Height and body mass index as modifiers of breast cancer risk in 22,588 carriers of *BRCA1* or *BRCA2* mutations: A Mendelian randomization study

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Abstract

Background *BRCA1/2* mutations confer high lifetime risk of breast cancer, other factors may modify this risk. Whether height or body mass index (BMI) modify 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 7,912 *BRCA2* mutation carriers, including 11,451 cases of breast cancer. 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. We examined both observed and genetically-determined height and BMI with breast cancer risk using weighted-Cox models.

Results Observed height was positively associated with breast cancer risk (hazard ratio [HR]: 1.09 per 10 cm increase, 95% confidence interval [CI]: 1.02–1.17; *P*=0.016). Height-GS was positively associated with breast cancer, though this was not statistically significant (HR: 1.04 per 10 cm increase in genetically predicted height, 95% CI: 0.93–1.17; *P*=0.47). Observed BMI was inversely associated with breast cancer risk (HR: 0.94 per 5 kg/m^2 increase, 95% CI: 0.90–0.98; *P*=0.007). BMI-GS was also inversely associated with breast cancer risk (HR: 0.87 per 5 kg/m^2 increase in genetically predicted BMI, 95% CI: 0.76–0.98; *P*=0.023). 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 GS, into risk assessment may improve cancer management.

Introduction

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, while 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 significant percent 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 (IVs). Since 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: 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 employed 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 7,912 *BRCA2* mutation carriers.

Methods

Information about CIMBA and genotyping protocols can be found in the Supplementary Methods and previous publications [9-11].

SNP Selection

SNPs associated with height and BMI were identified from the Genetic Investigation of Anthropometric Traits publications [16,17]. SNPs achieving genome-wide significance ($P<5\times10^{-8}$) with height or BMI were eligible. We excluded SNPs with an imputation quality<0.5. For height, we included 586 SNPs (85 genotyped) (**Supplementary Table 1**). For BMI, we included 93 SNPs (12 genotyped) (**Supplementary Table 2**).

Statistical Analysis

We calculated weighted-genetic scores (GS) for height and BMI using methods described previously, based on a polygenic additive model (i.e. ignoring interactions between variants) [14, 22]. We calculated each GS using the formulas: $GS_{height} = \sum_{i=1}^{586} \beta_i SNP_i$ and $GS_{BMI} = \sum_{i=1}^{93} \beta_i SNP_i$, where β_i is the reported per-allele effect of the *i*th-SNP for height and BMI [16,17] and SNP_i is the effect allele dosage (0,1,2) of the *i*th-SNP. We re-scaled GSs to calculate the genetically-predicted height and BMI by performing linear regressions of observed height and BMI on the corresponding GS in non-cases. 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- and BMI-GS using the equation: Scaled-GS=β_0+β_1GS. We estimated the variation explained by each GS and the association between each GS and traditional breast cancer risk factors.

Next, we modeled height- 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 non-random 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, since the mean and median ages at natural menopause in this population were 46 and 48, 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, i.e. breast cancer~$\beta_{YG}X$ (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: $\beta_{YX} = \frac{\beta_{YG}}{\beta_{XG}}$. The standard error for this estimate was estimated using the method proposed by Burgess: $SE_{YX} = \sqrt{\left(\frac{SE_{YG}}{\beta_{XG}}\right)^2}$ [27]. β_{YX} can be interpreted as 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 Egger's test to assess for possible pleiotropic effects of the variants (i.e. 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 one, we conducted a linear

regression of observed height or BMI on corresponding GS, principal components, birth cohort, country, mutation status, and residuals. In stage two, we used a Cox model to fit breast cancer risk against height and BMI, birth cohort, country, mutation status, and residuals from stage one. We performed 10,000 boot-straps 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 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). A two-sided *P*-value<0.05 was considered statistically significant unless stated otherwise.

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of the 22,588 participants (14,676 *BRCA1* and 7,912 *BRCA2* mutation carriers) with genotype information. 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 7,657 participants (4,502 *BRCA1* carriers and 3,155 *BRCA2* carriers) and BMI at date of questionnaire was available in 7,516 participants (4,401 *BRCA1* carriers and 3,115 *BRCA2* carriers).

Height Analysis

Observed height was positively associated with breast cancer risk (HR per 10-cm: 1.09, 95% CI: 1.02–1.17, *P*=0.016) (**Table 2**). In stratified analysis, we found that height was a

stronger predictor of risk in *BRCA2* carriers (HR=1.17, 95% CI: 1.04–1.31) than in *BRCA1* carriers (HR=1.06, 95% CI: 0.97–1.16), but the interaction was not statistically significant. The country-specific estimates showed low levels of heterogeneity (**Supplementary Figure 1a**).

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**). As shown in **Supplementary Figure 3a**, 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, though it was not statistically significant (HR: 1.04 per 10-cm increase in genetically-predicted height, 95% CI: 0.93–1.17; P=0.47) (**Table 4**). Effect was not different when stratified for menopausal or mutation status.

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: 0.93–1.19; P=0.42) (**Table 4**). There was low heterogeneity among SNPs (I^2=17.0%). Egger's test for small-study effects was not significant (P=0.61, **Supplementary Figure 4a**), 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: 0.93–1.27; P=0.27).

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: 0.90–0.98; P=0.007) (**Table 5**). The inverse association was stronger in *BRCA2* vs. *BRCA1* carriers (HR: 0.90 vs. 0.96) and for premenopausal vs. postmenopausal breast cancer (HR: 0.92 vs. 0.97), but there was no statistically significant interaction ($P_{interaction}$>0.05 for each comparison). We found a stronger inverse association of BMI in young adulthood with breast cancer risk (HR: 0.83, 95% CI: 0.76–0.90; $P=2.1\text{x}10^{-5}$). The country-specific estimates showed moderate levels of heterogeneity (**Supplementary Figure 1b**).

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**). We found a strong correlation between the effect on BMI by individual variants in prior reported GWAS and in CIMBA (r=0.52, **Supplementary Figure 3b**). 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: 0.76–0.98; P=0.023) (**Table 7**). The association was slightly stronger among *BRCA2* mutation carriers and for premenopausal breast cancer, though there was no significant interaction ($P_{interaction}$>0.05 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: 0.76–0.98, P=0.027) (**Table 7**). There was low overall heterogeneity (I^2=3.5%). Egger's test was not significant (P=0.44, **Supplementary Figure 4b**), suggesting that pleiotropic effects may not exist. The two-stage residual inclusion method yielded similar results (HR: 0.86, 95% CI: 0.70–1.07; P=0.18).

Individual Height- and BMI-associated Variants

Of the 586 height-related variants, 50 were found to be associated with breast cancer risk at P<0.05 (**Table 8**). Of the 93 BMI-related variants, 7 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 was 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 non-significant positive relationship with premenopausal breast cancer and a significant positive relationship with 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 (HR=0.92) but was not significantly associated with postmenopausal breast cancer (HR=0.97). 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 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 of 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. Interestingly, 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, due to the smaller number of cases. Currently, a 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, though the relationship with postmenopausal breast cancer remains inconclusive.

There are several potential mechanisms for the associations between height and BMI and breast cancer. For height, early life exposures including nutritional and hormonal status could impact 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 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 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 (rs7903146: HR=0.96; rs1558902: HR=0.97). Interestingly, rs7903146 is in weak linkage disequilibrium (LD) (r^2=0.45) with rs7904519 near *TCF7L2*, which was reported in a previous GWAS [40]. Moreover, rs1558902 was in strong LD (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, MR approach which 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 ~5-6 years after initial diagnosis. While 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 to 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 IVs (*F*-statistic>>10), they are not very strong IVs, 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 to 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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Conflicts of Interest

The authors declare no conflicts of interest.

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

Variable	*BRCA1* carriers N = 14,676	*BRCA2* carriers N = 7,912
Case participants, n	7,360	4,091
Year of birth, median (IQR)	1956 (1948 - 1964)	1954 (1945 - 1961)
Age at diagnosis, y (mean ± SD)	41.1 ± 9.3	44.2 ± 10.0
Control participants, n	7,316	3,821
Year of birth, median (IQR)	1963 (1953 - 1972)	1962 (1950 - 1971)
Age at censoring, y (mean ± SD)	42.0 ± 12.5	44.0 ± 13.5
Ethnicity, n (%)		
Caucasian, not otherwise specified	13,435 (91.5)	7,126 (90.1)
Ashkenazi Jewish	1,241 (8.5)	786 (9.9)
Height in cm, n	4,502	3,155
Mean ± SD	164.8 ± 6.8	164.5 ± 6.9
Weight at date of questionnaire in kg, n	4,436	3,133
Mean ± SD	68.1 ± 13.9	69.0 ± 14.5
Body mass index at baseline[1] in kg/m^2, n	4,401	3,115
Mean ± SD	25.1 ± 5.1	25.6 ± 5.2
Weight in early adulthood in kg, n	3,152	2,296
Mean ± SD	57.6 ± 9.2	57.9 ± 9.6
Body mass index in early adulthood in kg/m^2, n	3,134	2,283
Mean ± SD	21.2 ± 3.3	21.4 ± 3.3
Age at menarche in years, n	4,425	3,034
Mean ± SD	13.0 ± 1.5	13.0 ± 1.5
Parous, n (%)		
Yes	3,914 (77.8)	2,681(79.7)
No	1,117 (22.2)	682 (20.3)
Age at first live birth in years, n	3,711	2,579
Mean ± SD	25.3 ± 4.9	25.3 ± 4.9
Menopausal status, n (%)		
Premenopausal	2,330 (47.4)	1,610 (46.4)
Postmenopausal	2,588 (52.6)	1,858 (53.6)
Age at menopause, y (mean ± SD)	44.7 ± 6.0	45.6 ± 6.0

Table 2. Association of height and breast cancer risk using observed height, among 7,657 participants

	N/events	Hazard Ratio (95% CI)	*P*-value
Per 10 cm increase in observed height			
All participants (confounding adjustment sequentially)			
Unadjusted	7657/3653	1.14 (1.06 - 1.22)	0.0002
Adjusted for principal components	7657/3653	1.15 (1.07 - 1.23)	0.0002
Additionally adjusted for country	7657/3653	1.17 (1.09 - 1.26)	<0.0001
Additionally adjusted for birth cohort	7657/3653	1.09 (1.01 - 1.17)	0.021
Additionally adjusted for mutation status	7657/3653	1.09 (1.02 - 1.17)	0.012
Additionally adjusted for menopausal status	**7657/3653**	**1.09 (1.02 - 1.17)**	**0.016**
Additionally adjusted for parity and age at menarche	7090/3383	1.10 (1.02 - 1.18)	0.014
By mutation status*			
BRCA1 carrier	4502/2154	1.06 (0.97 - 1.16)	0.19
BRCA2 carrier	3155/1499	1.17 (1.04 - 1.31)	0.007
$P_{interaction}$			0.18
By menopausal status**			
Premenopausal	7657/2197	1.10 (1.01 - 1.20)	0.025
Postmenopausal	3076/1402	1.07 (0.95 - 1.19)	0.26
$P_{interaction}$			0.64

Notes:

* 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	Standard error	*P*-value	% variation explained
Measured height, cm					
All participants	7,657	1.012	0.029	7.0×10^{-241}	13.4
BRCA1 carriers	4,502	1.025	0.038	3.8×10^{-149}	14.0
BRCA2 carriers	3,155	0.996	0.047	2.5×10^{-94}	12.6
Case participants	3,653	1.028	0.041	2.6×10^{-128}	14.7
Control participants	4,004	1.000	0.042	1.1×10^{-116}	12.3
Traditional risk factors					
BMI, kg/m^2	7,516	-0.010	0.024	0.66	
Weight, kg	7,569	0.813	0.065	2.7×10^{-35}	
Age at baseline, y	8,578	0.123	0.036	7.3×10^{-4}	
Age at menarche, y	7,459	0.028	0.007	9.3×10^{-5}	
Parous, yes vs no	8,394	-0.010	0.011	0.35	
Age at first live birth, y	6,290	-0.014	0.025	0.58	
Menopausal status, pre vs post	8,386	0.011	0.009	0.20	
Age at menopause, y	4,336	-0.082	0.037	0.03	

Notes:

Regression coefficient is presented for continuous variables and natural log-scale odds ratio for binary variables, per unit increase of the weighted height genetic score

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	Hazard Ratio (95% CI)	*P*-value	Heterogeneity (I^2)
Height-GS*				
All participants (confounding adjustment sequentially)				
Unadjusted	22588/11451	1.11 (1.00 - 1.23)	0.05	
Adjusted for principal components	22588/11451	1.04 (0.93 - 1.17)	0.48	
Additionally adjusted for country	22588/11451	1.03 (0.92 - 1.16)	0.57	
Additionally adjusted for birth cohort	22588/11451	1.04 (0.92 - 1.16)	0.56	
Additionally adjusted for mutation status	22588/11451	1.04 (0.93 - 1.17)	0.45	
Additionally adjusted for menopausal status	22588/11451	**1.04 (0.93 - 1.17)**	**0.47**	
By mutation status**				
BRCA1 carrier	14676/7360	1.03 (0.91 - 1.18)	0.62	
BRCA2 carrier	7912/4091	1.07 (0.87 - 1.32)	0.50	
$P_{interaction}$			0.95	
By menopausal status†				
Premenopausal	22588/7410	1.09 (0.96 - 1.24)	0.20	
Postmenopausal	8459/3926	0.95 (0.79 - 1.13)	0.55	
$P_{interaction}$			0.18	
Meta-analysis method‡				
All participants	22588/11451	**1.05 (0.93 - 1.19)**	**0.42**	17.0%
BRCA1 carrier	14676/7360	1.04 (0.90 - 1.20)	0.57	11.8%
BRCA2 carrier	7912/4091	1.09 (0.87 - 1.36)	0.45	6.6%
$P_{interaction}$			0.75	
Two-stage residual inclusion method				
All participants	7657/3653	**1.09 (0.93 - 1.27)**	**0.27**	
BRCA1 carrier	4502/2154	1.16 (0.96 - 1.40)	0.13	
BRCA2 carrier	3155/1499	1.05 (0.80 - 1.37)	0.74	

Notes:

* Height genetic score 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 re-scaled 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.

Table 5. Association of BMI and breast cancer risk using observed BMI

Breast cancer group	N/events	Hazard Ratio (95% CI)	*P*-value
Per 5 kg/m^2 increase in BMI at date of questionnaire			
All participants (confounding adjustment sequentially)			
Unadjusted	7516/3594	0.92 (0.88 - 0.97)	0.0004
Adjusted for principal components	7516/3594	0.93 (0.89 - 0.97)	0.0007
Additionally adjusted for country	7516/3594	0.92 (0.88 - 0.96)	0.0003
Additionally adjusted for birth cohort	7516/3594	0.94 (0.90 - 0.98)	0.003
Additionally adjusted for mutation status	7516/3594	0.95 (0.91 - 0.99)	0.014
Additionally adjusted for menopausal status	7516/3594	**0.94 (0.90 - 0.98)**	**0.007**
Additionally adjusted for parity and age at menarche	6964/3331	0.93 (0.89 - 0.98)	0.003
By mutation status*			
BRCA1 carrier	4401/2114	0.96 (0.91 - 1.01)	0.11
BRCA2 carrier	3115/1480	0.90 (0.84 - 0.97)	0.003
$P_{interaction}$			0.26
By menopausal status**			
Premenopausal	7516/2153	0.92 (0.87 - 0.97)	0.001
Postmenopausal	3029/1389	0.97 (0.91 - 1.04)	0.40
$P_{interaction}$			0.14
Per 5 kg/m^2 increase in BMI in young adulthood			
All participants (confounding adjustment sequentially)			
Unadjusted	5417/2520	0.83 (0.76 - 0.91)	3.1E-05
Adjusted for principal components	5417/2520	0.83 (0.76 - 0.91)	5.4E-05
Additionally adjusted for country	5417/2520	0.81 (0.74 - 0.88)	2.8E-06
Additionally adjusted for birth cohort	5417/2520	0.81 (0.74 - 0.88)	1.8E-06
Additionally adjusted for mutation status	5417/2520	0.83 (0.76 - 0.90)	1.7E-05
Additionally adjusted for menopausal status	5417/2520	**0.83 (0.76 - 0.90)**	2.1E-05
Additionally adjusted for parity and age at menarche	5210/2436	0.82 (0.75 - 0.90)	2.7E-05
By mutation status*			
BRCA1 carrier	3134/1462	0.87 (0.78 - 0.97)	0.013
BRCA2 carrier	2283/1058	0.74 (0.63 - 0.85)	4.5E-05
$P_{interaction}$			0.06
By menopausal status**			
Premenopausal	5417/1519	0.85 (0.78 - 0.94)	0.002
Postmenopausal	2181/977	0.79 (0.69 - 0.91)	0.001
$P_{interaction}$			0.35

Notes:

* 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 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*	Standard error	*P*-value	% variation explained
Observed BMI at date of questionnaire, kg/m^2					
All participants	7,516	0.832	0.059	2.8×10^{-44}	2.6
BRCA1 carrier	4,401	0.786	0.076	9.9×10^{-25}	2.4
BRCA2 carrier	3,115	0.903	0.094	2.1×10^{-21}	2.9
Case participants	3,594	0.651	0.083	6.9×10^{-15}	1.7
Control participants	3,922	1.000	0.084	3.3×10^{-32}	3.5
Premenopausal control participants	2,246	0.941	0.110	2.6×10^{-17}	3.1
Postmenopausal control participants	1,441	1.113	0.139	3.0×10^{-15}	4.2
Observed BMI in young adulthood, kg/m^2					
All participants	5,417	0.794	0.083	2.3×10^{-21}	1.6
BRCA1 carrier	3,134	0.770	0.108	1.2×10^{-12}	1.6
BRCA2 carrier	2,283	0.830	0.131	2.8×10^{-10}	1.7
Case participants	2,520	0.540	0.110	1.0×10^{-6}	0.9
Control participants	2,897	1.000	0.122	3.3×10^{-16}	2.3
Premenopausal control participants	1,589	0.995	0.170	5.3×10^{-9}	2.1
Postmenopausal control participants	1,100	1.044	0.193	8.2×10^{-8}	2.6
Traditional risk factors					
Height	7,657	0.319	0.079	5.4×10^{-5}	
Age at baseline, y	8,578	-0.020	-0.020	0.79	
Age at menarche, y	7,459	-0.090	0.018	5.0×10^{-7}	
Parous, yes vs no	8,394	0.024	0.027	0.38	
Age at first live birth, y	6,290	-0.113	0.063	0.07	
Menopausal status, pre vs post	8,386	-0.019	0.022	0.39	
Age at menopause, y	4,336	-0.172	0.093	0.06	

Notes:

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

Table 7. Association of BMI genetic score 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*-value	Heterogeneity (I^2)
BMI-GS*				
All participants (confounding adjustment sequentially)				
Unadjusted	22588/11451	0.93 (0.81 - 1.05)	0.24	
Adjusted for principal components	22588/11451	0.89 (0.78 - 1.01)	0.071	
Additionally adjusted for country	22588/11451	0.90 (0.79 - 1.03)	0.13	
Additionally adjusted for birth cohort	22588/11451	0.88 (0.77 - 0.999)	0.049	
Additionally adjusted for mutation status	22588/11451	0.88 (0.78 - 0.99)	0.039	
Additionally adjusted for menopausal status	22588/11451	**0.87 (0.76 - 0.98)**	**0.023**	
By mutation status**				
BRCA1 carrier	14676/7360	0.88 (0.76 - 1.02)	0.09	
BRCA2 carrier	7912/4091	0.83 (0.65 - 1.05)	0.11	
$P_{interaction}$			0.63	
By menopausal status†				
Premenopausal	22588/7410	0.84 (0.73 - 0.98)	0.023	
Postmenopausal	8459/3926	0.89 (0.72 - 1.09)	0.26	
$P_{interaction}$			0.68	
Meta-analysis method‡				
All participants	**22588/11451**	**0.87 (0.76 - 0.98)**	**0.027**	3.5%
BRCA1 carrier	14676/7360	0.88 (0.76 - 1.03)	0.10	15.7%
BRCA2 carrier	7912/4091	0.82 (0.65 - 1.04)	0.10	0.0%
$P_{interaction}$			0.63	
Two-stage residual inclusion method				
All participants	7516/3594	**0.86 (0.70 - 1.07)**	**0.18**	
BRCA1 carrier	4401/2114	0.93 (0.69 - 1.23)	0.61	
BRCA2 carrier	3115/1480	0.82 (0.61 - 1.12)	0.23	

Notes:

* BMI-GS was constructed by combining 93 BMI-associated 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 re-scaled 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.

Table 8. Height or BMI SNPs significantly associated (P < 0.05) 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		
								Log hazard ratio**	Standard error	*P*-value
Height										
rs10744956	15	51269629	*AP4E1*	A	G	0.80	0.98	0.096	0.023	0.00003
rs7740107	6	130374461	*L3MBTL3*	T	A	0.75	1	0.081	0.021	0.0001
rs10995319	10	52762887	*PRKG1*	T	C	0.23	0.96	0.075	0.022	0.0006
rs8058684	16	53515118	*RBL2*	G	A	0.32	1	0.061	0.019	0.0013
rs11049611	12	28600244	*CCDC91*	C	T	0.28	1	-0.065	0.020	0.0015
rs8103992	19	19665643	*PBX4*	A	C	0.78	0.98	-0.064	0.022	0.0036
rs11618507	13	30172751	*SLC7A1*	G	T	0.20	1	0.061	0.023	0.0074
rs11244750	10	127673877	*FANK1*	C	T	0.35	0.83	0.055	0.021	0.0089
rs7701414	5	131585958	*PDLIM4*	A	G	0.46	1	0.047	0.018	0.01
rs7733195	5	172994624	*FAM44B*	G	A	0.37	1	0.049	0.019	0.0107
rs2306694	12	56680636	*CS*	A	G	0.06	1	0.096	0.038	0.012
rs6435143	2	203194256	*NOP5/NOP*	A	C	0.56	0.84	0.050	0.020	0.013
rs2284746	1	17306675	*MFAP2*	C	G	0.50	0.84	-0.049	0.020	0.013
rs1797625	3	112826415	*C3orf17*	A	T	0.36	0.91	-0.049	0.020	0.013
rs10495098	1	218516310	*TGFB2*	G	T	0.41	0.84	-0.051	0.021	0.013
rs301901	5	37046626	*NIPBL*	A	G	0.45	0.93	-0.046	0.019	0.015
rs42039	7	92244422	*CDK6*	C	T	0.26	1	0.051	0.021	0.016
rs1576900	9	18629792	*ADAMTSL1*	G	A	0.30	0.91	0.048	0.020	0.017
rs891088	19	7184762	*INSR*	A	G	0.27	0.83	0.052	0.022	0.020
rs273945	7	137611566	*CREB3L2*	A	C	0.58	1	-0.042	0.018	0.021
rs2682587	19	44082429	*XRCC1*	C	A	0.18	1	0.053	0.023	0.022
rs1257763	9	96893945	*PTPDC1*	A	G	0.96	0.72	-0.118	0.053	0.026
rs2888877	7	92228400	*CDK6*	T	C	0.79	0.96	-0.050	0.022	0.027
rs8042424	15	101762539	*CHSY1*	C	T	0.24	0.82	-0.052	0.024	0.028
rs7716219	5	54955071	*SLC38A9*	T	C	0.70	0.97	-0.044	0.020	0.029

rs7727731	5	64674446	*ADAMTS6*	C	T	0.12	0.67	-0.076	0.035	0.029
rs16964211	15	51530495	*CYP19A1*	G	A	0.06	0.99	-0.085	0.040	0.031
rs11880992	19	2176403	*DOT1L*	G	A	0.42	0.95	-0.040	0.019	0.033
rs2302580	4	8608634	*CPZ*	C	T	0.44	1	-0.040	0.019	0.033
rs12538407	7	23521316	*IGF2BP3*	A	G	0.39	0.99	0.040	0.019	0.034
rs2300921	3	185651001	*SFRS10*	T	C	0.41	0.98	0.041	0.019	0.034
rs897080	2	44774202	*C2orf34*	C	T	0.79	0.90	-0.050	0.024	0.034
rs4357716	11	69163161	*MYEOV*	C	T	0.14	1	0.055	0.026	0.034
rs11659752	18	77222862	*NFATC1*	T	G	0.30	0.82	-0.045	0.021	0.035
rs2166898	2	121612659	*GLI2*	G	A	0.17	0.55	0.067	0.032	0.036
rs6020202	20	48634821	*SNAI1*	G	A	0.24	1	0.045	0.022	0.036
rs3760318	17	29247715	*CENTA2*	G	A	0.37	1	-0.039	0.019	0.037
rs6746356	2	174815898	*SP3*	A	C	0.24	0.79	0.050	0.024	0.037
rs9428104	1	118855587	*SPAG17*	A	G	0.75	1	0.044	0.021	0.037
rs2834442	21	35690786	*KCNE2*	T	A	0.66	0.98	-0.040	0.019	0.038
rs1546391	3	114697457	*ZBTB20*	C	G	0.09	0.97	-0.069	0.033	0.038
rs12926008	16	2488211	*CCNF*	T	C	0.65	0.53	0.054	0.026	0.040
rs2123731	19	4929473	*UHRF1*	A	G	0.27	0.70	-0.049	0.024	0.043
rs2289195	2	25463483	*DNMT3A*	G	A	0.41	0.65	0.046	0.023	0.043
rs16834765	1	32371442	*PTP4A2*	C	T	0.05	0.82	0.091	0.045	0.044
rs10958476	8	57095808	*PLAG1*	T	C	0.20	1	0.045	0.022	0.045
rs17369123	1	172355841	*DNM3*	C	T	0.16	0.98	0.049	0.025	0.046
rs1415701	6	130345835	*L3MBTL3*	G	A	0.26	1	0.041	0.021	0.047
rs11152213	18	57852948	*MC4R*	A	C	0.23	0.99	-0.043	0.022	0.047
rs4802134	19	38346685	*SIPA1L3*	A	G	0.75	1	-0.041	0.021	0.049
BMI										
rs13107325	4	103188709	*SLC39A8*	C	T	0.09	0.76	0.101	0.037	0.007
rs10182181	2	25150296	*ADCY3*	A	G	0.45	0.64	-0.056	0.023	0.016
rs7903146	10	114758349	*TCF7L2*	C	T	0.30	1	0.044	0.020	0.025
rs9925964	16	31129895	*KAT8*	A	G	0.39	0.99	-0.040	0.019	0.034

rs4740619	9	15634326	*C9orf93*	T	C	0.46	0.97	0.040	0.019	0.034
rs1558902	16	53803574	*FTO*	T	A	0.42	1.00	-0.038	0.018	0.037
rs2207139	6	50845490	*TFAP2B*	A	G	0.16	0.99	0.049	0.024	0.044

Notes:

* Imputation quality of 1 indicates genotyped SNPs.

** 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