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 (Pinteraction < 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.
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.\(^{12-24}\)

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: 

\[
\text{Height GS} = \sum_{i=1}^{\text{SNPs}} \beta_{\text{GH}} \times \text{SNP}_i,
\]

\[
\text{BMI GS} = \sum_{i=1}^{\text{SNPs}} \beta_{\text{GB}} \times \text{SNP}_i,
\]

where \(\beta_{\text{GH}}\) 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 \(\beta_0\) (intercept = 165.455) and \(\beta_1\) (slope = 5.217) for height and \(\beta_0\) (22.607) and \(\beta_1\) (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.\(^{24,27}\) 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 \(\beta_{\text{GH}}\) for each SNP \(i\), which represents the per-allele magnitude of association with height or BMI from previous GWAS. Next, we calculated \(\beta_{\text{GB}}\) and \(\text{SE}(\beta_{\text{GB}})\) 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 \((\beta_{\text{GS}})\) is calculated using inverse-variance weighted estimate of each variant’s effect:

\[
\beta_{\text{GS}} = \sum_{i=1}^{\text{SNPs}} \frac{\beta_{\text{GH}} \times \text{SE}(\beta_{\text{GH}})^{-2} + \beta_{\text{GB}} \times \text{SE}(\beta_{\text{GB}})^{-2}}{\sum_{i=1}^{\text{SNPs}} \text{SE}(\beta_{\text{GH}})^{-2} + \text{SE}(\beta_{\text{GB}})^{-2}}
\]

Standard error was estimated as

\[
\text{SE}_{\beta_{\text{GS}}} = \sqrt{\frac{1}{\sum_{i=1}^{\text{SNPs}} \text{SE}(\beta_{\text{GH}})^{-2} + \text{SE}(\beta_{\text{GB}})^{-2}}}
\]

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.\(^{26}\) 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 assessed 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
Mendelian randomisation study of height and body mass index as modifiers…

F Qian et al.

182

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

| Variable                        | Ovarian cancer cases, N = 2923 | Non-cases, N = 19,665 | P valueb |
|---------------------------------|---------------------------------|------------------------|----------|
| Mutation carrier status         |                                 |                        | <0.0001  |
| BRCA1                           | 2319 (79.3)                     | 12,357 (62.8)          |          |
| BRCA2                           | 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, n (%)                |                                 |                        | 0.07     |
| Caucasian, not otherwise specified | 2060 (89.7)              | 13,613 (88.4)          |          |
| Ashkenazi Jewish                | 237 (10.3)                      | 1780 (11.6)            |          |
| Height in cm, n                 | 784                             | 6873                   |          |
| Mean ± SD                       | 163.2 ± 6.5                     | 164.8 ± 6.9            | <0.0001  |
| Weight at baselinea in kg, n    | 780                             | 6789                   |          |
| Mean ± SD                       | 69.0 ± 14.6                     | 68.5 ± 14.1            | 0.32     |
| Body mass index at baselinea in kg/m2, n | 772                             | 6744                   |          |
| Mean ± SD                       | 25.9 ± 5.3                      | 25.2 ± 5.1             | 0.002    |
| Weight in early adulthood in kg, n | 536                             | 4,912                  |          |
| Mean ± SD                       | 56.5 ± 8.3                      | 57.9 ± 9.5             | 0.007    |
| Body mass index in early adulthood in kg/m2, n | 536                             | 4881                   |          |
| Mean ± SD                       | 21.2 ± 3.0                      | 21.3 ± 3.3             | 0.43     |
| Age at menarche in years, n     | 771                             | 6688                   |          |
| Mean ± SD                       | 13.0 ± 1.5                      | 13.0 ± 1.5             | 0.90     |
| Parous, n (%)                   |                                 |                        | <0.0001  |
| Yes                             | 805                             | 5790 (77.4)            |          |
| No                              | 107                             | 1692 (22.6)            |          |
| Age at first live birth in years, n | 735                             | 5555                   |          |
| Mean ± SD                       | 24.4 ± 4.5                      | 25.4 ± 4.9             | <0.0001  |
| Menopausal status, n (%)        |                                 |                        | <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, n (%)         |                                 |                        |          |
| Invasive                        | 1228 (99.2)                     |                        |          |
| Borderline                      | 10 (0.8)                        |                        |          |
| Tumour histotype, n (%)         |                                 |                        |          |
| Serous                          | 892 (67.9)                      |                        |          |
| Mucinous                        | 20 (1.5)                        |                        |          |
| Endometrioid                    | 141 (10.7)                      |                        |          |
| Clear cell                      | 17 (1.3)                        |                        |          |
| Other                           | 243 (18.5)                      |                        |          |
| Tumour grade, n (%)             |                                 |                        |          |
| Well differentiated             | 43 (4.6)                        |                        |          |
| Moderately differentiated       | 196 (21.0)                      |                        |          |

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) (Table 3). 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 height was explained by the height GS. Besides height, we found weaker associations between the height GS and body weight and age at menarche.

Table 1 continued

| Variable                        | Ovarian cancer cases, N = 2923 | Non-cases, N = 19,665 | P valueb |
|---------------------------------|---------------------------------|------------------------|----------|
| Poorly/ undifferentiated        | 696 (74.4)                      |                        |          |
| Tumour stage, n (%)             |                                 |                        |          |
| 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

*Reported at the date of questionnaire

bP values for comparing cases and non-cases were calculated from logistic regression models with robust sandwich variance estimator.
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 studies15,16,35-36 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 2. Association of height and ovarian cancer risk using observed height among 7657 participants**

| N/events | HR (95% CI) | P value |
|----------|-------------|---------|
| 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 |
| Adjusted for parity and age at menarche | 7090/724 | 1.09 (0.94–1.26) | 0.24 |
| By mutation status | | |
| *BRCA1* carrier | 4502/552 | 1.07 (0.91–1.24) | 0.42 |
| *BRCA2* carrier | 3155/232 | 1.11 (0.85–1.45) | 0.44 |
| P_interaction | | 0.64 |
| By menopausal status | | |
| Premenopausal | 7657/105 | 1.02 (0.72–1.42) | 0.93 |
| Postmenopausal | 4328/679 | 1.09 (0.94–1.26) | 0.27 |
| P_interaction | | 0.71 |
| By tumour subtype | | |
| Serous | 7360/319 | 1.07 (0.87–1.31) | 0.52 |
| Non-serous | 7360/168 | 1.30 (1.01–1.68) | 0.045 |
| P_net | | 0.24 |
| By tumour grade | | |
| 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 |
| P_net | | 0.89 |

*HR* hazard ratio, *CI* confidence interval

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

* Adjusted for principal components, mutation status, birth cohort, and country of enrolment

* Includes 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 (I² = 15.9%), indicating a low likelihood of pleiotropic associations. Using a two-stage residual inclusion approach, we found a generally similar association (HR = 1.37, 95% CI: 0.84–2.24, P = 0.21).
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.1,2,37,39 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,5,12 while genetically predicted height had a stronger association with clear cell (OR = 1.49 in observed BMI and 1.38 in 5% increase (95% CI: 1.25–1.56) in genetically predicted BMI) 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
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 4. Association of body mass index (BMI) and ovarian cancer risk using observed BMI |
|---------------------------------|-----|-----------------|-----|
| Per 5 kg/m² increase in BMI at date of questionnaire | N/events | HR (95% CI) | P value |
| 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 status⁴ | | | |
| *BRCA1* carrier | 4401/543 | 1.06 (0.95–1.17) | 0.31 |
| *BRCA2* carrier | 3115/229 | 0.96 (0.81–1.15) | 0.67 |
| Pinteraction | | | 0.35 |
| By menopausal status⁵ | | | |
| Premenopausal | 7516/102 | **1.25 (1.06–1.48)** | **0.009** |
| Postmenopausal | 4257/670 | 0.98 (0.88–1.10) | 0.78 |
| Pinteraction | | | **0.02** |
| By tumour subtype⁶ | | | |
| Serous | 7223/312 | 0.98 (0.84–1.15) | 0.83 |
| Non-serous⁷ | 7223/167 | **1.25 (1.06–1.49)** | **0.01** |
| Phet | | | **0.04** |
| By tumour grade⁸ | | | |
| 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 |
| Phet | | | 0.47 |
| Per 5 kg/m² 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 status⁴ | | | |
| *BRCA1* carrier | 3134/380 | 0.92 (0.71–1.18) | 0.50 |
| *BRCA2* carrier | 2283/156 | 1.00 (0.74–1.36) | 0.99 |
| Pinteraction | | | 0.73 |
| By menopausal status⁵ | | | |
| Premenopausal | 5417/67 | **1.34 (0.97–1.84)** | **0.07** |
| Postmenopausal | 3094/469 | 0.82 (0.65–1.04) | 0.11 |
| Pinteraction | | | **0.01** |

**HR** hazard ratio, **CI** confidence interval

⁴Adjusted for principal components, birth cohort, country of enrolment, and menopausal status in weighted Cox model

⁵Adjusted for principal components, mutation status, birth cohort, and country of enrolment

⁶Adjusted for principal components, birth cohort, country of enrolment, mutation status, and menopausal status

⁷Includes endometrioid, mucinous, clear cell, and other histological types

Bolded lines refer to the model corresponding to our main results
circulating levels of progesterone compared with normal weight women. Higher progesterone levels may reduce ovarian cancer risk, through upregulation of p53, leading to tumour cell apoptosis. 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), a pathway that has been implicated in tumour transformation and may exert antiapoptotic and mitogenic effects. Moreover, BRCA1 may directly interact with the IGF-1 pathway to mediate cancer risk.

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-analysis 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 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 |
|---------------------------------|-----------------|-----------------|------------------|------------------|
| | N/events | HR (95% CI) | P value | Heterogeneity (I²) |
|-----------------|-----------------|-----------------|------------------|------------------|
| BMI-GSa | | | | |
| 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 statusb | | | | |
| BRCA1 carrier | 14,676/2319 | 1.16 (0.88–1.53) | 0.31 | |
| BRCA2 carrier | 7912/604 | 0.81 (0.46–1.43) | 0.46 | |
| By menopausal statusc | | | | |
| Premenopausal | 22,588/967 | 1.59 (1.08–2.33) | 0.02 | 0.006 |
| Postmenopausal | 9219/1955 | 0.80 (0.58–1.11) | 0.18 | |
| By tumour subtyped | | | | |
| 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 | |
| By tumour gradee | | | | |
| 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 | |
| Meta-analysis methodf | | | | |
| All participants | 22,588/2923 | 1.12 (0.86–1.46) | 0.39 | 15.9% |
| BRCA1 carrier | 14,676/2319 | 1.18 (0.88–1.57) | 0.26 | 17.2% |
| BRCA2 carrier | 7912/604 | 0.80 (0.45–1.43) | 0.45 | 0.0% |
| Two-stage residual inclusion methodf | | | | |
| All participants | 7516/772 | 1.37 (0.84–2.24) | 0.21 | |
| BRCA1 carrier | 4401/543 | 1.24 (0.67–2.27) | 0.49 | |
| BRCA2 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

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

Analysis was performed among 7516 participants with measured BMI

Bolded lines refer to the model corresponding to our main results
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 genetic variants in our study. Including these additional SNPs may explain a greater 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 genetic instrument should also be considered in future studies. 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.

### 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 qualitya | Association with ovarian cancer risk in CIMBA | Log hazard ratio | Standard error | P value |
|-------|------------|----------|--------------|---------------------------|-----------------------|-------------------------------|-------------------|----------------------------------------|---------------|-------------|--------|
| Height |
| rs11049611 | 12 | 28600244 | CCDC91 | C | T | 0.28 | 1 | 0.127 | 0.036 | 0.0004 |
| rs6902771 | 6 | 152157881 | ESR1 | C | T | 0.46 | 0.98 | 0.091 | 0.032 | 0.005 |
| rs584828 | 17 | 38599230 | IGFBP4 | C | T | 0.39 | 0.68 | 0.109 | 0.040 | 0.006 |
| rs3817428 | 15 | 89415247 | ACAN | G | T | 0.22 | 0.51 | 0.144 | 0.053 | 0.006 |
| rs7517682 | 1 | 103519589 | COL11A1 | G | A | 0.56 | 0.98 | 0.085 | 0.033 | 0.009 |
| rs12470505 | 2 | 219908369 | CCDC108 | T | G | 0.10 | 0.97 | −0.143 | 0.055 | 0.009 |
| rs26024 | 5 | 127696022 | FBN2 | A | C | 0.34 | 1 | −0.087 | 0.034 | 0.011 |
| rs13113518 | 4 | 56399686 | CLOCK | T | C | 0.37 | 0.99 | 0.081 | 0.033 | 0.014 |
| rs7319045 | 13 | 92027457 | GPC5 | G | A | 0.67 | 0.42 | 0.084 | 0.035 | 0.017 |
| rs2044124 | 17 | 61845425 | CCDC47 | C | T | 0.95 | 0.91 | 0.187 | 0.079 | 0.018 |
| rs9309101 | 2 | 43629612 | THADA | A | G | 0.35 | 1 | 0.076 | 0.033 | 0.021 |
| rs11867943 | 17 | 54229842 | ANKFN1 | A | T | 0.11 | 0.96 | 0.118 | 0.051 | 0.022 |
| rs12779328 | 10 | 12943973 | CCDC3 | T | C | 0.30 | 0.94 | −0.080 | 0.036 | 0.026 |
| rs8073371 | 17 | 46096276 | COP22 | T | C | 0.20 | 1.00 | −0.095 | 0.043 | 0.029 |
| rs2013265 | 8 | 24092500 | ADAM28 | T | C | 0.22 | 0.62 | 0.104 | 0.047 | 0.029 |
| rs11687941 | 2 | 242191410 | HDLBP | C | G | 0.26 | 0.96 | −0.079 | 0.037 | 0.031 |
| rs6838153 | 4 | 122720999 | EKOSC9 | A | G | 0.33 | 0.99 | −0.072 | 0.034 | 0.033 |
| rs7112925 | 11 | 66826160 | RHOD | C | T | 0.36 | 0.95 | −0.071 | 0.034 | 0.037 |
| rs16942341 | 15 | 89388905 | ACAN | T | C | 0.03 | 0.60 | 0.255 | 0.123 | 0.039 |
| rs6080830 | 20 | 17771113 | BANF2 | A | G | 0.43 | 0.68 | −0.080 | 0.039 | 0.041 |
| rs867245 | 4 | 2218888 | POLN | C | G | 0.07 | 1.00 | 0.122 | 0.060 | 0.043 |
| rs1155999 | 6 | 12686136 | C6orf173 | A | C | 0.51 | 0.99 | 0.064 | 0.033 | 0.049 |
| BMI |
| rs16851483 | 3 | 141275436 | RASA2 | G | T | 0.07 | 1 | −0.203 | 0.068 | 0.003 |
| rs2207139 | 6 | 50845490 | TFAP2B | A | G | 0.16 | 0.99 | 0.120 | 0.043 | 0.005 |
| rs2033732 | 8 | 85079709 | RALYL | T | C | 0.75 | 0.72 | −0.088 | 0.042 | 0.037 |
| rs6804842 | 3 | 25106437 | RARB | 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

### ACKNOWLEDGEMENTS

We thank all the families and clinicians who contributed to the studies; Sue Healey, in particular taking on the task of mutation classification with the late Olga Sinilnikova; Maggie Angelakos, Judi Massiel, Gillian Dite, Helen Tsimiklis; members and participants in the New York site of the Breast Cancer Family Registry; members and participants in the Ontario Familial Breast Cancer Registry; Villus Rudatis and Laimonas Grishkevicius; Drs Janis Eglitis, Anna Krilova and Aivaris Stengrevics; Yuan Chun Ding and Linda Steele for their work in participant enrollment and biospecimen and data management; Bent Ejertsen and Anne-Marie Genders for the recruitment and genetic counseling of participants; Alicia Barroso, Rosario Alonso and Guillermo Pita; Manoukian Siranoush, Bernard Peissel, Cristina Zanzottera, Milena Marian, Daniela Zaffaroni, Bernardo Bonanni, Monica Barile, Irene Feroce, Mariarosaria Calvello, Alessandra Veli, Riccardo Dolcetti, Giuseppe Giannini, Laura Papi, Gabriele Lorenzo Capone, Liliana Varesco, Viviana Gismondi, Maria Grazia Tibiletti, Daniela Furlan, Antonella Savarese, Alme Martayan, Stefania Tommasi, Brunella Pilato; the personnel of the Cogentech Cancer Genetic Test Laboratory, Milan, Italy; Ms. JoEllen Weaver and Dr. Betsy Bove; Marta Santamariña, Ana Blanco, Miguel Agudo, Uxía Esperón and Belinda Rodríguez. We thank all participants, clinicians, family doctors, researchers, and technicians for their work in participant enrollment and biospecimen and data management; Bent Ejertsen and Anne-Marie Genders for the recruitment and genetic counseling of participants; Alicia Barroso, Rosario Alonso and Guillermo Pita; Manoukian Siranoush, Bernard Peissel, Cristina Zanzottera, Milena Marian, Daniela Zaffaroni, Bernardo Bonanni, Monica Barile, Irene Feroce, Mariarosaria Calvello, Alessandra Veli, Riccardo Dolcetti, Giuseppe Giannini, Laura Papi, Gabriele Lorenzo Capone, Liliana Varesco, Viviana Gismondi, Maria Grazia Tibiletti, Daniela Furlan, Antonella Savarese, Alme Martayan, Stefania Tommasi, Brunella Pilato; the personnel of the Cogentech Cancer Genetic Test Laboratory, Milan, Italy; Ms. JoEllen Weaver and Dr. Betsy Bove; Marta Santamariña, Ana Blanco, Miguel Agudo, Uxía Esperón and Belinda Rodríguez. We thank all participants, clinicians, family doctors, researchers, and technicians for their contributions and commitment to the DKFZ study. Genetic Modifiers of Cancer Risk in BRCA1/2 MUNICATION Carriers (GEMO) study is a study from the National Cancer Genetics Network UNICANCER Genetic Group, France. We wish to pay a tribute to
Mendelian randomisation study of height and body mass index as modifiers… F Qian et al.

Olga M. Sinilnikova, who with Dominique Stoppa-Lyonnet initiated and coordinated GEMO until she sadly passed away on the 30 June 2014. The team in Lyon (Olga Sinilnikova, Mélanie Léoné, Laure Barjouh, Carole Vemy-Pierre, Sylvie Mazoyer, Francesca Damisola, Valérie Somin) managed the GEMO samples until the biological resource centre was transferred to Paris in December 2015 (Noura Mebirouk, Fabienne Lesueur, Dominique Stoppa-Lyonnet). We want to thank all the GEMO collaborating groups for their contributions to this study: the Clinical Follow Up Study led by Sara Dishon, the laboratory team led by Dr. Flavio Lejbkowicz, and the research field operations team led by Dr. Mila Pinchev; the investigators of the Australia New Zealand NRG Oncology group; members and participants in the Ontario Cancer Genetics Network; Leigha Senter, Kevin Sweet, Caroline Craven, Julia Cooper, and Michelle O'Connor; Yip Cheng Har, Nur Aishah Mohd Tab, Phuah See Yee, Norhashimah Hassan and all the research nurses, research assistants and doctors involved in the MyBcRa Study for assistance in patient recruitment, data collection and sample preparation; Philip Iau, Sng Jen-Hwei and Sharifah Nor Akmal for contributing samples from the Singapore Breast Cancer Study and the HJKM-HKL Study, respectively; the Meivag Comprehensive breast cancer centre team at the Sheba Medical Center; Christina Selikke; Åke Bog, Håkan Olsson, Helena Jernström, Karin Henriksson, Katja Harbst, Maria Soller, Ulf Kristoffersson; from Gothenburg Sahlgrenska University Hospital: Anna Olverholm, Margareta Nordling, Per Karlsson, Zakaria Einbergi; from Stockholm and Karolinska University Hospital: Anna von Wachenfeldt, Anneli Liljegren, Annika Lindblom, Brita Arver, Gisela Barbany Bastina, Johanna Rantalai; from Umeå University Hospital: Beatrice Melin, Christina Edwinsdotter Ardmon, Maria Emmanouel; from Uppsala University: Hans Ehrenrother, Marta Hellström Pigg, Richard Rosenquist; from Linköping University Hospital: Marie Stenmark-Askarmal, Sigrun Liedgren; Cecilia Zvocce, Qun Ni; Joyce Seldon and Lorna Kwan; Dr. Robert Nussbaum, Beth Crawford, Kate Loranger, Julie Mak, Nicola Stewart, Robin Lee, Arnie Blanco and Peggy Conrad and Salina Chan; Simon Gayther, Susan Ramus, Paul Pharaoh, Carole Pye, Patricia Harrington and Eva Woźniak; Geoffrey Lindeman, Marion Harris, Martin Delaytcky, Sarah Sawyer, Rebecca Dressen, and Ella Thompson for performing all DNA amplification.

ADDITIONAL INFORMATION
Supplementary information is available for this paper at https://doi.org/10.1038/s41416-019-0492-8.

Competing interests: G.P. received honoraria and grant from Pfizer, Roche, Novartis, Accord, AstraZeneca, Agen, Accord and Lilly. R.S. served on advisory board for Tesaro, Clavio, Astra Zeneca, Ethicon and Gennab, and speaker's bureau for Tesaro and Genentech. The other authors declare no competing interests.

Ethics approval and consent to participate: The current work and all contributing studies in CIMBA received approval from the local institutional review board or ethics committee. Written informed consent was provided by all of the participants participating in each individual CIMBA study. The institutional committees that approved individual studies are listed in Supplemental Materials.

Funding: CIMBA: the CIMBA data management and data analysis were supported by Cancer Research UK grants C12292/A20861, C12292/A11174. ACA is a Cancer Research UK Senior Cancer Research Fellow. G.P. received honoraria and grant from Pfizer, Roche, Novartis, Accord, AstraZeneca, Agen, Accord and Lilly. R.S. served on advisory board for Tesaro, Clavio, Astra Zeneca, Ethicon and Gennab, and speaker's bureau for Tesaro and Genentech. The other authors declare no competing interests.

Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial policies of the National Cancer Institute or any of the collaborating centres in the text reflect the views or
