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Article

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Height and Breast Cancer Risk: Evidence From Prospective Studies and Mendelian Randomization

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Abstract

Background: Epidemiological studies have linked adult height with breast cancer risk in women. However, the magnitude of the association, particularly by subtypes of breast cancer, has not been established. Furthermore, the mechanisms of the association remain unclear.

Methods: We performed a meta-analysis to investigate associations between height and breast cancer risk using data from 159 prospective cohorts totaling 5 216 302 women, including 113 178 events. In a consortium with individual-level data from 46 325 case patients and 42 482 control subjects, we conducted a Mendelian randomization analysis using a genetic score that comprised 168 height-associated variants as an instrument. This association was further evaluated in a second consortium using summary statistics data from 16 003 case patients and 41 335 control subjects.

Results: The pooled relative risk of breast cancer was 1.17 (95% confidence interval [CI] = 1.15 to 1.19) per 10 cm increase in height in the meta-analysis of prospective studies. In Mendelian randomization analysis, the odds ratio of breast cancer per 10 cm increase in genetically predicted height was 1.22 (95% CI = 1.13 to 1.32) in the first consortium and 1.21 (95% CI = 1.05 to 1.39) in the second consortium. The association was found in both premenopausal and postmenopausal women but restricted to hormone receptor–positive breast cancer. Analyses of height-associated variants identified eight new loci associated with breast cancer risk after adjusting for multiple comparisons, including three loci at 1q21.2, *DNAJC27*, and *CCDC91* at genome-wide significance level $P < 5 \times 10^{-8}$.

Conclusions: Our study provides strong evidence that adult height is a risk factor for breast cancer in women and certain genetic factors and biological pathways affecting adult height have an important role in the etiology of breast cancer.

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Breast cancer is a leading cause of cancer morbidity and mortality among women worldwide (1). Adult height has been found to be positively related to breast cancer risk in many epidemiological studies (2–30), reporting mostly a linear dose-response relationship. Results from previous studies, however, have been inconsistent, particularly with regard to the magnitude of the association and the association by subtypes of breast cancer. For example, relative risks of breast cancer associated with per 10 cm increase in adult height ranged from 1.08 to 1.38 in previous cohort studies. Furthermore, it remains unclear whether adult height is causally related to breast cancer risk through shared underlying genetic factors and biological pathways or serves only as a surrogate measure of certain environmental and lifestyle exposures that contribute to breast cancer risk. Answers to these questions may provide additional insight into breast tumorigenesis and strengthen the basis for classifying height as a breast cancer risk factor.

Mendelian randomization analysis can be used to minimize potential biases encountered in conventional observational studies and to determine the causal association of a

given exposure with disease risk (31). The causal association can also be manifested by common genetic and biological pathways that determine two sequentially developed phenotypes, such as adult height and breast cancer risk. Adult height is a classic quantitative trait determined, to a large extent, by genetic factors (32). Since 2007, genome-wide association studies (GWAS) have identified single-nucleotide polymorphisms (SNPs) in approximately 180 loci related to adult height (33–38). SNPs identified to date by GWAS explain approximately 10% of height variation in populations of European ancestry (38). The alleles associated with adult height should be randomly assigned to offspring from parents during mitosis, a process analogous to a random assignment of subjects to an exposure of interest in randomized clinical trials. Thus, a genetic score summarizing the effects of these height-associated SNPs can serve as an instrumental variable in a Mendelian randomization analysis of adult height and breast cancer risk (39).

Here we comprehensively assessed epidemiologic evidence from conventional observational studies regarding the association between height and breast cancer risk by performing a meta-analysis of 159 prospective cohorts including more than five million women of European ancestry. To determine the nature of the association, we conducted two Mendelian randomization analyses using data from two large consortia totaling 62 328 breast cancer case patients and 83 817 control subjects.

Methods

Meta-Analysis of Prospective Studies

We searched electronic databases to identify prospective studies that investigated the association between height and breast cancer risk among women of European ancestry published before December 2014 (Supplementary Figure 1, available online). We combined relative risks (RRs) of breast cancer with per 10 cm increase in height from each of the included studies using a random effects meta-analysis (40). We also performed subgroup meta-analyses based on method of height assessment (measured or self-reported), as well as menopausal, estrogen receptor (ER), and progesterone receptor (PR) status. We used the Cochran's Q statistic to test for heterogeneity (41) and the I^2 statistic to quantify heterogeneity across studies (42). Potential publication bias was assessed using Begg's and Egger's approaches (43,44). Sensitivity analyses were performed to evaluate the robustness of the results. We considered *P* values of less than .10 in tests of heterogeneity and publication bias and *P* values of less than .05 in the meta-analyses to be statistically significant. All tests were two-sided, with the exception of tests of heterogeneity and publication bias. Details of literature searches, study inclusion criteria, and meta-analysis are presented in the Supplementary Methods (available online).

Mendelian Randomization Analysis

Our Mendelian randomization analysis was conducted using data from two consortia, the Breast Cancer Association Consortium (BCAC), and the Discovery, Biology, and Risk of Inherited Variants in Breast Cancer (DRIVE) Project (Supplementary Figure 1, available online). In BCAC, we included individual-level data for 46 325 breast cancer case patients and 42 482 control subjects of European ancestry from 39 studies (Supplementary Table 1). In DRIVE, only summary statistics data were available to our study, and these data were obtained from 16 003 breast cancer case patients and 41 335 control subjects of European ancestry from 11 studies (Supplementary Table 2, available online). Details of the methodology used by the BCAC and DRIVE have been published elsewhere (45–48) and are available on these websites (http://ccge.medschl.cam.ac.uk/research/consortia/icogs/, accessed August 8, 2015, and http://gameon.dfci.harvard.edu/, accessed August 8, 2015). Study descriptions and methods for SNP selection, genotyping, and imputation are presented in the Supplementary Methods (available online).

We examined associations between the 168 SNPs and adult height (in cm) in the BCAC using general linear models with adjustment for age and principal components. A weighted height genetic score (wHGS) was constructed for our primary analysis by using the 168 SNPs with the formula: $\mathrm{wHGS} = 9.101559\left(\sum_{i=1}^{168}\beta_i SNP_i\right)$, where 9.101559 is the coefficient to rescale the original wHGS to a mean of 336 risk alleles (Supplementary Table 3, available online), β_i is the regression coefficient of the *i*th SNP for height, and SNP_i is the dosage of the effect alleles (0,1, or 2) of the *i*th SNP. We converted all effect alleles to correspond to taller height in the SNP-based analyses and construction of the wHGS. Associations of breast cancer risk with the wHGS and each of the 168 SNPs were evaluated using unconditional logistic regression models to derive odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for age and principal components. All analyses were performed for each study separately, and summary statistics were obtained using a fixed-effects meta-analysis.

In the first Mendelian randomization analysis, we estimated the potential causal association between height (X) and breast cancer risk (Y) by using the wHGS (G) as an instrumental variable. Specifically, the causal effect (β_{YX}) was calculated by using the Wald estimator: $\beta_{YX} = \frac{\beta_{YG}}{\beta_{XG}}$ (49), and the standard error for the causal effect (SE_{YX}) was derived using the delta method: $SE_{YX} = \sqrt{\left(\left(\frac{S_{YG}}{\beta_{XG}}\right)^2 + \frac{(S_{XG}\beta_{YG})^2}{\beta_{XG}^4} - \frac{2rS_{XG}S_{YG}\beta_{YG}}{\beta_{XG}^3}\right)}$ (50), where β_{YG} is the natural log-scale OR of breast cancer risk associated with the wHGS, β_{XG} is the regression coefficient of the wHGS on height, S_{YG} and S_{XG} are the corresponding standard errors, and *r* is the correlation between β_{YG} and β_{XG}. Sensitivity analyses were performed (Supplementary Table 3, available online), and the strength of instrumental variables was evaluated using *F* statistic (51). The second Mendelian randomization analysis was conducted using the inverse-variance weighted method for summary statistics data to further evaluate the association (52). Specifically, the causal effect (β_{YX}) was estimated using a fixed-effects meta-analysis model: $\beta_{YX} = \frac{\sum_{i=1}^{168}\left(\frac{\beta_{XGi}\beta_{YGi}}{S_{YGi}^2}\right)}{\sum_{i=1}^{168}\left(\frac{\beta_{XGi}}{S_{YGi}}\right)^2}$, with its standard error (SE_{YX}) estimated using formula: $SE_{YX} = \sqrt{\frac{1}{\sum_{i=1}^{168}\left(\frac{\beta_{XGi}}{S_{YGi}}\right)^2}}$, where β_{XGi} is the regression coefficient of the ith SNP on height obtained from approximately 110 500 women included in a GWAS of adult height published previously (38), and β_{YGi} and S_{YGi} are the natural log-scale odds ratio of breast cancer risk associated with the ith SNP and the corresponding standard error, obtained from the DRIVE Project. Details of methodology for statistical analyses are presented in the Supplementary Methods (available online).

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Table 1. Characteristics of prospective cohort studies included in the meta-analysis

Author (reference)	Year	Study	Height*	Number of cohorts	Population†	Country	Cohort size	Number of events‡	Years of recruitment	Follow-up§, y	Adjustment in model
Tornberg (5)	1988	CSHS	Measured	1	European	Sweden	46 570	1182	1963–1965	18–20	Multivariable
Tretli (6)	1989	NMRS	Measured	1	European	Norway	567 333	8427	1963–1975	6–18	Multivariable
Vatten (7)	1992	NNHSS	Measured	1	European	Norway	25 967	291	1974–1977	14	Multivariable
De Stavola (8)	1993	Guernsey	Measured	2	European	UK	6706	168	1968–1985	21/10	Multivariable
Michels-Blanck (9)	1996	CPS-I	Self-reported	1	European	USA	428 653	2226	1959–1960	13	Age
Freni (10)	1996	NHANES-I	Measured	1	European	USA	7622	182	1970–1975	12.9	Multivariable
Tulinius (11)	1997	ICRFS	Measured	1	European	Iceland	11 580	439	1967–1991	4–27	Multivariable
Kaaks (12)	1998	DOM	Measured	1	European	The Netherlands	11 480	275	1984–1986	10.6	Multivariable
Sonnenschein (13)	1999	NYUWHS	Self-reported	1	European	USA	8416	259	1985–1991	6.6	Multivariable
van den Brandt (14)	2000	TPP	Self-reported	7	European	Multiple	337 819	4385	1976–1987	3–7	Multivariable
Weiderpass (15)	2004	NSWLHCS	Self-reported	1	European	Norway and Sweden	99 717	733	1991–1992	6.7	Multivariable
Ahlgren (16)	2004	CSHRR	Measured	1	European	Denmark	117 415	3340	N/A	28.4	Multivariable
Macinnis (17)	2004	MCCS	Measured	1	European	Australia	13 598	357	1990–1994	9.1	Multivariable
McCullough (18)	2005	CPS-II	Self-reported	1	European	USA	430 236	4522	1982	20	Multivariable
Baer (19)	2006	NHS-II	Self-reported	1	European	USA	108 829	1315	1989	12	Multivariable
Lacey (20)	2009	PLCO	Self-reported	1	European	USA	70 575	2085	1993–2001	4.98	Multivariable
Green (21)	2011	MWS	Self-reported	1	European	UK	1 297 124	39 299	1996–2001	9·4	Multivariable
White (22)	2012	MEC	Self-reported	1	European	USA	19 815	835	1993–1996	8–11	Multivariable
Canchola (23)	2012	CTS	Self-reported	1	European	USA	52 642	2321	1995–1996	12.1	Multivariable
Mellemkjaer (24)	2012	DCH	Measured	1	European	Denmark	23 864	1209	1993–1997	11.8	Multivariable
Kabat (25)	2013	CNBSS	Measured	1	European	Canada	88 256	4224	1980–1985	16.2	Multivariable
Wormser (26)	2012	ERFC	Measured	121	European	Multiple	522 257	3926	N/A	13.7	Multivariable
Ritte (27)	2013	EPIC	Measured	1	European	Multiple	306 600	9307	1992–2000	10.8	Multivariable
Kabat (28)	2013	WHI	Measured	1	European	USA	144 701	6798	1993–1998	12.0	Multivariable
Wiren (29)	2014	Me-Can	Measured	7	European	Multiple	297 156	6161	1972–2005	12.7	Multivariable
Kabat (30)	2014	NIH-AARP	Self-reported	1	European	USA	192 514	9169	1995–1996	10.5	Multivariable

* Height was either measured or self-reported in the included study. CNBSS = the Canadian National Breast Screening Study; CPS-I = the American Cancer Society Cancer Prevention Study I; CPS-II = the American Cancer Society's Cancer Prevention Study II; CSHRR = the Copenhagen School Health Records Register; CSHS = Central Sweden Health Screening; CTS = the California Teachers Study Cohort; DCH = the Danish Diet, Cancer and Health Cohort; DOM = the Dutch Diagnostisch Onderzoek Mammacarcinoom Cohort; EPIC = the European Prospective Investigation into Cancer and Nutrition Cohort; ERFC = the Emerging Risk Factors Collaboration; ICRFS = the Icelandic Cardiovascular Risk Factor Study; MCCS = the Melbourne Collaborative Cohort Study; MEC = the Multiethnic Cohort; Me-Can = the Metabolic syndrome and Cancer project; MWS = the Million Women Study; N/A = no data were available; NHANES-I = the first National Health and Nutrition Examination Survey; NHS-II = the Nurses' Health Study II; NIH-AARP = the National Institutes of Health-American Association of Retired Persons Diet and Health Study; NMRS = National Mass Radiography Service; NNHSS = Norway National Health Screening Service; NSWLHCS = the Norwegian and Swedish Women's Lifestyle and Health Cohort Study; NYUWHS = the New York University Women's Health Study; PLCO = the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; TPP = the Pooling Project; WHI = the Women's Health Initiative.
† Population as reported for >80% of the included study.
‡ Events were fatal breast cancer cases in CPS-I, CPS-II, and ERFC.
§ Mean or median or range of duration of follow-up.

Analyses were performed using SAS (version 9.3), R (version 3.0.0), and PLINK (version 1.07). All tests were two-sided, and *P* values of less than .05 were considered statistically significant unless stated otherwise.

Results

Meta-Analysis of Association Between Height and Breast Cancer Risk

We identified 26 articles (5–30), containing information from 159 prospective cohorts that were eligible for inclusion in our meta-analyses (Table 1). Of these, 22 articles reported results from individual cohorts, while the remaining four articles provided results from combined analyses of two to 121 cohorts. After excluding overlapping cohorts, 5 216 302 participants of European ancestry were included in our analyses, including 113 178 women with breast cancer. Figure 1 presents relative risks (RRs) of breast cancer associated with per 10 cm increase in height for each of the published studies, all studies combined, and study subgroups. The pooled relative risk of breast cancer was 1.17 (95% confidence interval [CI] =1.15 to 1.19, $P < .001$) per 10 cm increase in height for all studies combined, with strong evidence of heterogeneity across studies ($P_{heterogeneity} < .001$,

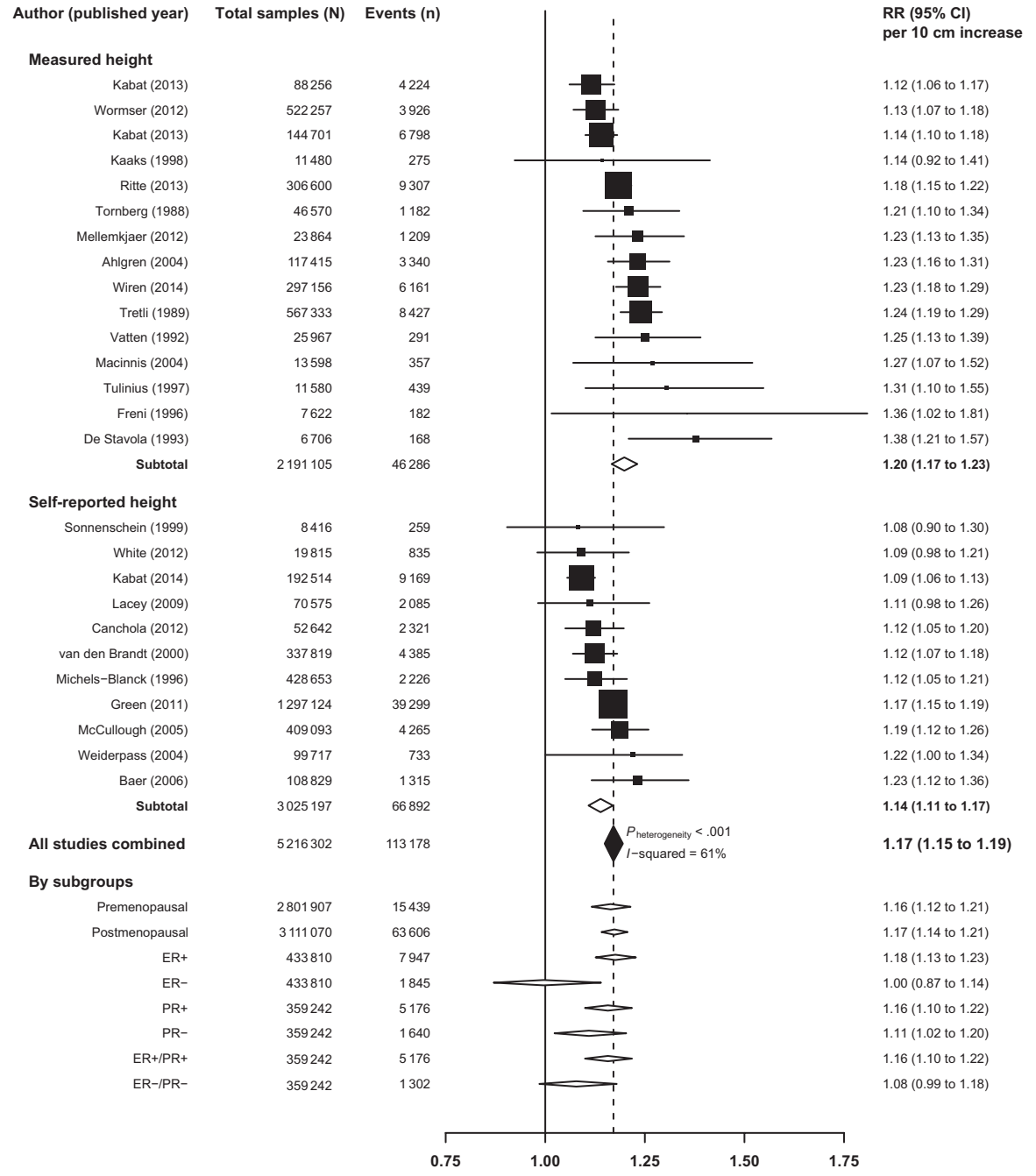

Figure 1. Meta-analysis of associations between height and risk of breast cancer in prospective cohort studies. All tests for meta-analyses were two-sided. CI = confidence interval; ER = estrogen receptor; PR = progesterone receptor; RR = relative risk.

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I^2 = 61%). Removal of the smallest, the largest, the first significant, or the study with adjustment only for age did not change the pooled risk estimate. There was little evidence of publication bias (P > .33).

The association between height and breast cancer risk was stronger in the meta-analysis of studies with measured height than in the studies with self-reported height (RR = 1.20, 95% CI = 1.17 to 1.23 vs RR = 1.14, 95% CI = 1.11 to 1.17, $P_{heterogeneity}$ = .001). The association was similar among postmenopausal and premenopausal women (RR = 1.17, 95% CI = 1.14 to 1.21 vs RR = 1.16, 95% CI = 1.12 to 1.21, $P_{interaction}$ = .79). Statistically significant associations of height with breast cancer risk were found for ER-positive case patients (RR = 1.18, 95% CI = 1.13 to 1.23), PR-positive case patients (RR = 1.16, 95% CI = 1.10 to 1.22), and ER/PR-positive case patients (RR = 1.16, 95% CI = 1.10 to 1.22). The association was not statistically significant for ER-negative and ER/PR-negative breast cancer and was only nominally significant for PR-negative breast cancer (P = .01).

Mendelian Randomization Analyses of Association Between Height and Breast Cancer Risk

Of the 168 height-associated variants, 146 showed an association with height at P values of less than .05 in the BCAC in the same direction and with comparable effect sizes as reported in previous GWAS (Supplementary Table 4, available online). The wHGS, constructed using all the 168 SNPs, ranged from 257 to 407 (mean = 336, standard deviation [SD] = 16.17) in BCAC participants, explaining approximately 8.99% of the height variation. A clear relation between the wHGS and height was found in the study (Table 2). The wHGS was associated, at a P value of .02 or lower, with age at menarche, parity, age at first live birth, use of menopausal hormone therapy, weight, and body mass index (BMI), and these associations were no longer statistically significant after adjusting for height. No association was observed between wHGS and other risk factors for breast cancer. The mean wHGS was higher in case patients than in control subjects (336.02 vs 335.98, P < .001). The wHGS was positively associated with breast cancer risk ($P = 6.97\times10^{-7}$) with an odds ratio of 1.22 (95% CI = 1.13 to 1.32) by an increment of the wHGS corresponding to a 10 cm increase in height (Figure 2). There was little evidence of heterogeneity across studies ($P_{heterogeneity}$ = .27, I^2 = 11%). This positive association between breast cancer risk and wHGS remained essentially unchanged after adjustment for breast cancer risk factors, including age at menarche, age at menopause, parity, family history of breast cancer, age at the first live birth, breast feeding, and use of oral contraceptive or postmenopausal hormone (data not shown). A 13% elevated risk of breast cancer was found to be associated with per 10 cm increment in measured or self-reported height in the BCAC (Table 3). Adjustment for measured/self-reported height eliminated the association between the wHGS and breast cancer risk (P = .20). On the other hand, the significant association between measured/self-reported height remained unchanged (OR = 1.13, 95% CI = 1.10 to 1.17, P < .0001) after adjusting for wHGS.

Table 3 presents associations of breast cancer risk with adult height as predicted using the wHGS as the instrument in Mendelian randomization analysis. As a comparison, results derived from the meta-analysis of prospective studies and the meta-analysis of studies included in BCAC are also presented. A 10 cm increase in height as predicted by the wHGS was associated with an approximately 22% elevated risk of breast cancer for all women combined (OR = 1.22, 95% CI = 1.13 to 1.32, $P = 7.52\times10^{-7}$), compared with the meta-analysis of prospective cohort studies and the meta-analysis of BCAC case-control studies, which showed a 17% and a 13% elevated risk per 10 cm increment in height, respectively (Table 3). Odds ratios associated with genetically predicted height did not vary by menopausal status ($P_{interaction}$ = .86). The association, however, was restricted primarily to hormone receptor–positive breast cancer.

Table 2. Associations of the weighted height genetic score with height and traditional breast cancer risk factors

Variable	Number of participants	Summary effect*	Standard error	P
Height, cm†				
All participants	50706	0.11	0.002	$<1\times10^{-500}$
Control subjects	20458	0.11	0.003	$<1\times10^{-200}$
Case patients	30248	0.11	0.002	$<1\times10^{-200}$
Traditional risk factors				
Age, y	80455	-0.0033	0.002	.17
Age at menarche, y	53990	0.0015	0.0004	2.67×10^{-4}
Menopausal status, post vs pre	61686	0.00043	0.0008	.61
Age at menopause, y	26921	-0.0013	0.002	.54
Family history of breast cancer, yes vs no	47417	0.00097	0.0007	.19
Parous, yes vs no	62683	-0.0012	0.0007	.09
Parity, numbers	61837	-0.00071	0.0003	.02
Age at first live birth, y	44736	0.0047	0.001	8.50×10^{-4}
Use of oral contraceptives, ever vs never	28941	0.00073	0.0009	.42
Use of menopausal hormone therapy, ever vs never	30983	0.0018	0.0008	.02
Breastfeeding, ever vs never	43321	-0.00076	0.0007	.26
Smoking, ever vs never	39562	-0.000068	0.0006	.92
Weight, kg	51634	0.070	0.004	2.01×10^{-82}
BMI, kg/m^2	47221	-0.0074	0.001	1.21×10^{-7}

* Regression coefficient is presented for continuous variables and natural log-scale odds ratio for dichotomous variables, per unit increase of the weighted height genetic score. BMI = body mass index.

† There was no heterogeneity in the association of the weighted height genetic score with height among case patients and control subjects (P = .72). All tests were two-sided.

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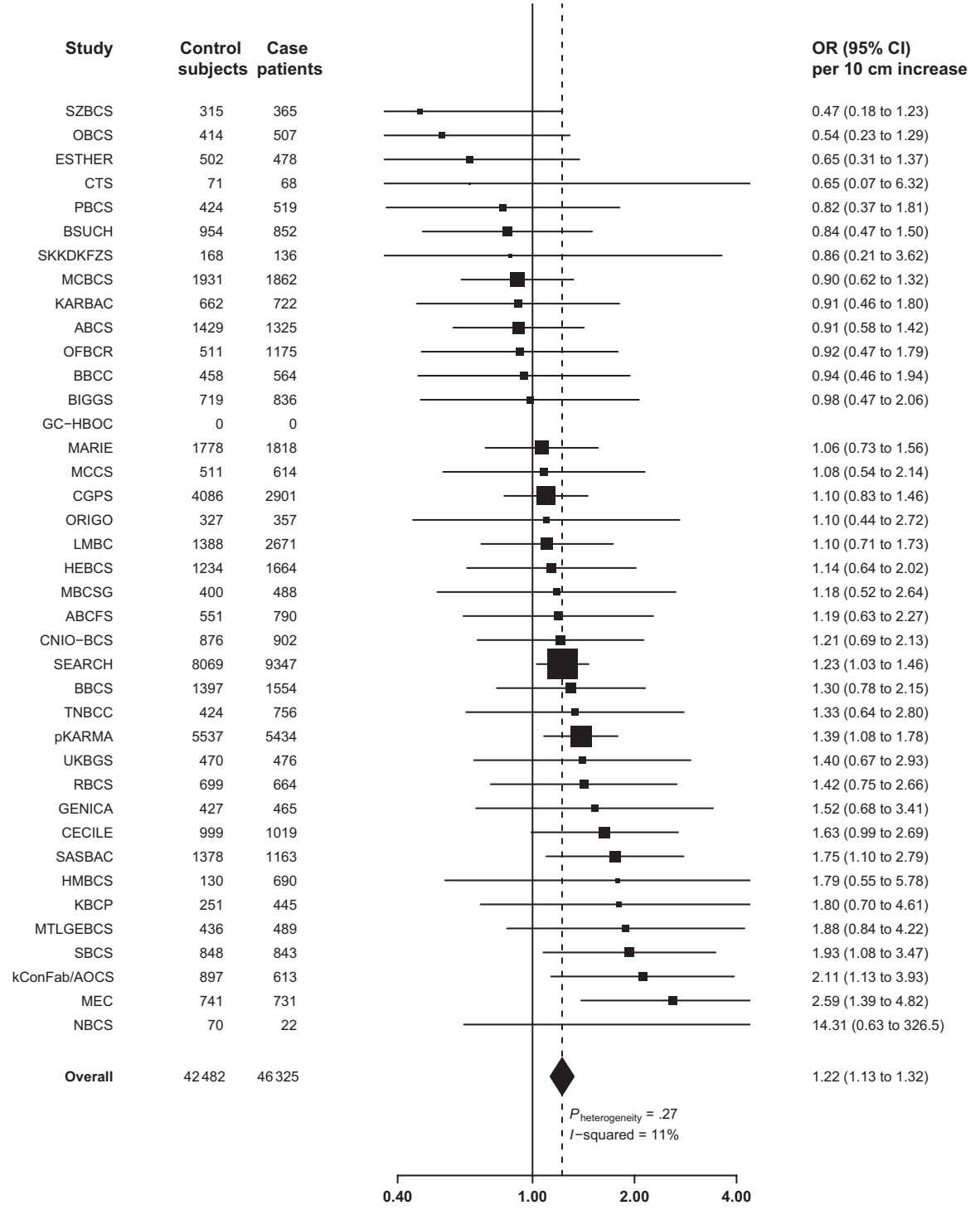

Figure 2. Association of the weighted height genetic score with breast cancer risk in the Breast Cancer Association Consortium. CI = confidence interval; OR = odds ratio.

For example, the odds ratios were 1.26 (95% CI = 1.14 to 1.38) and 1.02 (95% CI = 0.87 to 1.18), respectively, for ER-positive and ER-negative breast cancer ($P_{interaction}$ = .02), similar to the results obtained from meta-analyses of previous cohort studies and BCAC case-control studies. Sensitivity analyses were performed to evaluate the robustness of the associations between breast cancer risk and various height-associated genetic scores (all F statistics > 3500) (Figure 3). All analyses yielded similar results, with little evidence of heterogeneity (P > .66 for all tests). In the second Mendelian randomization analysis using summary statistics data from DRIVE for breast cancer risk and published GWAS for height, we found that a 10 cm increase in height as predicted by the 168 height-associated SNPs was associated with an approximately 21% elevated risk of breast cancer (OR = 1.21, 95% CI = 1.05 to 1.39, P = .008), highly consistent with that observed in the analysis using individual-level data from BCAC. Sensitivity analyses similar to those performed in the analysis of data from BCAC described above yielded similar results (data not shown).

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Table 3. Association of height and breast cancer risk in women

	Meta-analysis of prospective studies			Breast Cancer Association Consortium					
	Observational estimate			Instrumental variable estimate			Observational estimate		
Breast cancer group	N/events	RR (95% CI)*	*P*	Case patients/ control subjects	OR (95% CI)*	*P*	Case patients/ control subjects	OR (95% CI)*	*P*
All women combined									
All case patients	5 216 302/113 178	1.17 (1.15 to 1.19)	<.001	46 325/42 482	1.22 (1.13 to 1.32)	<.001	30 248/20 458	1.13 (1.10 to 1.16)	<.001
By menopausal status									
Premenopausal	2 801 907/15 439	1.16 (1.12 to 1.21)	<.001	10 209/9053	1.29 (1.07 to 1.56)	.007	8959/6225	1.11 (1.05 to 1.17)	<.001
Postmenopausal	3 111 070/63 606	1.17 (1.14 to 1.21)	<.001	23 069/19 355	1.32 (1.17 to 1.49)	<.001	20 197/13 311	1.14 (1.10 to 1.18)	<.001
$P_{interaction}$			.79			.86			.35
By ER status									
ER-positive	433 810/7947	1.18 (1.13 to 1.23)	<.001	27 074/42 482	1.26 (1.14 to 1.38)	<.001	19 953/20 458	1.16 (1.12 to 1.20)	<.001
ER-negative	433 810/1845	1.00 (0.87 to 1.13)	.95	7288/42 482	1.02 (0.87 to 1.18)	.84	4810/20 458	1.05 (1.00 to 1.10)	.07
$P_{interaction}$			.02			.02			.002
By PR status									
PR-positive	359 242/5176	1.16 (1.10 to 1.22)	<.001	19 749/42 482	1.23 (1.11 to 1.37)	<.001	14 796/20 458	1.14 (1.10 to 1.18)	<.001
PR-negative	359 242/1640	1.11 (1.02 to 1.20)	.01	9726/42 482	1.07 (0.94 to 1.23)	.31	6787/20 458	1.09 (1.04 to 1.14)	<.001
$P_{interaction}$			.44			.12			.09
By ER/PR status									
ER/PR-positive	359 242/5176	1.16 (1.10 to 1.22)	<.001	18 948/42 482	1.25 (1.12 to 1.39)	<.001	14 162/20 458	1.15 (1.11 to 1.19)	<.001
ER/PR-negative	359 242/1302	1.08 (0.99 to 1.18)	.10	5848/42 482	1.03 (0.87 to 1.23)	.70	3779/20 458	1.07 (1.01 to 1.13)	.03
$P_{interaction}$			.22			.07			.03

* Results are presented for per 10 cm increase of height. All tests were two-sided. CI = confidence interval; ER = estrogen receptor; OR = odds ratio; PR = progesterone receptor; RR = relative risk.

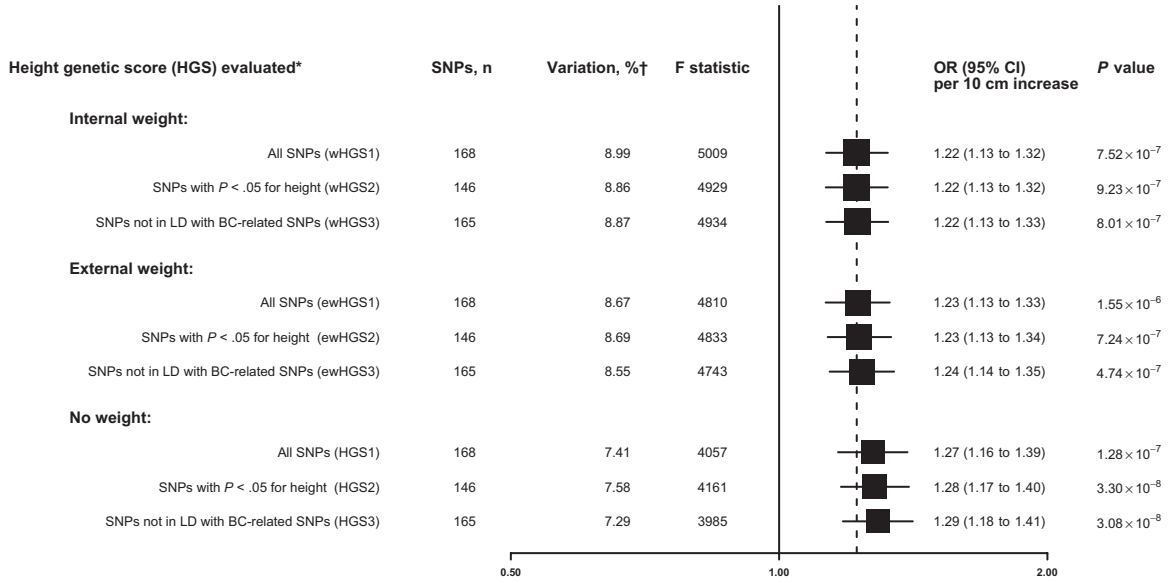

Figure 3. Sensitivity analyses for associations between genetically predicted height and breast cancer risk in the Breast Cancer Association Consortium. *The details of the formula to construct height genetic score are presented in Supplementary Table 3 (available online). †Phenotypic variation of height explained by height genetic scores in the study population. BC = breast cancer; HGS = height genetic score; LD = linkage disequilibrium; SNP = single-nucleotide polymorphism.

Height-Associated Variants and Breast Cancer Risk

Statistically significant associations with breast cancer at *P* values of less than .05 in the same direction as observed for height were found for 16 SNPs in BCAC and 18 SNPs in DRIVE, both higher than expected by chance ($P = .01$ for BCAC and $P = .002$ for DRIVE) (Supplementary Tables 4 and 5, available online). In the combined analysis of data from both consortia, 25 SNPs were associated with breast cancer risk at *P* value sof less than .05 in the same direction as observed for height (Supplementary Table 6, available online). In particular, the association for eight SNPs remained statistically significant after adjusting for multiple comparisons of 168 independent SNPs, significantly higher than expected by chance ($P < 10^{-15}$) (Table 4). The association for three SNPs, rs11205277 near the *SF3B4* gene at 1q21.2, rs4665736 in the *DNAJC27* gene at 2p23.3, and rs2638953 in the *CCDC91* gene at 12p11.22, reached the genome-wide significance level of *P* values of less than 5.0×10^{-8} (Table 4 and Figure 4). These three loci have not been previously reported in GWAS to be associated with breast cancer risk.

Discussion

The association between adult height and breast cancer risk in women has been investigated in many epidemiological studies (2–4). However, the magnitude of this association, particularly for subtypes of breast cancer, has not been established. In our meta-analysis of data from more than five million women, including approximately 110 000 breast cancer events, we estimated that a 10 cm increase in height was associated with a 17% elevated risk of breast cancer. The association was stronger in the meta-analysis of studies with measured height than in meta-analysis of studies with self-reported height. This association was confirmed in our Mendelian randomization analysis including 62 328 breast cancer case patients and 83 817 control subjects from two large consortia, in which a 21% to 22% elevated risk of breast cancer was associated with per 10 cm increase in genetically predicted height. The weaker association observed in the meta-analysis of previous cohort studies was expected because some of these conventional observational studies may have suffered from possible biases, including confounding biases and measurement errors. In both meta-analysis of prospective studies and Mendelian randomization analysis, the association between height and breast cancer risk was observed in both premenopausal and postmenopausal women but was limited primarily to hormone receptor–positive breast cancer. Using the Mendelian randomization approach, our study provides strong evidence for a possible causal association between adult height and breast cancer risk. Results from this study have clarified the nature of the height and breast cancer association and provided additional insight into the genetic and biological basis of breast cancer development.

The genetic score used in our Mendelian randomization analysis explains approximately 10% of the height variation in populations of European ancestry. The remaining 90% of height variation would be explained by both environmental factors and genetic variants not yet identified. Given the small height variation explained by the genetic score used in our study, we expected that the association between measured/reported height and breast cancer risk should be similar with or without adjusting for the height-associated genetic score. Indeed, this is what we observed in the study. It has been reported that in addition to genetic factors, adult height is influenced by energy intake and socioeconomic status during growth spurts (53). It has been suggested that certain nutritional factors during childhood and adolescence may be related to breast cancer risk (2–4). Height is also influenced by the timing of puberty, which is affected by endogenous estrogen, a hormone that plays a central role in breast cancer etiology (2–4). However, very few studies have collected sufficiently detailed data on childhood and adolescent nutrition and health status and pubertal development to clearly disentangle the association of breast cancer risk with adult height from these exposures that could also contribute to breast cancer risk (54). Therefore, it has been unclear whether height is just a simple surrogate measure of early life exposures of breast cancer risk factors, in

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Table 4. Association of breast cancer risk with eight height-associated SNPs that remained statistically significant after adjusting for 168 multiple comparisons ($P < .0003$)

SNP	Locus	Position*	Gene†	Alleles‡ (1/2)	BCAC§			DRIVE§			Combined (62 328/83 817)	
					RAF	OR (95% CI)	P_{trend}	RAF	OR (95% CI)	P_{trend}	OR (95% CI)	P_{meta}
rs11205277	1q21.2	148159496	*SF3B4*	G/A	0.43	1.06 (1.04 to 1.08)	4.58×10^{-10}	0.45	1.03 (1.00 to 1.08)	.08	1.06 (1.04 to 1.07)	2.02×10^{-10}
rs4665736	2p23.3	25041103	*DNAJC27*	T/C	0.53	1.06 (1.04 to 1.09)	3.11×10^{-7}	0.51	1.04 (1.01 to 1.08)	.02	1.06 (1.04 to 1.08)	2.65×10^{-8}
rs724016	3q23	142588260	*ZBTB38*	G/A	0.45	1.05 (1.03 to 1.07)	2.88×10^{-6}	0.45	1.05 (1.01 to 1.08)	.009	1.05 (1.03 to 1.06)	8.64×10^{-8}
rs17081935	4q12	57518233	*NOA1*	T/C	0.19	1.05 (1.02 to 1.07)	2.52×10^{-4}	0.19	1.02 (0.98 to 1.07)	.36	1.04 (1.02 to 1.06)	2.73×10^{-4}
rs3782089	11q13.1	65093395	*SSSCA1*	C/T	0.93	1.08 (1.04 to 1.12)	5.76×10^{-5}	0.93	1.03 (0.96 to 1.11)	.39	1.07 (1.03 to 1.11)	7.32×10^{-5}
rs2638953	12p11.22	28425682	*CCDC91*	C/G	0.68	1.05 (1.03 to 1.08)	2.90×10^{-7}	0.68	1.08 (1.04 to 1.12)	1.74×10^{-5}	1.06 (1.04 to 1.08)	4.95×10^{-11}
rs3764419	17q11.2	26188149	*ATAD5*	C/A	0.62	1.04 (1.02 to 1.06)	1.14×10^{-4}	0.61	1.05 (1.01 to 1.08)	.01	1.04 (1.02 to 1.06)	3.93×10^{-6}
rs4605213	17q21.33	46599746	*NME1-NME2*	C/G	0.35	1.03 (1.01 to 1.05)	.003	0.35	1.04 (1.01 to 1.08)	.03	1.03 (1.02 to 1.05)	2.31×10^{-4}

* The chromosome physical position is based on the National Center for Biotechnology Information database, Build 36.3. BCAC = Breast Cancer Association Consortium; CI = confidence interval; DRIVE = Discovery, Biology, and Risk of Inherited Variants in Breast Cancer; OR = odds ratio; RAF = risk allele frequency; SNP = single-nucleotide polymorphism.

† The closest gene(s).

‡ Alleles (1/2); Allele1 (risk allele) associated with increased height in initial study; Allele2, reference allele.

§ Results (RAF, OR, 95% CI, and *P* value) were derived from BCAC and DRIVE. Three loci (1q21.2, 2p23.3 and 12P11.22) were associated with breast cancer risk at genome-wide significant level $P < 5 \times 10^{-8}$. All tests were two-sided.

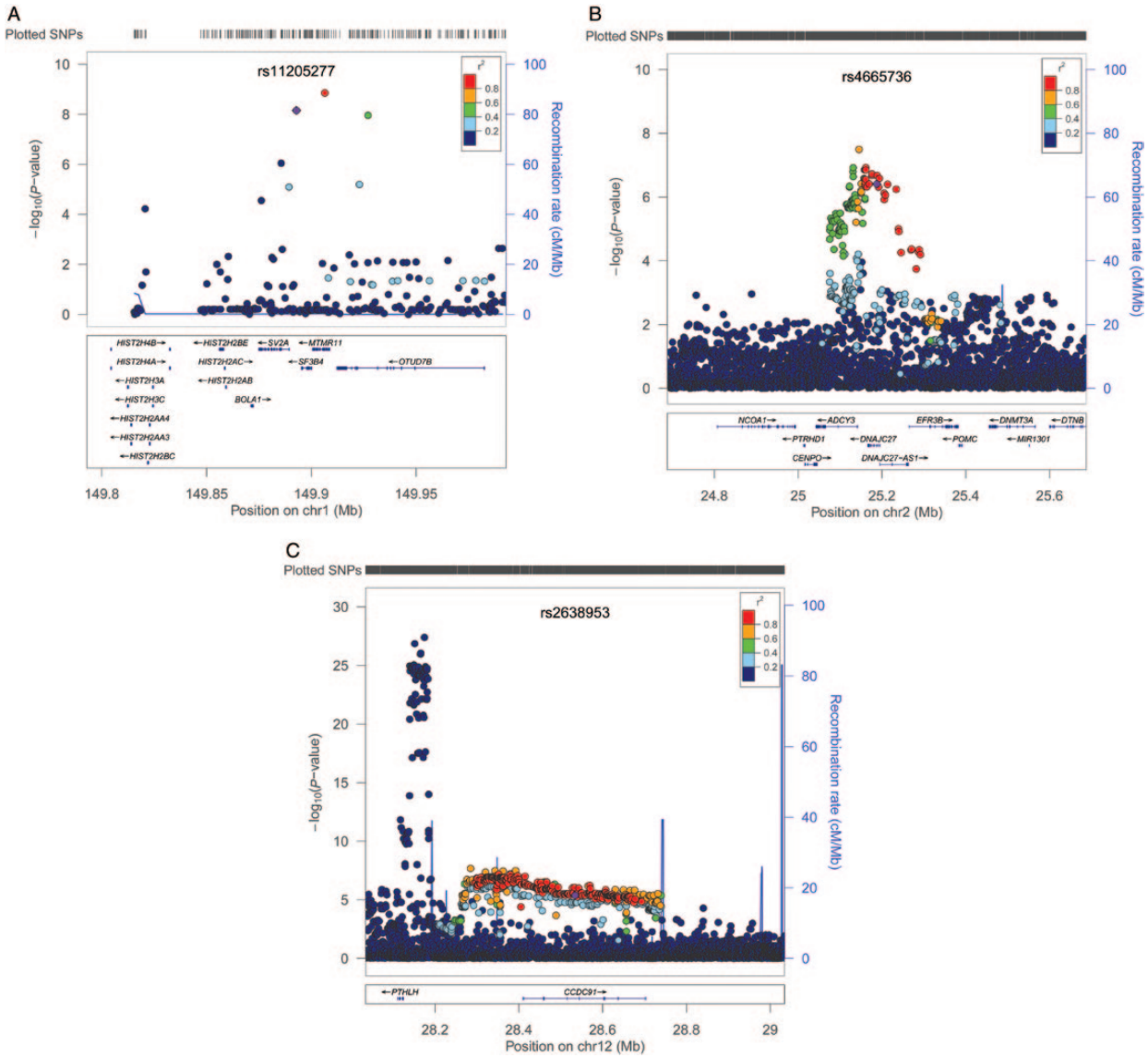

Figure 4. Regional association plots of the three new loci associated with breast cancer risk in the Breast Cancer Association Consortium. The **three plots** represent: **(A)** 1q21.2, **(B)** 2p23.3, and **(C)** 12p11.22. For each plot, the -$\log_{10}$ (P values) (y-axis) of single-nucleotide polymorphisms (SNPs) are shown according to their chromosomal positions (x-axis) in National Center for Biological Information (NCBI) Build 37. **Blue lines** represent the estimated recombination rates from the HapMap Project (NCBI Build 37). **Arrows** indicate genomic locations of genes within the LD block centered on the index SNPs in the NCBI Build 37 human assembly. The color of SNPs represents their LD (r^2, the 1000 Genomes Project Europeans), with the index SNP shown as a **purple diamond** at each locus.

which height per se is not causally related to breast cancer risk. It is also possible that the height–breast cancer association is causal, in which genetic and/or environmental factors determine height and subsequently contribute to breast cancer risk through the shared underlying biology. Using the Mendelian randomization approach, our study provides strong evidence for a possible causal association between adult height and breast cancer risk, suggesting that factors, both genetic variants and environmental exposures, that determine adult height, collectively, may be causally related to breast cancer risk. The primary goal of Mendelian randomization analyses is to minimize possible biases commonly encountered in conventional observational studies in order to provide strong evidence for causal influence. Like any other Mendelian randomization study, we cannot estimate the relative contribution of genetic variants and environmental exposures to the association between adult height and breast cancer risk in our study, particularly because many additional genetic variants related to height have not yet been identified. Given the incomplete understanding of the genetic component for complex traits, such as adult height, body weight, and blood lipids, no Mendelian randomization study conducted to date has attempted to determine relative contribution of genetics and environment in the association between these traits and disease risk (69–74).

Adult height is the result of various growth and development processes that are determined by many biological pathways. Among them, the insulin-like growth factor (IGF) signaling pathway is of particular interest. Multiple genetic variants in the IGF signal pathway have been identified by GWAS to be related to height (55). In fact, it is known that IGFs, particularly IGF1, are major regulators of growth in utero and during childhood and adolescence (56). IGF1 also plays an important role in carcinogenesis through promotion of epithelial cell proliferation and inhibition of apoptosis (57). Circulating IGF1 levels were found

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to be higher among taller compared with shorter women and were positively associated with breast cancer risk in a recent pooled analysis of 17 prospective studies (58). In contrast, low levels of IGF1 due to mutations in the *GHR* gene were associated with severe short stature and absence of breast cancer (or overall cancer) in individuals with Laron dwarfism in a prospective study (59). In addition to the IGF signal pathway, multiple other biological pathways have also been identified by GWAS to be associated with adult height, including Hedgehog, MARK, TGF-β, WNT, BMP, and mTOR (38,55,60). Some of these may also be involved in the pathogenesis of breast cancer (61–66). To our knowledge, to date no genetic variants in these pathways have been conclusively associated with breast cancer risk. Our study suggests that height and breast cancer susceptibility share some common genes and biological pathways, and thus focused search in future studies for variants in genes and biological pathways established for height may help to identify additional genetic risk variants for breast cancer.

By analyzing height-associated SNPs, we identified eight variants associated with breast cancer risk after adjusting for multiple comparisons. In particular, the association with three loci previously not reported in relation to breast cancer risk reached the genome-wide significance level of *P* values of less than 5.0×10^{-8}. At locus 1q21.2, the risk-associated SNP rs11205277 is located in an intergenic region between *SV2A* and *SF3B4*. Two other genes, *MTMR11* and *OTUD7B,* are also included in the linkage disequilibrium (LD) block tagged by the SNP. At the 2p23.3 locus, the risk-associated variant rs4665736 lies in intron 2 of the *DNAJC27* gene. This SNP is related to the expression of the *ADCY3* and *DNAJC27* genes in peripheral blood samples (67). At the 12p11.22 locus, rs2638953 maps to intron 6 of the *CCDC91* gene. Data from the ENCODE Project suggest that rs2638953 and other highly correlated SNPs ($r^2 > 0.8$) in the LD block might have regulatory functions (68). Additional studies are warranted to fine-map and functionally characterize the regions identified in our study.

Our analysis based on height-associated genetic score is consistent with a Mendelian randomization. The instrumental variable (wHGS) was strongly associated with adult height, the exposure of interest. The large *F*-statistic value (>3500) indicated that wHGS is a very strong instrumental variable. Although wHGS was related to some known breast cancer risk factors, all of the observed associations were much weaker than adult height, and all of the association can be explained by height. Indeed, we have shown that the associations between the wHGS and these breast cancer risk factors all disappeared after adjusting for measured/reported height. One possible limitation for the Mendelian randomization analysis is that of the 168 height-associated SNPs included in our study, 145 were imputed in BCAC, which could lead to an overall less precise estimate for the genetic association with height, underestimating the association between genetically predicted height and breast cancer risk. However, this bias should not be substantial because the imputation R^2 was greater than 0.50 for all of the SNPs included in the analysis with a mean value of 0.88. Furthermore, results from BCAC were replicated in DRIVE, and the results from these two large consortia were very close. Our meta-analysis of prospective cohort studies may be subject to potential biases inherent in the original studies. To minimize these biases, we included only prospective studies with age or multivariable-adjusted relative risks and excluded non-European studies from our analysis to minimize heterogeneity. We also conducted subgroup meta-analyses and found that the association of breast cancer risk was stronger with measured height than self-reported height. Most studies participating in BCAC are case-control studies, with height information obtained after cancer diagnosis. This may have contributed to the lower risk estimates for the association between adult height and breast cancer risk in BCAC than those obtained from the meta-analysis of prospective studies and the Mendelian randomization analysis. We present results from the analyses of prospective cohort studies, Mendelian randomization, and case-control studies in parallel to illustrate a potential biased estimate of the association between height and breast cancer risk from conventional case-control studies.

To our knowledge, this is the largest Mendelian randomization analysis conducted to date for any cancer. With 62 328 breast cancer case patients and 83 817 control subjects, our study has excellent power to quantify the association with overall breast cancer and by breast cancer subtypes. Our study, with data from a large meta-analysis of prospective cohort studies and Mendelian randomization analysis, provides strong evidence that adult height is a risk factor for breast cancer in women and that the association between adult height and breast cancer risk is likely to be causal. Furthermore, our study revealed that there are shared underlying genetic pathways affecting both height and the pathogenesis of breast cancer.

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