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Height and Body Mass Index as Modifiers of Breast Cancer Risk in *BRCA1/2* Mutation Carriers: A Mendelian Randomization Study

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Abstract

Background: *BRCA1/2* mutations confer high lifetime risk of breast cancer, although other factors may modify this risk. Whether height or body mass index (BMI) modifies breast cancer risk in *BRCA1/2* mutation carriers remains unclear.
Methods: We used Mendelian randomization approaches to evaluate the association of height and BMI on breast cancer risk, using data from the Consortium of Investigators of Modifiers of *BRCA1/2* with 14 676 *BRCA1* and 7912 *BRCA2* mutation carriers, including 11 451 cases of breast cancer. We created a height genetic score using 586 height-associated variants and a BMI genetic score using 93 BMI-associated variants. We examined both observed and genetically determined height and BMI with breast cancer risk using weighted Cox models. All statistical tests were two-sided.
Results: Observed height was positively associated with breast cancer risk (HR = 1.09 per 10 cm increase, 95% confidence interval [CI] = 1.0 to 1.17; $P = 1.17$). Height genetic score was positively associated with breast cancer, although this was not statistically significant (per 10 cm increase in genetically predicted height, HR = 1.04, 95% CI = 0.93 to 1.17; $P = .47$). Observed BMI was inversely associated with breast cancer risk (per 5 kg/m^2 increase, HR = 0.94, 95% CI = 0.90 to 0.98; $P = .007$). BMI genetic score was also inversely associated with breast cancer risk (per 5 kg/m^2 increase in genetically predicted BMI, HR = 0.87, 95% CI = 0.76 to 0.98; $P = .02$). BMI was primarily associated with premenopausal breast cancer.
Conclusion: Height is associated with overall breast cancer and BMI is associated with premenopausal breast cancer in *BRCA1/2* mutation carriers. Incorporating height and BMI, particularly genetic score, into risk assessment may improve cancer management.

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Breast cancer is the most common cancer in women and a leading cause of cancer deaths globally (1). Inheritance of a *BRCA1* or *BRCA2* mutation is associated with an increased lifetime risk of breast cancer (2,3). However, penetrance of *BRCA1/2* mutations is likely modified by lifestyle, reproductive factors, and genetic variants (4–8). Multiple genes have been found to modify the association between *BRCA1/2* and breast cancer risk (9–11). Accurate breast cancer risk prediction in *BRCA1/2* mutation carriers is crucial in preventing morbidity and mortality, while optimizing primary and secondary prevention.

The relationship between anthropometric characteristics such as height or body mass index (BMI) and breast cancer risk has been extensively studied (12,13). Adult height was found to be positively associated with breast cancer risk (14). Higher BMI is positively associated with postmenopausal breast cancer, but inversely associated with premenopausal breast cancer (15). However, the associations of height and BMI with breast cancer risk in *BRCA1/2* mutation carriers remain unclear. Retrospective studies are subject to potential biases, whereas prospective studies are often underpowered.

Notably, both height and BMI have a strong genetic basis. Genome-wide association studies (GWAS) (16–18) have identified variants that are associated with either trait. In aggregate, these variants explain a sizable proportion of the variation in each trait.

Mendelian randomization (MR) is a method to assess the association between an exposure and a disease using genetic markers associated with the exposure as instrumental variables. Because genes are inherited randomly, MR can be used to minimize the effects of recall bias, reverse causation, measurement error, and residual confounding (19). The assumptions underlying MR include the following: genetic variants are associated with the exposure of interest, variants only affect the outcome through the exposure, and variants are weakly or not associated with confounders in the exposure-outcome pathway (20,21). A causal relationship between exposure and disease could be concluded if these assumptions are held. In this study, we used MR approaches to evaluate the association between height and BMI and breast cancer, using data from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), including 22 588 women, with 14 676 *BRCA1* and 7912 *BRCA2* mutation carriers.

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Methods

Information about CIMBA and genotyping protocols can be found in the Supplementary Methods (available online) and previous publications (9–11). All participants provided written informed consent in accordance with the local institutional review boards.

Single-Nucleotide Polymorphism Selection

Single-nucleotide polymorphisms (SNPs) associated with height and BMI were identified from the Genetic Investigation of Anthropometric Traits publications (16,17). SNPs achieving genome-wide statistical significance ($P < 5 \times 10^{-8}$) with height or BMI were eligible. We excluded SNPs with an imputation quality of less than 0.5. For height, we included 586 SNPs (85 genotyped) (Supplementary Table 1, available online). For BMI, we included 93 SNPs (12 genotyped) (Supplementary Table 2, available online).

Statistical Analysis

We calculated weighted genetic scores (GS) for height and BMI using methods described previously, based on a polygenic additive model (ie, ignoring interactions between variants) (14,22). We calculated each GS using the formulas

$$\mathrm{GS_{height}} = \sum_{i=1}^{586} \beta_i \mathrm{SNP_i} \quad \text{and} \quad \mathrm{GS_{BMI}} = \sum_{i=1}^{93} \beta_i \mathrm{SNP_i},$$

where β_i is the reported per-allele effect of the ith SNP for height and BMI (16,17) and $\mathrm{SNP_i}$ is the effect allele dosage (0, 1, 2) of the ith SNP. We rescaled GSs to calculate the genetically predicted height and BMI by performing linear regressions of observed height and BMI on the corresponding GS in noncases. For height, we obtained from the regression equation β_0 (intercept = 165.648) and β_1 (slope = 5.119). The corresponding values for BMI were β_0 (22.058) and β_1 (6.408). We used these values to calculate the scaled height-GS and BMI-GS using this equation: Scaled-GS = $\beta_0 + \beta_1$GS. We estimated the variation explained by each GS and the association between each GS and traditional breast cancer risk factors, using linear regressions for continuous variables and logistic regressions for categorical variable.

Next, we modeled height-GS and BMI-GS with breast cancer risk using weighted Cox models. The primary outcome was breast cancer diagnosis. Observations were censored at ovarian cancer diagnosis, prophylactic mastectomy/salpingo-oophorectomy, death, or end of follow-up, whichever came first. Time to event was computed from birth to age at breast cancer diagnosis or censoring. Mutation carriers were not randomly selected and those with breast cancer had a higher probability of being identified. To account for nonrandom sampling, we applied a weighted cohort approach (23). Weights were assigned based on observed incidence rates of breast cancer for *BRCA1/2* carriers (24). To account for interdependence between carriers from the same family, we used a robust sandwich variance estimation approach. Stratified analyses were performed by *BRCA1/2* or menopausal status. Menopausal status was modeled as a time-varying covariate: The variable was coded as premenopausal from birth until age at censoring and was switched to postmenopausal at the age of natural menopause or bilateral salpingo-oophorectomy. If age at natural menopause or bilateral salpingo-oophorectomy was missing, we imputed the mean age as 46 years, because the mean and median ages at natural menopause in this population were 46 and 48 years, respectively. These ages were broadly consistent with those from a prior registry study of mutation carriers (25). Imputing missing age at menopause as 50 did not materially change the results. The analyses were also adjusted for the first eight principal components (as a proxy for population structure and ethnicity), birth cohort, and country of enrollment.

We also examined the association between height and BMI with breast cancer by modeling individual height and BMI variants separately. We assessed the direct association between each SNP and height and BMI (β_{XG}) and its association with breast cancer risk (β_{YG}). β_{XG} for each SNP was extracted from prior GWAS and represents the per-allele effect on height or BMI. β_{YG} was calculated using multivariable-adjusted weighted Cox model for each SNP using data from CIMBA, ie, breast cancer $\sim \beta_{YG}X$ (where $X = 0, 1, 2$ for the allele corresponding to increased height or BMI), principal components, birth cohort, mutated gene, and country of enrollment. We statistically combined these two effect estimates to measure the association between height and BMI and breast cancer risk (β_{YX}) (26,27). The causal effect (β_{YX}) was calculated using the Wald estimator β_{YX}

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$= \beta_{YG}/\beta_{XG}$. The standard error for this estimate was estimated using the method proposed by Burgess (27):

$$SE_{YX} = \sqrt{\left(\frac{SE_{YG}}{\beta_{XG}}\right)^2}.$$

β_{YX} can be interpreted as the log hazard ratio (HR) for breast cancer per 1 unit increase in genetically determined height and BMI. We then combined the effects of individual height- and BMI-associated variants using an inverse-variance fixed-effects meta-analysis. We also used the Egger test to assess for possible pleiotropic effects of the variants (ie, the effects are not mediated via the exposure), one of the assumptions for MR (28).

In a subset of participants with observed height or BMI (34%), we performed a formal instrumental variable analysis to estimate the unbiased effect of height and BMI on breast cancer risk using two-stage residual inclusion regression (29). In stage 1, we conducted a linear regression of observed height or BMI on corresponding GS, principal components, birth cohort, country, mutation status, and residuals. In stage 2, we used a Cox model to fit breast cancer risk against height and BMI, birth cohort, country, mutation status, and residuals from stage 1. We performed 10 000 bootstraps to obtain the variance estimates.

Lastly, we examined the association between observed height and BMI and breast cancer risk in participants with measurements using weighted Cox models, adjusted for traditional breast cancer risk factors including birth cohort, menopausal status, age at menarche (continuous), and parity (continuous). BMI was reported at date of questionnaire (baseline), usually close to the date of genetic testing and recalled for young adulthood (age 18). The BMI-GS mentioned above was rescaled to BMI reported at baseline because previous GWAS were based on adult BMI.

The proportional hazards assumption was tested by adding an interaction term of age and either height-GS or BMI-GS. In models with menopausal status as the time-varying variable, test for heterogeneity by menopausal status was also a test for proportional hazard assumption. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and Stata 14.0 (StataCorp, College Station, TX). All statistical tests were two-sided and a *P* value less than .05 was considered statistically significant unless stated otherwise. For association tests of individual SNPs, Bonferroni adjustment was conducted.

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

Variable	*BRCA1* carriers N = 14 676	*BRCA2* carriers N = 7912
Case participants, n	7360	4091
Year of birth, median (IQR)	1956 (1948–1964)	1954 (1945–1961)
Age at diagnosis, mean (SD), y	41.1 (9.3)	44.2 (10.0)
Control participants, n	7316	3821
Year of birth, median (IQR)	1963 (1953–1972)	1962 (1950–1971)
Age at censoring, mean (SD), y	42.0 (12.5)	44.0 (13.5)
Ethnicity, n (%)		
Caucasian, not otherwise specified	13 435 (91.5)	7126 (90.1)
Ashkenazi Jewish	1241 (8.5)	786 (9.9)
Height in cm, n	4502	3155
Mean (SD)	164.8 (6.8)	164.5 (6.9)
Weight at date of questionnaire in kg, n	4436	3133
Mean (SD)	68.1 (13.9)	69.0 (14.5)
BMI at date of questionnaire in kg/m^2, n	4401	3115
Mean (SD)	25.1 (5.1)	25.6 (5.2)
Weight in early adulthood in kg, n	3152	2296
Mean (SD)	57.6 (9.2)	57.9 (9.6)
BMI in early adulthood in kg/m^2, n	3134	2283
Mean (SD)	21.2 (3.3)	21.4 (3.3)
Age at menarche in years, n	4425	3034
Mean (SD), y	13.0 (1.5)	13.0 (1.5)
Parous, n (%)		
Yes	3914 (77.8)	2681(79.7)
No	1117 (22.2)	682 (20.3)
Age at first live birth in years, n	3711	2579
Mean (SD), y	25.3 (4.9)	25.3 (4.9)
Menopausal status, n (%)		
Premenopausal	2330 (47.4)	1610 (46.4)
Postmenopausal	2588 (52.6)	1858 (53.6)
Age at menopause, mean (SD), y	44.7 (6.0)	45.6 (6.0)

*BMI = body mass index; CIMBA = Consortium of Investigators of Modifiers of BRCA1/2; IQR = interquartile range.

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of the 22 588 participants (14 676 *BRCA1* and 7912 *BRCA2* mutation carriers) with genotype information. There were 11 451 cases of breast cancer in the overall consortium. The mean age of individuals at the time of breast cancer diagnosis (cases) was similar to the age of individuals who did not develop breast cancer at the time of censoring (controls). However, the birth year of cases tended to be earlier than controls. Height was available in 7657 participants (4502 *BRCA1* carriers and 3155 *BRCA2* carriers) and BMI at date of questionnaire was available in 7516 participants (4401 *BRCA1* carriers and 3115 *BRCA2* carriers).

Height Analysis

Observed height was positively associated with breast cancer risk (HR per 10 cm = 1.09, 95% CI = 1.02 to 1.17, *P* = .02) (Table 2). In stratified analysis, we found that height was a stronger predictor of risk in *BRCA2* carriers (HR = 1.17, 95% CI = 1.04 to 1.31) than in *BRCA1* carriers (HR = 1.06, 95% CI = 0.97 to 1.16), but the interaction was not statistically significant. The country-specific estimates showed low levels of heterogeneity (Supplementary Figure 1A, available online).

We found that height-GS was strongly associated with observed height by case/control and mutation status (all $P < 10^{-93}$) (Table 3). The height-GS explained 13.4% of the variation in height (Supplementary Figure 2A, available online). As shown in Supplementary Figure 3A (available online), there was a strong correlation ($r = 0.44$) between the estimated effect size for individual variants in our study and those reported in previous GWAS. Height-GS was positively associated with weight, baseline age, and age at menarche but the associations were weak.

Height-GS was positively associated with breast cancer risk with an effect weaker than that for observed height, although it was not statistically significant (HR = 1.04 per 10-cm increase in genetically predicted height, 95% CI = 0.93 to 1.17; *P* = .47) (Table 4). Effect was not different when stratified for menopausal or mutation status.

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

	N/events	HR (95% CI)	P*
Per 10-cm increase in observed height			
All participants (confounding adjustment sequentially)			
Unadjusted	7657/3653	1.14 (1.06 to 1.22)	2.0×10^{-4}
Adjusted for principal components	7657/3653	1.15 (1.07 to 1.23)	1.6×10^{-4}
Additionally adjusted for country	7657/3653	1.17 (1.09 to 1.26)	1.3×10^{-4}
Additionally adjusted for birth cohort	7657/3653	1.09 (1.01 to 1.17)	.02
Additionally adjusted for mutation status	7657/3653	1.09 (1.02 to 1.17)	.01
Additionally adjusted for menopausal status	7657/3653	1.09 (1.02 to 1.17)	.02
Additionally adjusted for parity and age at menarche	7090/3383	1.10 (1.02 to 1.18)	.01
By mutation status†			
BRCA1 carrier	4502/2154	1.06 (0.97 to 1.16)	.19
BRCA2 carrier	3155/1499	1.17 (1.04 to 1.31)	.007
$P_{interaction}$			.18
By menopausal status‡			
Premenopausal	7657/2197	1.10 (1.01 to 1.20)	.03
Postmenopausal	3076/1402	1.07 (0.95 to 1.19)	.26
$P_{interaction}$‡			.64

*P values were calculated from weighted Cox models. All *P* values are two-sided. HR = hazard ratio; CI = confidence interval.
†Adjusted for principal components, birth cohort, country of enrollment, and menopausal status.
‡Adjusted for principal components, mutation status, birth cohort, and country of enrollment.

Table 3. Associations of the height genetic score (height-GS) with height and traditional breast cancer risk factors*

Variable	Number of participants	Summary effect	SE	P†	% variation explained
Measured height, cm					
All participants	7657	1.012	0.029	7.0×10^{-241}	13.4
BRCA1 carriers	4502	1.025	0.038	3.8×10^{-149}	14.0
BRCA2 carriers	3155	0.996	0.047	2.5×10^{-94}	12.6
Case participants	3653	1.028	0.041	2.6×10^{-128}	14.7
Control participants	4004	1.000	0.042	1.1×10^{-116}	12.3
Traditional risk factors					
BMI, kg/m^2	7516	−0.010	0.024	.66	–
Weight, kg	7569	0.813	0.065	2.7×10^{-35}	–
Age at baseline, y	8578	0.123	0.036	7.3×10^{-4}	–
Age at menarche, y	7459	0.028	0.007	9.3×10^{-5}	–
Parous, yes vs no	8394	−0.010	0.011	.35	–
Age at first live birth, y	6290	−0.014	0.025	.58	–
Menopausal status, pre vs post	8386	0.011	0.009	.20	–
Age at menopause, y	4336	−0.082	0.037	.03	–

*Regression coefficient is presented for continuous variables and natural log-scale odds ratio for binary variables, per unit increase of the H-GS. BMI = body mass index; SE = standard error.
†P values were calculated from linear regression models for all variables except for parity and menopausal status (logistic regression models). All *P* values are two-sided.

When combining the breast cancer risk estimates for individual height variant using inverse-variance meta-analysis, the result was similar (HR = 1.05, 95% CI = 0.93 to 1.19; P = .42) (Table 4). There was low heterogeneity among SNPs (I^2=17.0%). The Egger test for small-study effects was not statistically significant (P = .61, Supplementary Figure 4A, available online), so we failed to reject the assumption of no pleiotropic effects for MR analysis. The two-stage residual inclusion analysis found a similar risk estimate to that for observed height (HR = 1.09, 95% CI = 0.93 to 1.27; P = .27).

BMI Analysis

For reported BMI at date of questionnaire, we found an inverse association with breast cancer risk after multivariable adjustment (HR per 5-kg/m^2 increase = 0.94, 95% CI = 0.90 to 0.98; P = .007) (Table 5). The inverse association was stronger in *BRCA2* vs *BRCA1* carriers [HR = 0.90 (95% CI = 0.84 to 0.97) vs 0.96 (95% CI = 0.91 to 1.01)] and for premenopausal vs postmenopausal breast cancer [HR = 0.92 (95% CI = 0.87 to 0.97) vs 0.97 (95% CI: 0.91 to 1.04), but there was no statistically significant interaction ($P_{interaction} > .05$ for each comparison). We found a stronger inverse association of BMI in young adulthood with breast cancer risk (HR = 0.83, 95% CI = 0.76 to 0.90; $P = 2.1 \times 10^{-5}$). The country-specific estimates showed moderate levels of heterogeneity (Supplementary Figure 1B, available online).

BMI-GS was strongly associated with reported BMI at date of questionnaire among controls and cases (each $P < 10^{-14}$) (Table 6). BMI-GS accounted for 2.6% of the variation in BMI at date of questionnaire (Supplementary Figure 2B, available online). We found a strong correlation between the effect on BMI by individual variants in prior reported GWAS and in CIMBA

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Table 4. Association of height genetic score and breast cancer risk in 22 588 participants in CIMBA, per 10-cm increase in genetically predicted height

Breast cancer group	N/events	HR (95% CI)	P*	Heterogeneity (I^2)
Height-GS†				
All participants (confounding adjustment sequentially)				
Unadjusted	22 588/11 451	1.11 (1.00 to 1.23)	.05	–
Adjusted for principal components	22 588/11 451	1.04 (0.93 to 1.17)	.48	–
Additionally adjusted for country	22 588/11 451	1.03 (0.92 to 1.16)	.57	–
Additionally adjusted for birth cohort	22 588/11 451	1.04 (0.92 to 1.16)	.56	–
Additionally adjusted for mutation status	22 588/11 451	1.04 (0.93 to 1.17)	.45	–
Additionally adjusted for menopausal status	22 588/11 451	1.04 (0.93 to 1.17)	.47	
By mutation status‡				
BRCA1 carrier	14 676/7360	1.03 (0.91 to 1.18)	.62	–
BRCA2 carrier	7912/4091	1.07 (0.87 to 1.32)	.50	–
$P_{interaction}$			.95	
By menopausal status§				
Premenopausal	22 588/7410	1.09 (0.96 to 1.24)	.20	–
Postmenopausal	8459/3926	0.95 (0.79 to 1.13)	.55	–
$P_{interaction}$			.18	
Meta-analysis method§				
All participants	22 588/11451	1.05 (0.93 to 1.19)	.42	17.0%
BRCA1 carrier	14 676/7360	1.04 (0.90 to 1.20)	.57	11.8%
BRCA2 carrier	7912/4091	1.09 (0.87 to 1.36)	.45	6.6%
$P_{interaction}$			.75	
Two-stage residual inclusion method				
All participants	7657/3653	1.09 (0.93 to 1.27)	.27	–
BRCA1 carrier	4502/2154	1.16 (0.96 to 1.40)	.13	–
BRCA2 carrier	3155/1499	1.05 (0.80 to 1.37)	.74	–

*P values were calculated using weighted Cox models. All P values are two-sided. CIMBA = Consortium of Investigators of Modifiers of BRCA1/2; H-GS = height genetic score; HR = hazard ratio; CI = confidence interval.
†H-GS combining 586 height-associated single-nucleotide polymorphisms (SNPs).
‡Adjusted for principal components, birth cohort, country of enrollment, and menopausal status.
§Adjusted for principal components, mutation status, birth cohort, and country of enrollment.
||Hazard ratios were calculated using inverse-variance meta-analysis and rescaled to the corresponding units by calculating the height measurements per z score among controls. Effect estimates for breast cancer for each SNP were calculated from weighted Cox model adjusting for principal components, birth cohort, country of enrollment, menopausal status, and mutation status.

($r = 0.52$, Supplementary Figure 3B, available online). Similarly, the BMI-GS was associated with reported BMI in young adulthood, with stronger effects among controls ($P < 10^{-15}$, $r^2 = 2.3\%$). The BMI-GS was positively associated with height and inversely associated with age at menarche.

In the analysis of BMI-GS and breast cancer risk, each 5-kg/m^2 increment in genetically predicted BMI was associated with a 13% reduction in breast cancer risk (HR = 0.87, 95% CI = 0.76 to 0.98; $P = .02$) (Table 7). The association was slightly stronger among *BRCA2* mutation carriers and for premenopausal breast cancer, although there was no statistically significant interaction ($P_{interaction} > .05$ for each).

When we statistically combined the effect of individual BMI variants on breast cancer risk, we found a similar association (HR = 0.87, 95% CI = 0.76 to 0.98, $P = .03$) (Table 7). There was low overall heterogeneity ($I^2 = 3.5\%$). The Egger test was not statistically significant ($P = .44$, Supplementary Figure 4B, available online), suggesting that pleiotropic effects may not exist. The two-stage residual inclusion method yielded similar results (HR = 0.86, 95% CI = 0.70 to 1.07; $P = .18$).

Individual Height- and BMI-Associated Variants

Of the 586 height-related variants, 50 were found to be associated with breast cancer risk at *P* less than .05 (Table 8). Of the 93 BMI-related variants, seven were associated with breast cancer risk. One SNP (rs10744956) was statistically significant after Bonferroni adjustment.

Discussion

Using data from a large international study of women with a *BRCA1/2* mutation and analyzed by several MR methods, we found that both observed and genetically predicted BMI were associated with a reduced risk of breast cancer whereas observed and genetically predicted height were associated with an increased risk of breast cancer.

We found that each 10-cm increment in observed height was associated with a 9% increase in breast cancer risk, whereas a 10-cm increment in genetically predicted height was associated with a 4%–8% increase in risk in *BRCA1/2* mutation carriers. Our findings are broadly consistent with previous studies in the general population (14,20). A recent meta-analysis of prospective studies of height reported a relative risk (RR) of 1.17 per 10-cm increase, and the MR analysis using 168 height-associated variants found an odds ratio (OR) of 1.22 per 10-cm increase in genetically predicted height (14). A subsequent MR analysis with 423 height-associated variants reported a similar result (OR = 1.19) (20). One study of height in 719 *BRCA1/2* mutation carriers showed a statistically nonsignificant positive relationship with premenopausal breast cancer and a statistically significant positive relationship with

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Table 5. Association of BMI and breast cancer risk using observed body mass index (BMI)

Breast cancer group	N/events	HR (95% CI)	P*
Per 5-kg/m^2 increase in BMI at date of questionnaire			
All participants (confounding adjustment sequentially)			
Unadjusted	7516/3594	0.92 (0.88 to 0.97)	4.3×10^{-4}
Adjusted for principal components	7516/3594	0.93 (0.89 to 0.97)	7.3×10^{-4}
Additionally adjusted for country	7516/3594	0.92 (0.88 to 0.96)	3.1×10^{-4}
Additionally adjusted for birth cohort	7516/3594	0.94 (0.90 to 0.98)	.003
Additionally adjusted for mutation status	7516/3594	0.95 (0.91 to 0.99)	.01
Additionally adjusted for menopausal status	7516/3594	0.94 (0.90 to 0.98)	.007
Additionally adjusted for parity and age at menarche	6964/3331	0.93 (0.89 to 0.98)	.003
By mutation status†			
BRCA1 carrier	4401/2114	0.96 (0.91 to 1.01)	.11
BRCA2 carrier	3115/1480	0.90 (0.84 to 0.97)	.003
$P_{interaction}$‡			.26
By menopausal status§			
Premenopausal	7516/2153	0.92 (0.87 to 0.97)	.001
Postmenopausal	3029/1389	0.97 (0.91 to 1.04)	.40
$P_{interaction}$‡			.14
Per 5-kg/m^2 increase in BMI in young adulthood			
All participants (confounding adjustment sequentially)			
Unadjusted	5417/2520	0.83 (0.76 to 0.91)	3.1×10^{-5}
Adjusted for principal components	5417/2520	0.83 (0.76 to 0.91)	5.4×10^{-5}
Additionally adjusted for country	5417/2520	0.81 (0.74 to 0.88)	2.8×10^{-6}
Additionally adjusted for birth cohort	5417/2520	0.81 (0.74 to 0.88)	1.8×10^{-6}
Additionally adjusted for mutation status	5417/2520	0.83 (0.76 to 0.90)	1.7×10^{-5}
Additionally adjusted for menopausal status	5417/2520	0.83 (0.76 to 0.90)	2.1×10^{-5}
Additionally adjusted for parity and age at menarche	5210/2436	0.82 (0.75 to 0.90)	2.7×10^{-5}
By mutation status†			
BRCA1 carrier	3134/1462	0.87 (0.78 to 0.97)	.01
BRCA2 carrier	2283/1058	0.74 (0.63 to 0.85)	4.5×10^{-5}
$P_{interaction}$			.06
By menopausal status‡			
Premenopausal	5417/1519	0.85 (0.78 to 0.94)	.002
Postmenopausal	2181/977	0.79 (0.69 to 0.91)	.001
$P_{interaction}$			.35

*P values calculated using weighted Cox models. All P values are two-sided; HR = hazard ratio; CI = confidence interval.
†Adjusted for principal components, birth cohort, country of enrollment, and menopausal status.
‡Adjusted for principal components, mutation status, birth cohort, and country of enrollment.

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postmenopausal breast cancer (30). Thus, height is likely a predictor for breast cancer risk in *BRCA1/2* mutation carriers and the general population.

Several studies have examined the relationship between BMI and breast cancer risk in *BRCA1/2* carriers (5,30,31) with inconsistent findings, possibly because of limited sample size. In the general population, every 5-kg/m^2 increase in BMI was positively associated with postmenopausal breast cancer (RR = 1.12) and inversely associated with premenopausal breast cancer (RR = 0.92) (15). We found that for *BRCA1/2* carriers observed BMI at date of questionnaire was inversely associated with premenopausal breast cancer but was not statistically significantly associated with postmenopausal breast cancer. Our MR analysis found that a 5-kg/m^2 increase in genetically predicted BMI was associated with a 16% reduction in premenopausal breast cancer. Similarly, a MR analysis in the general population found that each 5-kg/m^2 increase in genetically predicted BMI had an OR of 0.65, with consistent effects across menopausal status (22). Altogether, there is strong evidence for the protective effect of higher BMI on premenopausal breast cancer in both the general population and *BRCA1/2* mutation carriers. Unlike with MR, the association with observed BMI is potentially subject to recall bias or reverse causation. Conversely, BMI-GS may only capture early-life body weight and cannot predict weight changes later in life, which are influenced by lifestyle factors. The association between BMI at age 18 and premenopausal breast cancer (HR = 0.83) was quite similar to that for BMI-GS and premenopausal breast cancer (HR = 0.84), supporting the notion that early-life BMI/adiposity play a role in breast carcinogenesis. The seemingly inconsistent findings for observed BMI and postmenopausal breast cancer might reflect differences in study populations and methodology. Our study may be underpowered to assess the impact of observed and genetically predicted BMI on postmenopausal breast cancer, given the smaller number of cases. An ongoing prospective consortium of *BRCA1/2* carriers may clarify the relationship between BMI and postmenopausal breast cancer. Hence higher BMI, particularly genetically predicted BMI, is associated with lower risk of premenopausal breast cancer, although the relationship with postmenopausal breast cancer remains inconclusive.

There are several potential mechanisms for the associations between height or BMI and breast cancer. For height, early-life exposures including nutritional and hormonal status could affect obtained height and account for the association between height and breast cancer risk (32,33). The insulin-like growth factor (IGF) signaling pathway has been implicated in the

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Table 6. Associations of the body mass index genetic score (BMI-GS) with BMI and traditional breast cancer risk factors*

Variable	Number of participants	Summary effect*	SE	P†	% variation explained
Observed BMI at date of questionnaire, kg/m^2					
All participants	7516	0.832	0.059	2.8×10^{-44}	2.6
BRCA1 carrier	4401	0.786	0.076	9.9×10^{-25}	2.4
BRCA2 carrier	3115	0.903	0.094	2.1×10^{-21}	2.9
Case participants	3594	0.651	0.083	6.9×10^{-15}	1.7
Control participants	3922	1.000	0.084	3.3×10^{-32}	3.5
Premenopausal control participants	2246	0.941	0.110	2.6×10^{-17}	3.1
Postmenopausal control participants	1441	1.113	0.139	3.0×10^{-15}	4.2
Observed BMI in young adulthood, kg/m^2					
All participants	5417	0.794	0.083	2.3×10^{-21}	1.6
BRCA1 carrier	3134	0.770	0.108	1.2×10^{-12}	1.6
BRCA2 carrier	2283	0.830	0.131	2.8×10^{-10}	1.7
Case participants	2520	0.540	0.110	1.0×10^{-6}	0.9
Control participants	2897	1.000	0.122	3.3×10^{-16}	2.3
Premenopausal control participants	1589	0.995	0.170	5.3×10^{-9}	2.1
Postmenopausal control participants	1100	1.044	0.193	8.2×10^{-8}	2.6
Traditional risk factors					
Height	7657	0.319	0.079	5.4×10^{-5}	–
Age at baseline, y	8578	−0.020	−0.020	.79	–
Age at menarche, y	7459	−0.090	0.018	5.0×10^{-7}	–
Parous, yes vs no	8394	0.024	0.027	.38	–
Age at first live birth, y	6290	−0.113	0.063	.07	–
Menopausal status, pre vs post	8386	−0.019	0.022	.39	–
Age at menopause, y	4336	−0.172	0.093	.06	–

*Regression coefficient is presented for continuous variables and natural log-scale odds ratio for binary variables, per unit increase of the weighted BMI genetic score. SE = standard error.

†*P* values calculated from linear regression models for all variables except for parity and menopausal status (logistic regression models). All *P* values are two-sided.

pathogenesis of multiple malignancies, with possibly stronger effects on premenopausal breast cancer (34,35). Recent investigations have also implicated the *LIN28B–let-7* microRNA pathway, which affects adult height, mammalian body size, and carcinogenesis (36–38). Furthermore, potential mechanisms that could account for the association between BMI and reduced risk of breast cancer include circulating IGF-1 (15), greater likelihood of having anovulatory cycles, and lower circulating levels of estradiol/
progesterone (39).

Several SNPs included in the present analysis were reported to be statistically significantly associated with breast cancer risk in the general population. Guo et al. (22) reported rs7903146 near *TCF7L2* (OR = 0.96) and rs1558902 (OR = 0.93) near *FTO*. Our findings were similar. Interestingly, rs7903146 is in weak linkage disequilibrium ($r^2 = 0.45$) with rs7904519 near *TCF7L2*, which was reported in a previous GWAS (40). Moreover, rs1558902 was in strong linkage disequilibrium ($r^2 = 0.92$) with rs17817449 near *FTO* (40,41).

The strengths of our study include a large sample size, inclusion of numerous height and BMI variants, an MR approach that reduces confounding, and consistent findings between observed and genetically predicted phenotypes. Our study has several limitations. Observed height and BMI for breast cancer cases were typically measured approximiately 5–6 years after initial diagnosis. Whereas height is unlikely to be affected by breast cancer diagnosis, changes in weight after diagnosis may affect the relationship between observed BMI and breast cancer risk. The height-GS explained 13.4% of height variation, compared with 15.9% in previous GWAS (17). The BMI-GS accounted for 2.6% of BMI variation, compared to 2.7% in previous GWAS (16,17). Although both GSs had sufficient strength to be valid instrumental variables (*F* statistic >> 10), they are not very strong, leading to wide CIs in the MR analysis. Although the GSs were correlated with some breast cancer risk factors, these associations were much weaker compared with height or BMI, suggesting minimal residual confounding and upholding MR assumptions. Another limitation is that our study only included women of European ancestry, which limits generalizability to women of other racial/ethnic groups.

Our study suggests that for *BRCA1/2* mutation carriers, a higher BMI is associated with lower risk of premenopausal breast cancer, whereas greater height may be associated with increased risk of overall breast cancer. The inconsistent findings between observed and genetically predicted BMI and postmenopausal breast cancer warrants future studies. These findings may have implications for risk stratification to help carriers and their physicians to decide age-appropriate risk-tailored interventions, including increased surveillance and prophylactic surgeries. Future studies could elucidate the biological mechanisms underlying these associations.

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Table 7. Association of body mass index genetic score (BMI-GS) and breast cancer risk among 22 588 participants in CIMBA, per 5-kg/m^2 increase in genetically predicted BMI

Breast cancer group	N/events	HR (95% CI)	P*	Heterogeneity (I^2)
BMI-GS†				
All participants (confounding adjustment sequentially)				
Unadjusted	22 588/11 451	0.93 (0.81 to 1.05)	.24	
Adjusted for principal components	22 588/11 451	0.89 (0.78 to 1.01)	.07	
Additionally adjusted for country	22 588/11 451	0.90 (0.79 to 1.03)	.13	
Additionally adjusted for birth cohort	22 588/11 451	0.88 (0.77 to 0.999)	.049	
Additionally adjusted for mutation status	22 588/11 451	0.88 (0.78 to 0.99)	.04	
Additionally adjusted for menopausal status	22 588/11 451	0.87 (0.76 to 0.98)	.02	
By mutation status‡				
BRCA1 carrier	14 676/7360	0.88 (0.76 to 1.02)	.09	
BRCA2 carrier	7912/4091	0.83 (0.65 to 1.05)	.11	
$P_{interaction}$			.63	
By menopausal status§				
Premenopausal	22 588/7410	0.84 (0.73 to 0.98)	.02	
Postmenopausal	8459/3926	0.89 (0.72 to 1.09)	.26	
$P_{interaction}$			.68	
Meta-analysis method‖				
All participants	22 588/11 451	0.87 (0.76 to 0.98)	.03	3.5%
BRCA1 carrier	14 676/7360	0.88 (0.76 to 1.03)	.10	15.7%
BRCA2 carrier	7912/4091	0.82 (0.65 to 1.04)	.10	0.0%
$P_{interaction}$			.63	
Two-stage residual inclusion method				
All participants	7516/3594	0.86 (0.70 to 1.07)	.18	–
BRCA1 carrier	4401/2114	0.93 (0.69 to 1.23)	.61	–
BRCA2 carrier	3115/1480	0.82 (0.61 to 1.12)	.23	–

* P values were calculated using weighted Cox models. All P values are two-sided. CIMBA = Consortium of Investigators of Modifiers of BRCA1/2; SE = standard error; HR = hazard ratio; CI = confidence interval.

†BMI-GS was constructed by combining 93 BMI-associated single-nucleotide polymorphisms (SNPs).

‡Adjusted for principal components, birth cohort, country of enrollment, and menopausal status.

§Adjusted for principal components, mutation status, birth cohort, and country of enrollment.

‖Hazard ratios were calculated using inverse-variance meta-analysis and rescaled to the corresponding units by calculating the BMI measurements per z score among controls. Effect estimates for breast cancer for each SNP were calculated from weighted Cox model adjusting for principal components, birth cohort, country of enrollment, menopausal status, and mutation status.

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Table 8. Height or body mass index (BMI) single-nucleotide polymorphisms (SNPs) statistically significantly associated ($P < .05$) with breast cancer risk in CIMBA

Rsid	Chromosome	Position	Nearest gene	Reference allele in CIMBA	Effect allele in CIMBA	Effect allele frequency in CIMBA	Imputation quality*	Association with breast cancer in CIMBA		
								HR†	SE	P‡
Height										
rs10744956	15	51 269 629	*AP4E1*	A	G	0.80	0.98	0.096	0.023	3×10^{-5}
rs7740107	6	130 374 461	*L3MBTL3*	T	A	0.75	1	0.081	0.021	1×10^{-4}
rs10995319	10	52 762 887	*PRKG1*	T	C	0.23	0.96	0.075	0.022	6×10^{-4}
rs8058684	16	53 515 118	*RBL2*	G	A	0.32	1	0.061	0.019	.001
rs11049611	12	28 600 244	*CCDC91*	C	T	0.28	1	−0.065	0.020	.002
rs8103992	19	19 665 643	*PBX4*	A	C	0.78	0.98	−0.064	0.022	.004
rs11618507	13	30 172 751	*SLC7A1*	G	T	0.20	1	0.061	0.023	.007
rs11244750	10	127 673 877	*FANK1*	C	T	0.35	0.83	0.055	0.021	.009
rs7701414	5	131 585 958	*PDLIM4*	A	G	0.46	1	0.047	0.018	.01
rs7733195	5	172 994 624	*FAM44B*	G	A	0.37	1	0.049	0.019	.01
rs2306694	12	56 680 636	*CS*	A	G	0.06	1	0.096	0.038	.01
rs6435143	2	203 194 256	*NOP5/NOP*	A	C	0.56	0.84	0.050	0.020	.01
rs2284746	1	17 306 675	*MFAP2*	C	G	0.50	0.84	−0.049	0.020	.01
rs1797625	3	112 826 415	*C3orf17*	A	T	0.36	0.91	−0.049	0.020	.01
rs10495098	1	218 516 310	*TGFB2*	G	T	0.41	0.84	−0.051	0.021	.01
rs301901	5	37 046 626	*NIPBL*	A	G	0.45	0.93	−0.046	0.019	.02
rs42039	7	92 244 422	*CDK6*	C	T	0.26	1	0.051	0.021	.02
rs1576900	9	18 629 792	*ADAMTSL1*	G	A	0.30	0.91	0.048	0.020	.02
rs891088	19	7 184 762	*INSR*	A	G	0.27	0.83	0.052	0.022	.02
rs273945	7	137 611 566	*CREB3L2*	A	C	0.58	1	−0.042	0.018	.02
rs2682587	19	44 082 429	*XRCC1*	C	A	0.18	1	0.053	0.023	.02
rs1257763	9	96 893 945	*PTPDC1*	A	G	0.96	0.72	−0.118	0.053	.03
rs2888877	7	92 228 400	*CDK6*	T	C	0.79	0.96	−0.050	0.022	.03
rs8042424	15	101 762 539	*CHSY1*	C	T	0.24	0.82	−0.052	0.024	.03
rs7716219	5	54 955 071	*SLC38A9*	T	C	0.70	0.97	−0.044	0.020	.03
rs7727731	5	64 674 446	*ADAMTS6*	C	T	0.12	0.67	−0.076	0.035	.03
rs16964211	15	51 530 495	*CYP19A1*	G	A	0.06	0.99	−0.085	0.040	.03
rs11880992	19	2 176 403	*DOT1L*	G	A	0.42	0.95	−0.040	0.019	.03
rs2302580	4	8 608 634	*CPZ*	C	T	0.44	1	−0.040	0.019	.03
rs12538407	7	23 521 316	*IGF2BP3*	A	G	0.39	0.99	0.040	0.019	.03
rs2300921	3	185 651 001	*SFRS10*	T	C	0.41	0.98	0.041	0.019	.03
rs897080	2	44 774 202	*C2orf34*	C	T	0.79	0.90	−0.050	0.024	.03
rs4357716	11	69 163 161	*MYEOV*	C	T	0.14	1	0.055	0.026	.03
rs11659752	18	77 222 862	*NFATC1*	T	G	0.30	0.82	−0.045	0.021	.04
rs2166898	2	121 612 659	*GLI2*	G	A	0.17	0.55	0.067	0.032	.04
rs6020202	20	48 634 821	*SNAI1*	G	A	0.24	1	0.045	0.022	.04
rs3760318	17	29 247 715	*CENTA2*	G	A	0.37	1	−0.039	0.019	.04
rs6746356	2	174 815 898	*SP3*	A	C	0.24	0.79	0.050	0.024	.04
rs9428104	1	118 855 587	*SPAG17*	A	G	0.75	1	0.044	0.021	.04
rs2834442	21	35 690 786	*KCNE2*	T	A	0.66	0.98	−0.040	0.019	.04
rs1546391	3	114 697 457	*ZBTB20*	C	G	0.09	0.97	−0.069	0.033	.04
rs12926008	16	2 488 211	*CCNF*	T	C	0.65	0.53	0.054	0.026	.04
rs2123731	19	4 929 473	*UHRF1*	A	G	0.27	0.70	−0.049	0.024	.04
rs2289195	2	25 463 483	*DNMT3A*	G	A	0.41	0.65	0.046	0.023	.04
rs16834765	1	32 371 442	*PTP4A2*	C	T	0.05	0.82	0.091	0.045	.04
rs10958476	8	57 095 808	*PLAG1*	T	C	0.20	1	0.045	0.022	.045
rs17369123	1	172 355 841	*DNM3*	C	T	0.16	0.98	0.049	0.025	.046
rs1415701	6	130 345 835	*L3MBTL3*	G	A	0.26	1	0.041	0.021	.047
rs11152213	18	57 852 948	*MC4R*	A	C	0.23	0.99	−0.043	0.022	.047
rs4802134	19	38 346 685	*SIPA1L3*	A	G	0.75	1	−0.041	0.021	.049
BMI										
rs13107325	4	103 188 709	*SLC39A8*	C	T	0.09	0.76	0.101	0.037	.007
rs10182181	2	25 150 296	*ADCY3*	A	G	0.45	0.64	−0.056	0.023	.02
rs7903146	10	114 758 349	*TCF7L2*	C	T	0.30	1	0.044	0.020	.03

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Table 8. (continued)

Rsid	Chromosome	Position	Nearest gene	Reference allele in CIMBA	Effect allele in CIMBA	Effect allele frequency in CIMBA	Imputation quality*	Association with breast cancer in CIMBA		
								HR†	SE	P‡
rs9925964	16	31 129 895	*KAT8*	A	G	0.39	0.99	−0.040	0.019	.03
rs4740619	9	15 634 326	*C9orf93*	T	C	0.46	0.97	0.040	0.019	.03
rs1558902	16	53 803 574	*FTO*	T	A	0.42	1.00	−0.038	0.018	.04
rs2207139	6	50 845 490	*TFAP2B*	A	G	0.16	0.99	0.049	0.024	.04

*Imputation quality of 1 indicates genotyped SNPs. Rsid = Reference SNP cluster ID; CIMBA = Consortium of Investigators of Modifiers of BRCA1/2; HR = log hazard ratio; SE = standard error.

†Per-allele association with breast cancer was adjusted for principal components, birth cohort, menopausal status, age at menopause, country of enrollment, and mutation status in weighted Cox models.

‡*P* values were calculated using weighted Cox models. All *P* values are two-sided.

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