001
Premenopausal	112 (11.5)	3816 (51.1)	
Postmenopausal	863 (88.5)	3654 (48.9)	
Age at menopause, years (mean ± SD)	46.8 ± 5.7	44.7 ± 6.1	<0.0001
Tumour behaviour, <i>n</i> (%)			
Invasive	1228 (99.2)		
Borderline	10 (0.8)		
Tumour histotype, <i>n</i> (%)			
Serous	892 (67.9)		
Mucinous	20 (1.5)		
Endometrioid	141 (10.7)		
Clear cell	17 (1.3)		
Other	243 (18.5)		
Tumour grade, <i>n</i> (%)			
Well differentiated	43 (4.6)		
Moderately differentiated	196 (21.0)		

Table 1 continued

Variable	Ovarian cancer cases, <i>N</i> = 2923	Non-cases, <i>N</i> = 19,665	<i>P</i> value ^b
Poorly/undifferentiated	696 (74.4)		
Tumour stage, <i>n</i> (%)			
Borderline	2 (0.3)		
Stage 1	121 (16.4)		
Stage 2	93 (12.6)		
Stage 3	412 (55.7)		
Stage 4	112 (15.1)		

CIMBA Consortium of Investigators for the Modifiers of *BRCA1/2*, *IQR* interquartile range, *SD* standard deviation
^aReported at the date of questionnaire
^b*P* values for comparing cases and non-cases were calculated from logistic regression models with robust sandwich variance estimator

13.4% of the variation in height was explained by the height GS. Besides height, we found weaker associations between the height GS and body weight and age at menarche.

In MR analysis, height GS had a nonsignificant positive association with ovarian cancer risk, HR = 1.02 per 10-cm increase in genetically predicted height, 95% CI: 0.85–1.23, *P* = 0.82 (Table 3). We found similar associations by subgroups of mutation, menopausal status, and tumour grade.

Combining the effects of all 586 height-associated variants using inverse-variance weighted meta-analysis, we obtained similar findings (HR = 1.02, 95% CI: 0.83–1.26, *P* = 0.83) (λ). Among the SNPs that were combined, there was a low degree of heterogeneity (*I*² = 0%). Examining small-study effects using Egger's test did not suggest likely pleiotropic effects. In the two-stage residual inclusion analysis, the estimated relative risk was larger though with wide CIs, which overlapped with those derived using other methods (HR = 1.20, 95% CI: 0.86–1.69, *P* = 0.29).

Observed and predicted BMI on risk of ovarian cancer

After multivariable adjustment, we found a nonsignificant positive association between BMI at the date of questionnaire completion and ovarian cancer risk, HR = 1.04 per 5-kg/m² increase in BMI, 95% CI: 0.95–1.14, *P* = 0.42 (Table 4). In a pre-specified analysis, the association between BMI and ovarian cancer risk was stronger in premenopausal women (HR = 1.25, 95% CI: 1.06–1.48; *P* = 0.009), whereas no association was found in postmenopausal women (HR = 0.98, 95% CI: 0.88–1.10), with significant interaction (*P* = 0.02). We found that BMI was a significant predictor of non-serous ovarian cancer risk (HR = 1.25, 95% CI: 1.06–1.49) but not for serous ovarian cancer (HR = 0.98, 95% CI: 0.84–1.15).

Similar to BMI at the date of questionnaire completion, we detected a significant interaction of BMI in young adulthood and menopausal status (*P* = 0.01), with a stronger association for premenopausal women (HR = 1.34, 95% CI: 0.97–1.84) compared with postmenopausal women (HR = 0.82, 95% CI: 0.65–1.04).

BMI-GS was strongly associated with BMI at both the date of questionnaire completion and young adulthood (Supplementary Table 4). Overall, the BMI-GS explained 2.6% of the variation in BMI at the date of questionnaire completion and 1.7% of the variation in young adulthood BMI. We found associations between the BMI-GS and height and age at menarche, though the strength of the association was weaker than the association with BMI.

In the entire consortium, the BMI-GS had a nonsignificant positive association with ovarian cancer risk with a HR = 1.10 per 5-kg/m² of genetically predicted BMI, 95% CI: 0.86–1.42, *P* = 0.44 (Table 5). We found heterogeneity by menopausal status (*P* = 0.006). BMI-GS was positively associated with ovarian cancer risk in premenopausal

Table 2. Association of height and ovarian cancer risk using observed height among 7657 participants

	N/events	HR (95% CI)	P value
Per 10 cm increase in observed height			
All participants (confounding adjustment sequentially)			
Adjusted for principal components	7657/784	1.12 (0.97–1.29)	0.12
Additionally adjusted for country	7657/784	1.15 (1.00–1.32)	0.06
Additionally adjusted for birth cohort	7657/784	1.05 (0.91–1.21)	0.53
Additionally adjusted for mutation status	7657/784	1.06 (0.92–1.22)	0.42
Additionally adjusted for menopausal status	7657/784	1.07 (0.94–1.23)	0.31
Additionally adjusted for parity and age at menarche	7090/724	1.09 (0.94–1.26)	0.24
By mutation status ^a			
<i>BRCA1</i> carrier	4502/552	1.07 (0.91–1.24)	0.42
<i>BRCA2</i> carrier	3155/232	1.11 (0.85–1.45)	0.44
<i>P</i> _{interaction}			0.64
By menopausal status ^b			
Premenopausal	7657/105	1.02 (0.72–1.42)	0.93
Postmenopausal	4328/679	1.09 (0.94–1.26)	0.27
<i>P</i> _{interaction}			0.71
By tumour subtype ^c			
Serous	7360/319	1.07 (0.87–1.31)	0.52
Non-serous ^d	7360/168	1.30 (1.01–1.68)	0.045
<i>P</i> _{het}			0.24
By tumour grade ^e			
Well or moderately differentiated	7252/111	1.12 (0.83–1.52)	0.46
Poorly/undifferentiated	7252/268	1.15 (0.93–1.43)	0.19
<i>P</i> _{het}			0.89

HR hazard ratio, CI confidence interval

^aAdjusted for principal components, birth cohort, country of enrolment, and menopausal status in weighted Cox model^bAdjusted for principal components, mutation status, birth cohort, and country of enrolment^cAdjusted for principal components, birth cohort, country of enrolment, mutation status, and menopausal status^dIncludes endometrioid, mucinous, clear cell, and other histologic types

Bolded line refers to the model corresponding to our main results

women (HR = 1.59, 95% CI: 1.08–2.33) but not in postmenopausal women (HR = 0.80, 95% CI: 0.58–1.11). BMI-GS also tended to be more associated with non-serous (HR = 1.60, 95% CI: 0.83–3.08) than serous tumours (HR = 0.92, 95% CI: 0.59–1.43).

We found similar results when we statistically combined the associations of the 93 BMI-associated variants, with an overall HR = 1.12, 95% CI: 0.86–1.46. Heterogeneity was low ($I^2 = 15.9\%$), indicating a low likelihood of pleiotropic associations. Using the two-stage residual inclusion approach, we found a generally similar association (HR = 1.37, 95% CI: 0.84–2.24, $P = 0.21$).

Individual SNPs and ovarian cancer risk

We found 22 height-associated and 4 BMI-associated SNPs that were nominally associated with ovarian cancer risk ($P < 0.05$; Table 6). None of these SNPs were significantly associated with ovarian cancer risk after correcting for multiple testing. We cross-checked these identified SNPs with the most up-to-date list of ovarian cancer susceptibility SNPs and did not find any overlaps.³²

DISCUSSION

Using data from a large international consortium of *BRCA1/2* mutation carriers, we found no statistically significant association between height and ovarian cancer risk. Interestingly, we observed interactions between BMI (both observed and genetically predicted) and menopausal status on ovarian cancer risk, with increasing BMI associated with increased risk in premenopausal but not in postmenopausal women.

Our finding of a positive association between BMI and overall ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers is corroborated by several prior studies in the general population.^{12,14,15,33} One MR analysis using 77 BMI-associated SNPs, conducted in the general population, found that each 1-standard deviation (SD) increment in genetically-predicted adult BMI corresponded to an odds ratio (OR) of 1.35 (95% CI: 1.05–1.72).³⁴ We found that 5-kg/m² (about 1 SD) increment in genetically predicted BMI was associated with an HR = 1.10 (95% CI: 0.86–1.42) in mutation carriers. However, the association of BMI with ovarian cancer risk is likely to vary by menopausal status. In the general population, significant differential association of BMI with ovarian cancer risk by menopausal status has been found in some studies^{15,16,35,36} but not in others.^{12,37} A pooled analysis of 47 epidemiologic studies with 25,157 ovarian cancer cases showed that the relative risk per 5-kg/m² increase in BMI was 1.12 (95% CI: 1.07–1.17) in premenopausal women and 1.08 (95% CI: 1.04–1.12) in postmenopausal women.¹² The largest single cohort study, with 3686 ovarian cancer cases, found that the HR per 5-kg/m² increase in BMI was 1.21 (99% CI: 1.09–1.33) in premenopausal and 1.07 (99% CI: 1.02–1.12) in postmenopausal women.¹⁵ An MR analysis conducted in the general population also observed stronger associations for non-high-grade serous carcinomas in premenopausal women (OR = 1.62, 95% CI: 0.88–3.01) compared with postmenopausal hormone replacement therapy (HRT) users (OR = 1.26, 95% CI: 0.57–2.82) and postmenopausal HRT non-users (OR = 1.17, 95% CI: 0.61–2.24), though no formal statistical tests examining heterogeneity were performed.¹⁴ Similarly, we found in *BRCA1/2* mutation carriers that 5-kg/m² increment in genetically predicted BMI was associated with an HR = 1.59 (95% CI: 1.08–2.33) for premenopausal ovarian cancer and an HR = 0.80 (95% CI: 0.58–1.11) for postmenopausal ovarian cancer. Studies that have not demonstrated significant variation by menopausal status tended to show that the positive association between BMI and ovarian cancer risk was primarily among those who had never used HRT.¹² Taken together, our results and previous literature are suggestive that higher BMI may increase ovarian cancer risk in premenopausal women but not in postmenopausal women.

In addition, several studies that had sufficient numbers of cases to evaluate the relationship between BMI and ovarian cancer risk by histologic subtype have shown significant heterogeneity. Observational studies in the Ovarian Cancer Cohort Consortium found stronger associations between BMI and endometrioid (OR = 1.17 per 5-kg/m², 95% CI: 1.11–1.23) or mucinous ovarian cancer (OR = 1.19, 95% CI: 1.06–1.32) but no association with serous ovarian cancer (OR = 0.98, 95% CI: 0.94–1.02).¹⁶ A more recent MR analysis in the same consortium using a genetic score comprised of 87 SNPs showed that a genetically predicted BMI had a stronger association with endometrioid (OR = 1.17, 95% CI: 0.87–1.59) or mucinous ovarian cancer (OR = 1.18, 95% CI: 0.84–1.67) than high-grade

Table 3. Association of height and ovarian cancer risk among 22,588 participants in CIMBA per 10-cm increase in genetically predicted height

	N/events	HR (95% CI)	P value	Heterogeneity (I^2)
Height GS^a				
All participants (confounding adjustment sequentially)				
Adjusted for principal components	22,588/2923	0.99 (0.82–1.19)	0.89	
Additionally adjusted for country	22,588/2923	0.97 (0.81–1.17)	0.77	
Additionally adjusted for birth cohort	22,588/2923	0.98 (0.82–1.18)	0.83	
Additionally adjusted for mutation status	22,588/2923	1.02 (0.85–1.22)	0.13	
Additionally adjusted for menopausal status	22,588/2923	1.02 (0.85–1.23)	0.82	
By mutation status^b				
<i>BRCA1</i> carrier	14,676/2319	1.02 (0.83–1.25)	0.87	
<i>BRCA2</i> carrier	7912/604	1.04 (0.68–1.57)	0.87	
$P_{\text{interaction}}$			0.99	
By menopausal status^c				
Premenopausal	22,588/967	0.96 (0.73–1.26)	0.77	
Postmenopausal	9219/1955	1.08 (0.85–1.38)	0.52	
$P_{\text{interaction}}$			0.50	
By tumour subtype^d				
Serous	20,978/892	1.36 (0.97–1.90)	0.08	
Non-serous	20,978/421	0.95 (0.58–1.56)	0.84	
P_{het}			0.25	
By tumour grade^d				
Well or moderately differentiated	20,600/239	1.63 (0.86–3.09)	0.14	
Poorly/undifferentiated	20,600/696	1.20 (0.82–1.74)	0.35	
P_{het}			0.42	
Meta-analysis method^e				
All participants	22,588/2923	1.02 (0.83–1.26)	0.83	0.0%
<i>BRCA1</i> carrier	14,676/2319	1.02 (0.81–1.28)	0.89	0.0%
<i>BRCA2</i> carrier	7912/604	1.05 (0.67–1.66)	0.82	7.0%
$P_{\text{interaction}}$			0.89	
Two-stage residual inclusion method^f				
All participants	7657/784	1.20 (0.86–1.69)	0.29	
<i>BRCA1</i> carrier	4502/552	1.40 (0.94–2.10)	0.10	
<i>BRCA2</i> carrier	3155/232	0.93 (0.49–1.74)	0.81	

HR hazard ratio, CI confidence interval, CIMBA Consortium of Investigators for the Modifiers of *BRCA1/2*, GS genetic score

^aHeight genetic score combining 586 height-associated single-nucleotide polymorphisms (SNPs)

^bAdjusted for principal components, birth cohort, country of enrolment, and menopausal status in weighted Cox model

^cAdjusted for principal components, mutation status, birth cohort, and country of enrolment

^dAdjusted for principal components, mutation status, menopausal status, birth cohort, and country of enrolment

^eHRs were calculated using inverse-variance meta-analysis and re-scaled to the corresponding units by calculating the height measurements per z-score among controls. Effect estimates for ovarian cancer for each SNP were calculated from weighted Cox model adjusting for principal components, birth cohort, country of enrolment, menopausal status, and mutation status

^fAnalysis was performed among 7657 participants with measured height

Bolded line refers to the model corresponding to our main results

serous cancer (OR = 1.06, 95% CI: 0.89–1.27), though the 95% CIs for these estimates were largely overlapping.¹⁴ Consistent with findings in the general population, our study in *BRCA1/2* mutation carriers showed that BMI was positively associated with non-serous ovarian cancer (HR = 1.25 per 5-kg/m², 95% CI: 1.06–1.49 in observed BMI and HR = 1.60, 95% CI: 0.83–3.08, per 5-kg/m² in genetically predicted BMI), of which endometrioid is a major subtype. Of note, obesity is an established risk factor for endometrial cancer.³⁸ However, subsequent studies with greater number of cases of different ovarian cancer subtypes are needed to assess whether the effect of obesity truly differs by tumour subtype.

Our finding of a nonsignificant positive association between height and ovarian cancer risk is also consistent with prior epidemiological studies in the general population.^{12,37,39} In the

general population, 5-cm increment in height was associated with a 7% increase (95% CI: 5–9%) in ovarian cancer risk,¹² and 5-cm increment in genetically predicted height was associated with a 6% (95% CI: 1–11%) increase in ovarian cancer risk.³⁹ The associations for observed height did not differ significantly between ovarian histological types,^{2,12} while genetically predicted height had a stronger association with clear cell (OR = 1.20, 95% CI: 1.04–1.38) or low-grade/borderline serous ovarian cancers (OR = 1.15, 95% CI: 1.01–1.30) compared to high-grade serous (OR = 1.05, 95% CI: 0.99–1.11).³⁹ We did not find statistically significant heterogeneity by histology in our study of mutation carriers, though point estimates varied across histology.

Several biological mechanisms potentially explain the associations observed in our study. Overweight/obese women are more

Table 4. Association of body mass index (BMI) and ovarian cancer risk using observed BMI

	N/events	HR (95% CI)	P value
Per 5 kg/m ² increase in BMI at date of questionnaire			
All participants (confounding adjustment sequentially)			
Adjusted for principal components	7516/772	1.00 (0.90–1.10)	0.96
Additionally adjusted for country	7516/772	0.99 (0.90–1.09)	0.84
Additionally adjusted for birth cohort	7516/772	1.02 (0.93–1.12)	0.72
Additionally adjusted for mutation status	7516/772	1.06 (0.96–1.16)	0.26
Additionally adjusted for menopausal status	7516/772	1.04 (0.95–1.14)	0.42
Additionally adjusted for parity and age at menarche	6964/715	1.04 (0.94–1.14)	0.48
By mutation status ^a			
<i>BRCA1</i> carrier	4401/543	1.06 (0.95–1.17)	0.31
<i>BRCA2</i> carrier	3115/229	0.96 (0.81–1.15)	0.67
<i>P</i> _{interaction}			0.35
By menopausal status ^b			
Premenopausal	7516/102	1.25 (1.06–1.48)	0.009
Postmenopausal	4257/670	0.98 (0.88–1.10)	0.78
<i>P</i>_{interaction}			0.02
By tumour subtype ^c			
Serous	7223/312	0.98 (0.84–1.15)	0.83
Non-serous^d	7223/167	1.25 (1.06–1.49)	0.01
<i>P</i> _{het}			0.04
By tumour grade ^c			
Well or moderately differentiated	7252/109	1.05 (0.84–1.32)	0.65
Poorly/undifferentiated	7252/268	0.95 (0.82–1.11)	0.54
<i>P</i> _{het}			0.47
Per 5 kg/m ² increase in BMI in young adulthood			
All participants (confounding adjustment sequentially)			
Unadjusted	5417/536	0.86 (0.69–1.07)	0.17
Adjusted for country	5417/536	0.86 (0.69–1.08)	0.19
Additionally adjusted for birth cohort	5417/536	0.87 (0.70–1.08)	0.21
Additionally adjusted for mutation status	5417/536	0.91 (0.73–1.13)	0.39
Additionally adjusted for menopausal status	5417/536	0.93 (0.76–1.16)	0.53
Additionally adjusted for parity and age at menarche	5210/516	0.92 (0.74–1.14)	0.42
By mutation status ^a			
<i>BRCA1</i> carrier	3134/380	0.92 (0.71–1.18)	0.50
<i>BRCA2</i> carrier	2283/156	1.00 (0.74–1.36)	0.99
<i>P</i> _{interaction}			0.73
By menopausal status ^b			
Premenopausal	5417/67	1.34 (0.97–1.84)	0.07
Postmenopausal	3094/469	0.82 (0.65–1.04)	0.11
<i>P</i>_{interaction}			0.01

HR hazard ratio, CI confidence interval

^aAdjusted for principal components, birth cohort, country of enrolment, and menopausal status in weighted Cox model^bAdjusted for principal components, mutation status, birth cohort, and country of enrolment^cAdjusted for principal components, birth cohort, country of enrolment, mutation status, and menopausal status^dIncludes endometrioid, mucinous, clear cell, and other histological types

Bolded lines refer to the model corresponding to our main results

likely to have anovulatory cycles and fertility issues, particularly when caused by polycystic ovarian syndrome (PCOS), and thus have an increased risk of ovarian cancer.^{40,41} The association of PCOS with ovarian cancer risk was mainly confined to premenopausal women.⁴² Some studies have suggested that *BRCA1/2* mutation carriers may have subclinical ovarian insufficiency, which could mediate the relationship between obesity-related infertility and increased ovarian cancer risk.⁴³ Obesity itself also creates a

proinflammatory state and adipocyte-secreted inflammatory markers have been implicated in ovarian cancer development.⁴⁴ Circulating levels of oestradiol, androgen, and progesterone have also been implicated in the risk of ovarian cancer.^{45,46} One study in *BRCA1/2* mutation carriers showed higher oestradiol levels during each menstrual cycle compared with non-carriers, supporting the potential role of sex hormones in ovarian tumorigenesis in this population.⁴⁷ Obese premenopausal women tend to have lower

Table 5. Association of body mass index genetic score (BMI-GS) and ovarian cancer risk among 22,588 participants in CIMBA, per 5 kg/m² increase in genetically predicted BMI

Breast cancer group	N/events	HR (95% CI)	P value	Heterogeneity (I ²)
BMI-GS^a				
All participants (confounding adjustment sequentially)				
Adjusted for principal components	22,588/2923	1.12 (0.87–1.45)	0.37	
Additionally adjusted for country	22,588/2923	1.11 (0.86–1.44)	0.41	
Additionally adjusted for birth cohort	22,588/2923	1.12 (0.87–1.45)	0.36	
Additionally adjusted for mutation status	22,588/2923	1.11 (0.86–1.42)	0.43	
Additionally adjusted for menopausal status	22,588/2923	1.10 (0.86–1.42)	0.44	
By mutation status ^b				
<i>BRCA1</i> carrier	14,676/2319	1.16 (0.88–1.53)	0.31	
<i>BRCA2</i> carrier	7912/604	0.81 (0.46–1.43)	0.46	
<i>P</i> _{interaction}			0.27	
By menopausal status ^c				
Premenopausal	22,588/967	1.59 (1.08–2.33)	0.02	
Postmenopausal	9219/1955	0.80 (0.58–1.11)	0.18	
<i>P</i> _{interaction}			0.006	
By tumour subtype ^d				
Serous	20,978/892	0.92 (0.59–1.43)	0.71	
Non-serous	20,978/421	1.60 (0.83–3.08)	0.16	
<i>P</i> _{het}			0.17	
By tumour grade ^d				
Well or moderately differentiated	20,600/239	1.20 (0.52–2.75)	0.67	
Poorly/undifferentiated	20,600/696	0.74 (0.45–1.21)	0.23	
<i>P</i> _{het}			0.33	
Meta-analysis method ^e				
All participants	22,588/2923	1.12 (0.86–1.46)	0.39	15.9%
<i>BRCA1</i> carrier	14,676/2319	1.18 (0.88–1.57)	0.26	17.2%
<i>BRCA2</i> carrier	7912/604	0.80 (0.45–1.43)	0.45	0.0%
<i>P</i> _{interaction}			0.24	
Two-stage residual inclusion method ^f				
All participants	7516/772	1.37 (0.84–2.24)	0.21	
<i>BRCA1</i> carrier	4401/543	1.24 (0.67–2.27)	0.49	
<i>BRCA2</i> carrier	3115/229	1.57 (0.67–3.66)	0.30	

HR hazard ratio, CI confidence interval, CIMBA Consortium of Investigators for the Modifiers of *BRCA1/2*

^aBMI-GS was constructed by combining 93 BMI-associated single-nucleotide polymorphisms (SNPs)

^bAdjusted for principal components, birth cohort, country of enrolment, and menopausal status in weighted Cox model

^cAdjusted for principal components, mutation status, birth cohort, and country of enrolment

^dAdjusted for principal components, mutation status, menopausal status, birth cohort, and country of enrolment

^eHazard ratios were calculated using inverse-variance meta-analysis and re-scaled to the corresponding units by calculating the height measurements per z-score among controls. Effect estimates for ovarian cancer for each SNP were calculated from weighted Cox model adjusting for principal components, birth cohort, country of enrolment, menopausal status, and mutation status

^fAnalysis was performed among 7516 participants with measured BMI

Bolded lines refer to the model corresponding to our main results

circulating levels of progesterone compared with normal weight women.⁴⁸ Higher progesterone levels may reduce ovarian cancer risk, through upregulation of p53, leading to tumour cell apoptosis.^{46,49–51} Taken together, these pathways may explain the association of higher BMI with premenopausal ovarian cancer risk. In addition, height has been associated with higher levels of circulating insulin-like growth factor-1 (IGF-1),^{52,53} a pathway that has been implicated in tumour transformation and may exert antiapoptotic and mitogenic effects.^{54,55} Moreover, *BRCA1* may directly interact with the IGF-1 pathway to mediate cancer risk.⁵⁶

Our study has several strengths, including large sample size, genetic scores utilising most identified height and BMI variants, several MR methods, and consistent findings between observed

and genetically predicted phenotypes. Several limitations of our study should be considered. First, even with a large sample size, the CIs for most risk estimates were wide, which limits inferences about causation. While both the height- and BMI-GS were clearly associated with their respective traits, they were only able to explain 13.4% and 2.6% of the variation, respectively. This reduced the statistical precision of our risk estimates. During the preparation of our manuscript, a new genome-wide meta-analysis⁵⁷ found a substantial number of new genetic loci related to height and BMI, increasing the amount of variation that could be explained for these two traits to 24.6% and 6.0%, respectively, although the variation that could be explained when examining these SNPs in a validation cohort was 14.0% and 2.3%. This is comparable to the

Table 6. Height or body mass index (BMI) single-nucleotide polymorphisms (SNPs) statistically significantly associated ($P < 0.05$) with ovarian cancer risk in CIMBA

rs ID	Chromosome	Position	Nearest gene	Reference allele in CIMBA	Effect allele in CIMBA	Effect allele frequency in CIMBA	Imputation quality ^a	Association with ovarian cancer in CIMBA		
								Log hazard ratio ^b	Standard error	P value
Height										
rs11049611	12	28600244	<i>CCDC91</i>	C	T	0.28	1	0.127	0.036	0.0004
rs6902771	6	152157881	<i>ESR1</i>	C	T	0.46	0.98	0.091	0.032	0.005
rs584828	17	38599230	<i>IGFBP4</i>	C	T	0.39	0.68	0.109	0.040	0.006
rs3817428	15	89415247	<i>ACAN</i>	C	G	0.22	0.51	0.144	0.053	0.006
rs7517682	1	103519589	<i>COL11A1</i>	G	A	0.56	0.98	0.085	0.033	0.009
rs12470505	2	219908369	<i>CCDC108</i>	T	G	0.10	0.97	-0.143	0.055	0.009
rs26024	5	127696022	<i>FBN2</i>	A	C	0.34	1	-0.087	0.034	0.011
rs13113518	4	56399648	<i>CLOCK</i>	T	C	0.37	0.99	0.081	0.033	0.014
rs7319045	13	92024574	<i>GPC5</i>	A	G	0.61	0.92	0.084	0.035	0.017
rs2044124	17	61845425	<i>CCDC47</i>	T	C	0.95	0.91	0.187	0.079	0.018
rs9309101	2	43629612	<i>THADA</i>	A	G	0.35	1	0.076	0.033	0.021
rs11867943	17	54229842	<i>ANKFN1</i>	A	T	0.11	0.96	0.118	0.051	0.022
rs12779328	10	12943973	<i>CCDC3</i>	C	T	0.30	0.94	-0.080	0.036	0.026
rs8073371	17	46096276	<i>COP22</i>	C	T	0.20	1.00	-0.095	0.043	0.029
rs2013265	8	24092500	<i>ADAM28</i>	C	T	0.22	0.62	0.104	0.047	0.029
rs11687941	2	242191410	<i>HDLBP</i>	C	G	0.26	0.96	-0.079	0.037	0.031
rs6838153	4	122720999	<i>EXOSC9</i>	A	G	0.33	0.99	-0.072	0.034	0.033
rs7112925	11	66826160	<i>RHOD</i>	C	T	0.36	0.95	-0.071	0.034	0.037
rs16942341	15	89388905	<i>ACAN</i>	C	T	0.03	0.60	0.255	0.123	0.039
rs6080830	20	17771113	<i>BANF2</i>	A	G	0.43	0.68	-0.080	0.039	0.041
rs867245	4	2218888	<i>POLN</i>	C	G	0.07	1.00	0.122	0.060	0.043
rs1155939	6	126866133	<i>C6orf173</i>	C	A	0.51	0.99	0.064	0.033	0.049
BMI										
rs16851483	3	141275436	<i>RASA2</i>	G	T	0.07	1	-0.203	0.068	0.003
rs2207139	6	50845490	<i>TFAP2B</i>	A	G	0.16	0.99	0.120	0.043	0.005
rs2033732	8	85079709	<i>RALYL</i>	T	C	0.75	0.72	-0.088	0.042	0.037
rs6804842	3	25106437	<i>RARB</i>	A	G	0.58	0.58	0.087	0.044	0.046

CIMBA Consortium of Investigators for the Modifiers of *BRCA1/2*^aImputation quality of 1 indicates genotyped SNPs^bPer-allele association with ovarian cancer was adjusted for principal components, birth cohort, menopausal status, age at menopause, country of enrolment, and mutation status in weighted Cox models

amount of variation that could be explained using the set of genetic variants in our study. Including these additional SNPs may be able to improve the precision of our estimates for both height and BMI. Moreover, the inclusion of rare variants to strengthen the height and BMI genetic instruments should also be considered in future studies.⁵⁸ Our study did not explicitly examine whether adding height or BMI (either observed or genetically predicted) to existing polygenic risk scores for ovarian cancer could further refine risk prediction. Histology was only available in a subset of ovarian cancer patients, which limits our capacity to understand subtype-specific effects of BMI and height. Our study only included women of European ancestry, which may preclude generalisation to women of other racial/ethnic groups.

In summary, our study suggests that higher BMI may be causally associated with ovarian cancer risk in *BRCA1/2* carriers, possibly more so for premenopausal women. BMI could be used to identify premenopausal women at elevated risk of ovarian cancer. Our finding of a stronger association between BMI and non-serous ovarian cancer warrants confirmation in future studies.

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AFFILIATIONS

Frank Qian¹, Matti A. Rookus², Goska Leslie³, Harvey A. Risch⁴, Mark H. Greene⁵, Cora M. Aalfs⁶, Muriel A. Adank⁷, Julian Adlard⁸, Bjarni A. Agnarsson^{9,10}, Munaza Ahmed¹¹, Kristiina Aittomäki¹², Irene L. Andrulis^{13,14}, Norbert Arnold^{15,16}, Banu K. Arun¹⁷, Margreet G. E. M. Ausems¹⁸, Jacopo Azzollini¹⁹, Daniel Barrowdale³, Julian Barwell²⁰, Javier Benitez^{21,22}, Katarzyna Białkowska²³, Valérie Bonadona²⁴, Julika Borde^{25,26,27}, Ake Borg²⁸, Angela R. Bradbury²⁹, Joan Brunet³⁰, Saundra S. Buys³¹, Trinidad Caldes³², Maria A. Caligo³³, Ian Campbell^{34,35}, Jonathan Carter³⁶, Jocelyne Chiquette³⁷, Wendy K. Chung³⁸, Kathleen B. M. Claes³⁹, J. Margriet Collée⁴⁰, Marie-Agnès Collonge-Rame⁴¹, Fergus J. Couch⁴², Mary B. Daly⁴³, Capucine Delnatte⁴⁴, Orland Diez⁴⁵, Susan M. Domchek²⁹, Cecilia M. Dorfling⁴⁶, Jacqueline Eason⁴⁷, Douglas F. Easton^{3,48}, Ros Eeles⁴⁹, Christoph Engel⁵⁰, D. Gareth Evans^{51,52}, Laurence Faivre^{53,54}, Lidia Feliubadaló⁵⁵, Lenka Foretova⁵⁶, Eitan Friedman^{57,58}, Debra Frost³, Patricia A. Ganz⁵⁹, Judy Garber⁶⁰, Vanesa Garcia-Barberan³¹, Andrea Gehrig⁶¹, Gord Glendon¹³, Andrew K. Godwin⁶², Encarna B. Gómez García⁶³, Ute Hamann⁶⁴, Jan Hauke^{24,25,26}, John L. Hopper⁶⁵, Peter J. Hulick^{66,67}, Evgeny N. Imyanitov⁶⁸, Claudine Isaacs⁶⁹, Louise Izatt⁷⁰, Anna Jakubowska^{22,71}, Ramunas Janavicius^{72,73}, Esther M. John⁷⁴, Beth Y. Karlan⁷⁵, Carolien M. Kets⁷⁶, Yael Laitman⁵⁷, Conxi Lázaro⁵⁵, Dominique Leroux⁷⁷, Jenny Lester⁷⁵, Fabienne Lesueur^{78,79,79}, Jennifer T. Loud⁵, Jan Lubiński²³, Alicja Łukomska²³, Lesley McGuffog³, Noura Mebirouk^{78,79,80}, Hanne E. J. Meijers-Heijboer⁸¹, Alfons Meindl⁸², Austin Miller⁸³, Marco Montagna⁸⁴, Thea M. Mooij², Emmanuelle Mouret-Fourme⁸⁵, Katherine L. Nathanson²⁹, Bitu Nehoray⁸⁶, Susan L. Neuhausen⁸⁷, Heli Nevanlinna⁸⁸, Finn C. Nielsen⁸⁹, Kenneth Offit^{90,91}, Edith Olah⁹², Kai-ren Ong⁹³, Jan C. Oosterwijk⁹⁴, Laura Ottini⁹⁵, Michael T. Parsons⁹⁶, Paolo Peterlongo⁹⁷, Georg Pfeiler⁹⁸, Nisha Pradhan⁹⁰, Paolo Radice⁹⁹, Susan J. Ramus^{100,101}, Johanna Rantala¹⁰², Gad Rennert¹⁰³, Mark Robson⁹¹, Gustavo C. Rodriguez¹⁰⁴, Ritu Salani¹⁰⁵, Maren T. Scheuner¹⁰⁶, Rita K. Schmutzler^{26,27}, Payal D. Shah²⁹, Lucy E. Side¹⁰⁷, Jacques Simard¹⁰⁸, Christian F. Singer⁹⁸, Doris Steinemann¹⁰⁹, Dominique Stoppa-Lyonnet^{85,110,111}, Yen Yen Tan⁹⁸, Manuel R. Teixeira^{112,113}, Mary Beth Terry¹¹⁴, Mads Thomassen¹¹⁵, Marc Tischkowitz^{116,117}, Silvia Tognazzo⁸⁴, Amanda E. Toland¹¹⁸, Nadine Tung¹¹⁹, Christi J. van Asperen¹²⁰, Klaartje van Engelen¹²¹, Elizabeth J. van Rensburg⁴⁶, Laurence Venat-Bouvet¹²², Jeroen Vierstraete³⁹, Gabriel Wagner⁹⁸, Lisa Walker¹²³, Jeffrey N. Weitzel⁸⁶, Drakoulis Yannoukacos¹²⁴, KConFab Investigators^{34,35}, HEBO Investigators¹²⁵, GEMO Study Collaborators⁸⁵, EMBRACE Collaborators³, Antonis C. Antoniou³, David E. Goldgar¹²⁶, Olufunmilayo I. Olopade¹²⁷, Georgia Chenevix-Trench⁹⁶, Timothy R. Rebbeck^{128,129} and Dezheng Huo^{127,130}, on behalf of CIMBA

¹Department of Medicine, University of Chicago, Chicago, IL, USA; ²Department of Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; ³Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; ⁴Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT, USA; ⁵Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA; ⁶Department of Clinical Genetics, Amsterdam UMC, Location AMC, Amsterdam, The Netherlands; ⁷Family Cancer Clinic, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; ⁸Yorkshire Regional Genetics Service, Chapel Allerton Hospital, Leeds, UK; ⁹Department of Pathology, Landspítali University Hospital, Reykjavik, Iceland; ¹⁰School of Medicine, University of Iceland, Reykjavik, Iceland; ¹¹North East Thames Regional Genetics Service, Great Ormond Street Hospital, London, UK; ¹²Department of Clinical Genetics, Helsinki University Hospital, University of Helsinki, Helsinki, Finland; ¹³Fred A. Litwin Center for Cancer Genetics, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, ON, Canada; ¹⁴Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada; ¹⁵Department of Gynaecology and Obstetrics, University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel, Kiel, Germany; ¹⁶Institute of Clinical Molecular Biology, University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel, Kiel, Germany; ¹⁷Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; ¹⁸Division Laboratories, Pharmacy and Biomedical Genetics, Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands; ¹⁹Unit of Medical Genetics, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; ²⁰Leicestershire Clinical Genetics Service, University Hospitals of Leicester NHS Trust, Leicester, UK; ²¹Human Cancer Genetics Programme, Spanish National Cancer Research Centre (CNIO), Madrid, Spain; ²²Biomedical Network on Rare Diseases (CIBERER), Madrid, Spain; ²³Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland; ²⁴Unité de Prévention et d'Epidémiologie Génétique, Centre Léon Bérard, Lyon, France; ²⁵Center for Integrated Oncology (CIO), University Hospital of Cologne, Cologne, Germany; ²⁶Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany; ²⁷Center for Hereditary Breast and Ovarian Cancer, University Hospital of Cologne, Cologne, Germany; ²⁸Department of Oncology, Lund University and Skåne University Hospital, Lund, Sweden; ²⁹Department of Medicine, Abramson Cancer Center, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; ³⁰Genetic Counseling Unit, Hereditary Cancer Program, IDIBGI (Institut d'Investigació Biomèdica de Girona), Catalan Institute of Oncology, CIBERONC, Girona, Spain; ³¹Department of Medicine, Huntsman Cancer Institute, Salt Lake City, UT, USA; ³²Medical Oncology Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos (IdISSC), Centro Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain; ³³Section of Molecular Genetics, Dept. of Laboratory Medicine, University Hospital of Pisa, Pisa, Italy; ³⁴Peter MacCallum Cancer Center, Melbourne, Victoria, Australia; ³⁵Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, VIC, Australia; ³⁶Department of Gynaecological Oncology, Chris O'Brien Lifehouse and The University of Sydney, Camperdown, NSW, Australia; ³⁷CRCHU de Québec- oncologie, Centre des maladies du sein Deschênes-Fabia, Hôpital du Saint-Sacrement, Québec, QC, Canada; ³⁸Departments of Pediatrics and Medicine, Columbia University, New York, NY, USA; ³⁹Centre for Medical Genetics, Ghent University, Ghent, Belgium; ⁴⁰Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands; ⁴¹Service de Génétique, CHU de Besançon, Besançon, France; ⁴²Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA; ⁴³Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, PA, USA; ⁴⁴Unité d'Oncogénétique, ICO-Centre René Gauducheau, Saint Herblain, France; ⁴⁵Oncogenetics Group, Clinical and Molecular Genetics Area, Vall d'Hebron Institute of Oncology (VHIO), University Hospital Vall d'Hebron, Barcelona, Spain; ⁴⁶Department of Genetics, University of Pretoria, Arcadia, South Africa; ⁴⁷Nottingham Clinical Genetics Service, Nottingham University Hospitals NHS Trust, Nottingham, UK; ⁴⁸Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK; ⁴⁹Oncogenetics Team, The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK; ⁵⁰Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany; ⁵¹Division of Evolution and Genomic Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, University

of Manchester, Manchester Academic Health Science Centre, Manchester, UK; ⁵²Manchester Centre for Genomic Medicine, St Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; ⁵³Unité d'oncogénétique, Centre de Lutte Contre le Cancer, Centre Georges-François Leclerc, Dijon, France; ⁵⁴Centre de Génétique, CHU Dijon, Dijon, France; ⁵⁵Molecular Diagnostic Unit, Hereditary Cancer Program, ICO-IDIBELL (Bellvitge Biomedical Research Institute, Catalan Institute of Oncology), CIBERONC, Barcelona, Spain; ⁵⁶Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic; ⁵⁷The Susanne Levy Gertner Oncogenetics Unit, Chaim Sheba Medical Center, Ramat Gan, Israel; ⁵⁸Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel; ⁵⁹Schools of Medicine and Public Health, Division of Cancer Prevention & Control Research, Jonsson Comprehensive Cancer Centre, UCLA, Los Angeles, CA, USA; ⁶⁰Cancer Risk and Prevention Clinic, Dana-Farber Cancer Institute, Boston, MA, USA; ⁶¹Centre of Familial Breast and Ovarian Cancer, Department of Medical Genetics, Institute of Human Genetics, University Würzburg, Würzburg, Germany; ⁶²Department of Pathology and Laboratory Medicine, Kansas University Medical Center, Kansas City, KS, USA; ⁶³Department of Clinical Genetics and GROW, School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands; ⁶⁴Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany; ⁶⁵Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia; ⁶⁶Center for Medical Genetics, NorthShore University HealthSystem, Evanston, IL, USA; ⁶⁷The University of Chicago Pritzker School of Medicine, Chicago, IL, USA; ⁶⁸N.N. Petrov Institute of Oncology, St. Petersburg, Russia; ⁶⁹Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA; ⁷⁰Clinical Genetics, Guy's and St Thomas' NHS Foundation Trust, London, UK; ⁷¹Independent Laboratory of Molecular Biology and Genetic Diagnostics, Pomeranian Medical University, Szczecin, Poland; ⁷²Hematology, oncology and transfusion medicine center, Dept. of Molecular and Regenerative Medicine, Vilnius University Hospital Santariskiu Clinics, Vilnius, Lithuania; ⁷³State Research Institute, Innovative Medicine Center, Vilnius, CA, Lithuania; ⁷⁴Department of Medicine, Division of Oncology, and Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA; ⁷⁵Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA; ⁷⁶Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands; ⁷⁷Département de Génétique, CHU de Grenoble, Grenoble, France; ⁷⁸Genetic Epidemiology of Cancer team, Inserm U900, Paris, France; ⁷⁹Institut Curie, Paris, France; ⁸⁰Mines ParisTech, Fontainebleau, France; ⁸¹Department of Clinical Genetics, Amsterdam UMC, Location VU University Medical Center, Amsterdam, The Netherlands; ⁸²Department of Gynecology and Obstetrics, Ludwig Maximilian University of Munich, Munich, Germany; ⁸³NRG Oncology, Statistics and Data Management Center, Roswell Park Cancer Institute, Buffalo, NY, USA; ⁸⁴Immunology and Molecular Oncology Unit, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy; ⁸⁵Service de Génétique, Institut Curie, Paris, France; ⁸⁶Clinical Cancer Genomics, City of Hope, Duarte, CA, USA; ⁸⁷Department of Population Sciences, Beckman Research Institute of City of Hope, Duarte, CA, USA; ⁸⁸Department of Obstetrics and Gynecology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland; ⁸⁹Center for Genomic Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; ⁹⁰Clinical Genetics Research Lab, Department of Cancer Biology and Genetics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; ⁹¹Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; ⁹²Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary; ⁹³West Midlands Regional Genetics Service, Birmingham Women's Hospital Healthcare NHS Trust, Birmingham, UK; ⁹⁴Department of Genetics, University Medical Center Groningen, University Groningen, Groningen, The Netherlands; ⁹⁵Department of Molecular Medicine, University La Sapienza, Rome, Italy; ⁹⁶Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia; ⁹⁷Genome Diagnostics Program, IFOM - the FIRC (Italian Foundation for Cancer Research) Institute of Molecular Oncology, Milan, Italy; ⁹⁸Department of OB/GYN and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; ⁹⁹Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori (INT), Milan, Italy; ¹⁰⁰School of Women's and Children's Health, Faculty of Medicine, University of NSW Sydney, Sydney, NSW, Australia; ¹⁰¹The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, NSW, Australia; ¹⁰²Clinical Genetics, Karolinska Institutet, Stockholm, Sweden; ¹⁰³Clalit National Cancer Control Center, Carmel Medical Center and Technion Faculty of Medicine, Haifa, Israel; ¹⁰⁴Division of Gynecologic Oncology, NorthShore University HealthSystem, University of Chicago, Evanston, IL, USA; ¹⁰⁵Wexner Medical Center, The Ohio State University, Columbus, OH, USA; ¹⁰⁶Cancer Genetics and Prevention Program, University of California San Francisco, San Francisco, CA, USA; ¹⁰⁷Wessex Clinical Genetics Service, University Hospitals Southampton NHS Trust, Southampton, UK; ¹⁰⁸Genomics Center, Centre Hospitalier Universitaire de Québec – Université Laval, Research Center, Québec City, QC, Canada; ¹⁰⁹Institute of Cell and Molecular Pathology, Hannover Medical School, Hannover, Germany; ¹¹⁰Department of Tumour Biology, INSERM U830, Paris, France; ¹¹¹Université Paris Descartes, Paris, France; ¹¹²Department of Genetics, Portuguese Oncology Institute, Porto, Portugal; ¹¹³Biomedical Sciences Institute (ICBAS), University of Porto, Porto, Portugal; ¹¹⁴Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA; ¹¹⁵Department of Clinical Genetics, Odense University Hospital, Odense C, Denmark; ¹¹⁶Program in Cancer Genetics, Departments of Human Genetics and Oncology, McGill University, Montréal, QC, Canada; ¹¹⁷Department of Medical Genetics, University of Cambridge, Cambridge, UK; ¹¹⁸Department of Cancer Biology and Genetics, The Ohio State University, Columbus, OH, USA; ¹¹⁹Department of Medical Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA; ¹²⁰Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands; ¹²¹Department of Clinical Genetics, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; ¹²²Department of Medical Oncology, CHU Dupuytren, Limoges, France; ¹²³Oxford Regional Genetics Service, Churchill Hospital, Oxford, UK; ¹²⁴Molecular Diagnostics Laboratory, INRASTES, National Centre for Scientific Research 'Demokritos', Athens, Greece; ¹²⁵The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON), Coordinating Center: The Netherlands Cancer Institute, Amsterdam, The Netherlands; ¹²⁶Department of Dermatology, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA; ¹²⁷Center for Clinical Cancer Genetics, The University of Chicago, Chicago, IL, USA; ¹²⁸Harvard T.H. Chan School of Public Health, Boston, MA, USA; ¹²⁹Dana-Farber Cancer Institute, Boston, MA, USA and ¹³⁰Department of Public Health Sciences, University of Chicago, Chicago, IL, USA