Adult height is associated with increased risk of ovarian cancer: a Mendelian randomisation study

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Abstract

Background: Observational studies suggest greater height is associated with increased ovarian cancer risk, but cannot exclude bias and/or confounding as explanations for this. Mendelian randomization (MR) can provide evidence which may be less prone to bias.

Methods: We pooled data from 39 Ovarian Cancer Association Consortium studies (16,395 cases; 23,003 controls). We applied two-stage predictor-substitution MR, using a weighted genetic risk score combining 609 single nucleotide polymorphisms. Study-specific odds ratios (OR) and 95% confidence intervals (CI) for the association between genetically-predicted height and risk were pooled using random-effects meta-analysis.

Results: Greater genetically-predicted height was associated with increased ovarian cancer risk overall (pooled-OR [pOR]=1.06; 95%CI 1.01-1.11 per 5-cm increase in height), and separately for invasive (pOR=1.06; 95%CI 1.01-1.11) and borderline (pOR=1.15; 95%CI 1.02-1.29) tumours.

Conclusion: Women with a genetic propensity to being taller have increased risk of ovarian cancer. This suggests genes influencing height are involved in pathways promoting ovarian carcinogenesis.

Key words

Adult Height; Ovarian cancer; Mendelian randomization; Genetic risk score

Introduction

Observational studies have reported a positive association between adult height and ovarian cancer risk (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012; Emerging Risk Factors Collaboration, 2012; Schouten *et al*, 2008; World Cancer Research Fund/American Institute for Cancer Research, 2014). However, these studies were subject to the biases inherent in conventional observational studies, including selection bias, differential and non-differential reporting bias, and confounding. The degree to which these factors could account for the observed association is uncertain. Mendelian randomization (MR) uses genetic markers as proxies for environmental exposures and, due to the singular qualities of genotype data, can provide complementary evidence by overcoming many biases affecting conventional studies (Davey Smith & Ebrahim, 2003). We used MR to examine the relationship between height and ovarian cancer risk in the Ovarian Cancer Association Consortium (OCAC) (Gayther *et al*, 2007), aiming to provide more certainty about the relationship between height and ovarian cancer risk. We hypothesised that greater genetically-predicted height would be associated with increased risk.

Materials and Methods

Study population and outcomes

We pooled data from 16,395 genetically European women with primary ovarian/fallopian tube/peritoneal cancer and 23,003 controls from 39 OCAC studies (Table 1; Supplementary Table 1). The dataset and methods have been described previously (Dixon *et al*, 2016). Participants were genotyped via the Collaborative Oncological Gene-Environment Study (Pharoah *et al*, 2013). Twenty-two studies provided height data (16 provided parity, oral contraceptive [OC] use, education, and age at menarche information) for >50% of their participants. We first considered all cases, then stratified by tumour behaviour. Secondary analyses stratified by histologic subtype/behaviour.

Genetic risk score

The Genetic Investigation of ANthropometric Traits (GIANT) Consortium had previously identified 697 single nucleotide polymorphisms (SNPs) significantly associated with height (Wood *et al*, 2014). In our sample, 92 of these SNPs had been genotyped and the remainder were imputed using 1000 Genome Project data (Abecasis *et al*, 2010; Pharoah *et al*, 2013). After excluding poorly-imputed SNPs (quality r^2<0.6), 609 remained (92

genotyped/517 imputed) (Supplementary Table 2). In controls, minor allele frequencies (MAFs) were >5% (except for 16 SNPs, MAFs 1.7-4.9%).

We constructed a weighted genetic risk score (GRS) for height by summing height-increasing alleles across the 609 SNPs ('GRS-609'/'the GRS'), weighting alleles by β-coefficients for their association with height reported by GIANT. The score represents predicted additional height conferred by these variants, compared to having no height-increasing alleles. We report results for 5-cm increments.

Statistical analysis

Statistical methods have been described previously (Dixon *et al*, 2016). Briefly, we used individual-level OCAC data for two-stage predictor-substitution MR (Burgess, 2013; Didelez *et al*, 2010): first we predicted height from the weighted GRS for all participants using coefficients from linear regression in 17,649 controls with height data; second, within each study, we used logistic regression to model disease status on GRS-predicted height. Models adjusted for age and five principal components for population structure (Pharoah *et al*, 2013). We combined study-specific estimates using meta-analysis (Stukel *et al*, 2001), generating pooled odds ratios (pOR) and 95% confidence intervals (CI) for the trend in risk per 5-cm increase in predicted height. We had 97% power to detect an OR of 1.10 (mRnd tool (Brion *et al*, 2013)).

Sensitivity analyses included removing 16 SNPs with MAFs <5%, and restricting to SNPs with imputation $r^2 \geq 0.9$ ('GRS-363'), SNPs representing distinct loci (Wood *et al*, 2014) ('GRS-377'), and directly-genotyped SNPs ('GRS-92'). We examined whether potential confounders of the association in observational studies were associated with the GRS. To assess robustness to pleiotropy (where SNPs may influence risk via pathways not mediated through height), we conducted MR-Egger regression (Bowden *et al*, 2015) and assessed smaller GRSs excluding SNPs with the highest probability of acting via other pathways from GRS to outcome (SNPs associated with ovarian/other hormonal cancers [breast, prostate], hormone levels, and in/near tumour initiation/growth genes). We identified these potentially-pleiotropic, pathway-specific SNPs via the NHGRI GWAS Catalog (Welter *et al*, 2014), the UCSC Genome/Table Browsers (Karolchik *et al*, 2004; Kent *et al*, 2002), and from lists of SNPs nominated for iCOGS genotyping by ovarian, breast, and prostate cancer researchers (to capture SNPs of interest unpublished at the time of analysis).

Secondary analyses defined cases by histologic subtype/behaviour. Among 16 studies with height/confounder data, we conducted conventional analysis (adjusted for parity, OC use, education, menarche age; stratified by study, 5-year age group), and compared results with MR-estimates among the same women.

Analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) and Stata 13.0 (StataCorp LP, College Station, TX). This work and each contributing study was approved by the appropriate institutional review board/ethics committee. All participants provided informed consent.

Results

Population characteristics

We included 16,395 cases (14,549 invasive tumours, 1,691 borderline, 155 of unknown behaviour), and 23,003 controls (Table 1). The median diagnosis year was 2003, with 74% diagnosed post-2000. Participants were aged 18-94 (median 56) years at diagnosis/interview. Mean height ranged from 159 to 167 cm across 22 studies with data, and was 163 (standard error [SE]=0.05) cm for controls and 164 (SE=0.06) cm for cases (p<0.0001).

Genetic risk score characteristics

The GRS-609 was normally distributed in controls, ranging from 15.45 to 18.99 (median=17.23; interquartile range=16.92-17.54). It explained 13% of variance in height, 17% after adjusting for age and principal components (partial-R^2=12%; first-stage regression partial-F-statistic=2505.8 [df=1], p<0.001). A 1-unit GRS-609 increase was associated with 5.2cm greater height. Average height was 6.2cm greater in the highest vs. lowest GRS quartile.

Cochran's I^2 and p-values for heterogeneity (Higgins & Thompson, 2002) showed no evidence of inter-study heterogeneity in the relationship between either the GRS-609 (I^2=34%, p-heterogeneity=0.07) or the simplified GRS-363 (I^2=32%, p-heterogeneity=0.08) and height among controls (Supplementary Figure 1a/1b). The GRS-609 was not associated with most potential confounders of the height-ovarian cancer association in observational studies, including age, parity, OC use, and education (Supplementary Table 3). The GRS was marginally positively associated with age at menarche (p=0.03), consistent with known genetic overlap between these traits (Bulik-Sullivan *et al*, 2015).

Primary outcomes

Women with greater genetically-predicted height had a modestly increased risk of developing ovarian cancer (pOR=1.06, 95%CI 1.01-1.11 per 5-cm) (Figure 1a; Table 2) with a greater magnitude of association for borderline (pOR=1.15; 95%CI 1.02-1.29) than invasive tumours (pOR=1.06; 95%CI 1.01-1.11; Figure 1b/1c; Table 2). No significant inter-study heterogeneity was noted (Figure 1a/1b/1c). GRS-363 (pOR=1.06, 95%CI 1.00-1.11, all tumours) and GRS-377 (OR=1.07; 95%CI 1.01-1.12) results were similar to the GRS-609. The association was stronger when we restricted to 92 genotyped SNPs (pOR=1.14; 95%CI 1.04-1.25). Estimates from analyses excluding low-MAF SNPs, excluding case-only studies, or adjusting for age at menarche, were similar to primary analyses. When we sequentially excluded SNPs associated with ovarian or other hormonal cancers, hormone levels, and tumour development, estimates were similar or stronger than GRS-609 results. MR-Egger suggested minimal bias from pleiotropy (p=0.1; MR-Egger beta=0.163 corresponded to an OR per 5 cm of 1.13 (95% CI 1.02-1.25), confirming a significant positive association).

In contrast, for women with height and confounder data (16 studies), the conventional analysis suggested no association (adjusted-OR=1.01, 95%CI 0.99-1.04 per 5-cm). Conducting MR within the same 16 studies yielded results similar to overall analyses (OR=1.06, 95%CI 1.00-1.13) (Supplementary Table 4).

Secondary outcomes

After stratifying by subtype/behaviour, the strongest associations were seen for clear cell (OR=1.20, 95%CI 1.04-1.38) and low-grade/borderline serous cancers (OR=1.15, 95%CI 1.01-1.30) (Table 2). However, confidence intervals were wide and overlapping due to lower statistical power in these subgroup analyses. The estimate for clear cell cancers was also significantly elevated in our conventional analyses (Supplementary Table 4).

Discussion

We used a 609-SNP GRS to examine the relationship between height and ovarian cancer risk for women of European ancestry. Our data indicate a modest positive association between genetically-predicted height and ovarian cancer risk, which may be stronger for borderline cancers. Height may be relevant to cancer risk as a marker for lifetime growth-factor levels (e.g. IGF-1) and/or early-life exposures (socio-

economic/environmental/nutritional) (Clayton *et al*, 2011; Stefan *et al*, 2016; World Cancer Research Fund/American Institute for Cancer Research, 2014).

Observational studies are subject to biases (reverse causality, selection bias, differential/non-differential reporting, confounding) which cannot be ruled out as possible explanations for observed associations. By using genotype, the MR technique can overcome some of these biases, given three assumptions. We confirmed the two verifiable assumptions: the GRS was associated with height, and not with most known confounders. The GRS-menarche age association is unlikely to explain the observed association, because age at menarche is only weakly associated with ovarian cancer, and women with later menarche have if anything lower ovarian cancer risk, so if this affected our results we would expect the true effect to be at least as strong as the reported association. Also, removing hormone-related SNPs, or adjusting for menarche age, did not attenuate estimates. Due to limited current biological understanding of all 609 SNPs, we could not conclusively exclude the presence of alternate pathways from height genes to ovarian cancer (assumption three). However, MR-Egger and sensitivity analyses excluding pathway-specific SNPs provided some evidence for their absence, minimising the likelihood that our observed association is explained by pathways separate from height/growth. While height data were not available for the entire population, this is unlikely to have affected our results as we used these data only to refine the height predictions from the GRS, and there is no reason to believe the GRS-height relationship would be different for women with and without height data. Further strengths of our analysis include the large number of SNPs and power to detect modest differences.

Despite potential limitations of conventional observational studies, our MR-estimate is almost identical to previously-reported associations, suggesting previous estimates were not appreciably biased. The World Cancer Research Fund/American Institute for Cancer Research meta-analysis of 24 prospective studies, and a study pooling 47 prospective/case-control studies, both reported a significant 7-8% increase in risk (combining invasive/borderline cancers) per 5-cm height increase (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012; World Cancer Research Fund/American Institute for Cancer Research, 2014). The lack of association seen in the OCAC conventional height analysis reflects the greater potential for bias in case-control studies and illustrates the value of MR in overcoming these biases. Few previous studies have examined borderline cancers separately, a strength of our analysis. Previous observational studies have not reported consistent patterns by histologic subtype (Collaborative Group on Epidemiological Studies of Ovarian Cancer,

2012; Jordan *et al*, 2005; Schouten *et al*, 2008); our secondary analyses were under-powered to resolve this question.

Using MR, we have established that the previously-observed association between height and ovarian cancer risk is unlikely to have been explained by bias, and that genetic factors influencing height play roles in ovarian cancer development. Height could therefore be used, with other risk factors, to identify women at elevated risk. Further research should continue to explore mechanisms underpinning this association.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interest.

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Tables and figures

Table 1: Characteristics of 39 OCAC studies and 39,398 participants of European ancestry [a] included in the Mendelian randomization analysis

Study acronym [b]	Country	Diagnosis (years)	Median (range) age at diagnosis/ interview	Invasive cases (N)	Borderline cases (N)	All cases (N) [c]	Controls (N)	Mean (SD) height (cm) [d]
AUS	Australia	2002-2006	58 (19-80)	859	1	860	977	163 (6.9)
BAV	Germany	2002-2008	58 (24-83)	96	5	102	143	164 (5.8)
BEL	Belgium	2007-2010	46 (19-87)	275	0	275	1,347	--
DOV	USA	2002-2009	57 (35-74)	904	327	1,231	1,487	166 (6.5)
GER	Germany	1993-1998	57 (21-75)	189	24	213	413	163 (6.0)
GRR	USA	1981-2012	48 (21-83)	125	0	125	0	--
HAW	USA	1993-2008	56 (27-87)	60	20	80	157	163 (6.6)
HJO	Germany	2007-2011	54 (18-88)	261	13	290	273	--
HMO	Belarus	2006-2011	45 (22-76)	142	0	143	138	--
HOC	Finland	1975-1999	46 (18-86)	210	8	239	447	--
HOP	USA	2003-2009	58 (25-94)	567	71	723	1,464	163 (6.8)
HSK	Germany	2000-2007	58 (18-81)	147	9	156	0	165 (5.6)
LAX	USA	1989-2008	58 (31-88)	278	0	278	0	--
MAL	Denmark	1994-1999	57 (31-80)	440	138	578	828	166 (6.1)
MAY	USA	2000-2010	61 (20-93)	699	79	778	743	165 (6.3)
MCC	Australia	1990-2008	65 (45-79)	66	0	66	66	159 (7.0)
MDA	USA	1997-2009	62 (23-88)	375	0	375	384	--
MSK	USA	1997-2010	57 (18-89)	450	0	450	593	--
NCO	USA	1999-2008	57 (20-75)	722	171	896	792	163 (6.4)
NEC	USA	1992-2003	52 (21-78)	654	232	904	1,009	163 (6.7)
NJO	USA	2002-2009	60 (25-88)	169	0	169	181	163 (6.9)
NOR	Norway	2001-2010	51 (18-86)	236	12	248	371	--
NTH	Netherlands	1997-2008	55 (18-83)	292	3	295	323	167 (6.0)
ORE	USA	2007-2011	58 (22-86)	55	9	65	0	--
OVA	Canada	2002-2009	58 (19-80)	640	161	801	748	--

Study acronym [b]	Country	Diagnosis (years)	Median (range) age at diagnosis/ interview	Invasive cases (N)	Borderline cases (N)	All cases (N) [c]	Controls (N)	Mean (SD) height (cm) [d]
POC	Poland	1998-2008	55 (23-82)	423	0	423	417	--
POL	Poland	2000-2004	56 (24-74)	236	0	236	223	162 (5.6)
PVD	Denmark	2004-2009	63 (30-88)	168	0	168	0	165 (6.5)
RMH	UK	1993-1996	52 (26-73)	148	7	155	0	--
SEA	UK	1998-2011	57 (19-78)	1,447	76	1,530	6,004	162 (6.3)
SOC	UK	1993-1998	62 (22-92)	268	20	288	0	--
SRO	UK	1999-2001	59 (34-84)	158	0	158	0	--
STA	USA	1997-2002	50 (20-64)	251	10	261	313	165 (6.7)
TOR	Canada	1995-2007	58 (26-85)	603	0	605	440	163 (7.1)
UCI	USA	1993-2005	56 (18-86)	277	141	418	367	165 (6.6)
UKO	UK	2006-2010	63 (19-89)	718	0	718	1,104	162 (6.7)
UKR	UK	1991-2009	54 (24-77)	47	0	47	0	--
USC	USA	1992-2010	57 (22-82)	693	152	845	1,047	165 (6.8)
WOC	Poland	1997-2010	44 (20-81)	201	2	203	204	--

OCAC, Ovarian Cancer Association Consortium; SD, standard deviation.

[1] All participants were of >90% European ancestry according to genetic markers of ancestry.

[2] OCAC is an international collaboration of largely case-control studies. See Supplementary Table 1 for study names and references. To maximise power, nine case-only studies were grouped for analysis with case-control studies from the same region: HSK combined with GER; GRR with HOP; PVD with MAL; RMH, SOC, SRO, UKR with SEA and UKO ('UK group'); ORE with DOV; LAX with UCI.

[3] Cases had primary ovarian (n=15,636), fallopian tube (n=180), or peritoneal (n=552) cancer, or ovarian/tubal/peritoneal tumours of undetermined site (n=27).

[4] Usual adult height. Height is summarised for 22 studies (20 case-control studies) where >50% participants had data available (AUS, BAV, DOV, GER, HAW, HOP, HSK, MAL, MAY, MCC, NCO, NEC, NJO, NTH, POL, PVD, SEA, STA, TOR, UCI, UKO, USC). Sixteen of these 22 studies were also used in conventional height analyses, as they provided data on potential confounders (age, parity, use of oral contraceptives, education, and age at menarche) for >50% of participants (AUS, DOV, GER, HAW, HOP, MAL, NCO, NEC, NJO, NTH, POL, STA, TOR, UCI, UKO, USC).

Table 2: Association between increasing height (per 5 cm) - predicted by a weighted 609-locus genetic risk score [a] - and risk of ovarian cancer, stratified by study

Histologic subtype [b]	N studies	N controls	N cases	Odds Ratios (95% CI)[c]
Primary outcomes				
All ovarian cancers	39	23,003	16,395	1.06 (1.01-1.11)
Invasive	39	23,003	14,549	1.06 (1.01-1.11)
Borderline [d]	20	16,463	1,680	1.15 (1.02-1.29)
Secondary outcomes, by histologic subtype and behaviour				
Serous				
High-grade [e]	39	23,003	7,933	1.05 (0.99-1.11)
Invasive low-grade & borderline	32	21,131	1,408	1.15 (1.01-1.30)
Mucinous (invasive & borderline)	38	22,410	1,567	1.08 (0.96-1.21)
Endometrioid (invasive)	39	23,003	2,059	1.05 (0.95-1.16)
Clear cell (invasive)	35	22,051	948	1.20 (1.04-1.38)

CI, confidence interval.

[1] Weights applied were β-coefficients for the relationship between each SNP and height as reported in the meta-analysis of genome-wide association studies conducted by the Genetic Investigation of ANthropometric Traits (GIANT) Consortium (Wood et al, 2014). Based on the additive SNP effects suggested by GIANT, the score summed alleles across the 609 SNPs. For the 92 genotyped SNPs, where values were missing (<2.5% per SNP), we used imputed probabilities.

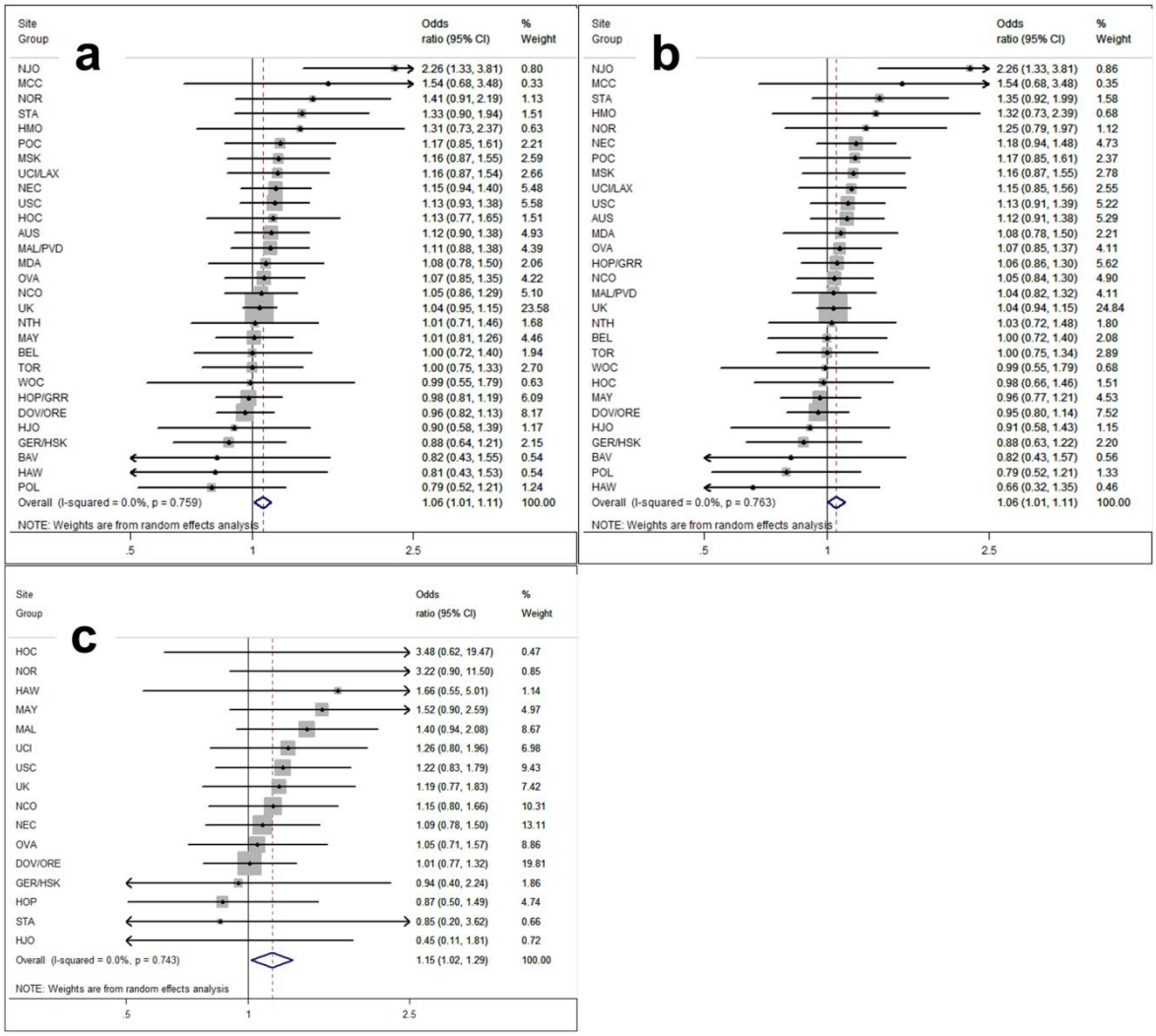
[2] Includes studies with >5 cases.

[3] Pooled study-specific odds ratios are reported for primary outcomes; odds ratios stratified by study are reported for secondary outcomes (secondary analyses used single models stratified by study to maximise power).

[4] Of the 1,691 borderline tumours included in the all-case analysis, 1,680 were from 20 studies with >5 cases each.

[5] Includes all invasive serous cancers except low-grade (G1) (n=469) as well as invasive serous cancers of unknown grade (n=1,957) and primary peritoneal cancers of unknown behaviour (n=44), because in both instances the majority would be high-grade serous.

Figure 1: Association between increasing genetically-predicted height and risks of all, invasive, and borderline ovarian tumours. Increasing height per 5 cm predicted by weighted 609-locus genetic risk score among 39 studies. Risk of (a) all (b) invasive and (c) borderline ovarian tumours. The U.K. grouping includes RMH, SOC, SRO, UKR, SEA and UKO for (a) and (b), and RMH, SOC, and SEA for (c).



Supplementary Information

Adult height is associated with increased risk of ovarian cancer: a Mendelian randomisation study

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Supplementary Table 1. Studies included in the analysis.

Acronym	Name of study/studies	Reference
AUS	Australian Ovarian Cancer Study/Australian Cancer Study (Ovarian Cancer)	1
BAV	Bavarian Ovarian Cancer Cases and Controls	2
BEL	Belgian Ovarium Cancer Study	2
DOV	Diseases of the Ovary and their Evaluation	3
GER	German Ovarian Cancer Study	4
GRR	Gilda Radner Familial Ovarian Cancer Registry	5, 6
HAW	Hawaii Ovarian Cancer Case-Control Study	7
HJO	Hannover-Jena Ovarian Cancer Study	2
HMO	Hannover-Minsk Ovarian Cancer Study	8
HOC	Helsinki Ovarian Cancer Study	9
HOP	Hormones and Ovarian cancer PrEdiction	10
HSK	Dr Horst Schmidt Kliniken	11, 12
LAX	Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute	13
MAL	MALignant OVArian cancer	14-16
MAY	Mayo Clinic Ovarian Cancer Case-Control Study	17, 18
MCC	Melbourne Collaborative Cohort Study	19
MDA	MD Anderson Cancer Center	13
MSK	Memorial Sloan-Kettering Cancer Center	13
NCO	North Carolina Ovarian Cancer Study	20, 21
NEC	New England Case Control Study	22, 23
NJO	New Jersey Ovarian Cancer Study	24, 25
NOR	University of Bergen, Haukeland University Hospital, Norway	26, 27
NTH	Nijmegen Ovarian Cancer Study	28, 29
ORE	Oregon Ovarian Cancer Registry	30, 31
OVA	Ovarian Cancer in Alberta and British Columbia	32
POC	Polish Ovarian Cancer Study	13
POL	Polish Ovarian Cancer Case Control Study	33
PVD	Danish Pelvic Mass Study	34, 35
RMH	Royal Marsden Hospital Ovarian Cancer Study	36
SEA	Study of Epidemiology and Risk Factors in Cancer Heredity	37
SOC	Southampton Ovarian Cancer Study	38, 39
SRO	Scottish Randomised Trial in Ovarian Cancer	40, 41
STA	Family Registry for Ovarian Cancer, and Genetic Epidemiology of Ovarian Cancer	42
TOR	Familial Ovarian Tumour Study, and Health Watch	43
UCI	University California Irvine Ovarian Study	44
UKO	United Kingdom Ovarian cancer Population Study	45
UKR	UK Familial Ovarian Cancer Registry	46
USC	Los Angeles County Case-Control Studies of Ovarian Cancer	47-49
WOC	Warsaw Ovarian Cancer Study	50

Supplementary Table 2. Single nucleotide polymorphisms identified by GIANT[51] , grouped by inclusion in our height genetic risk scores[a b]

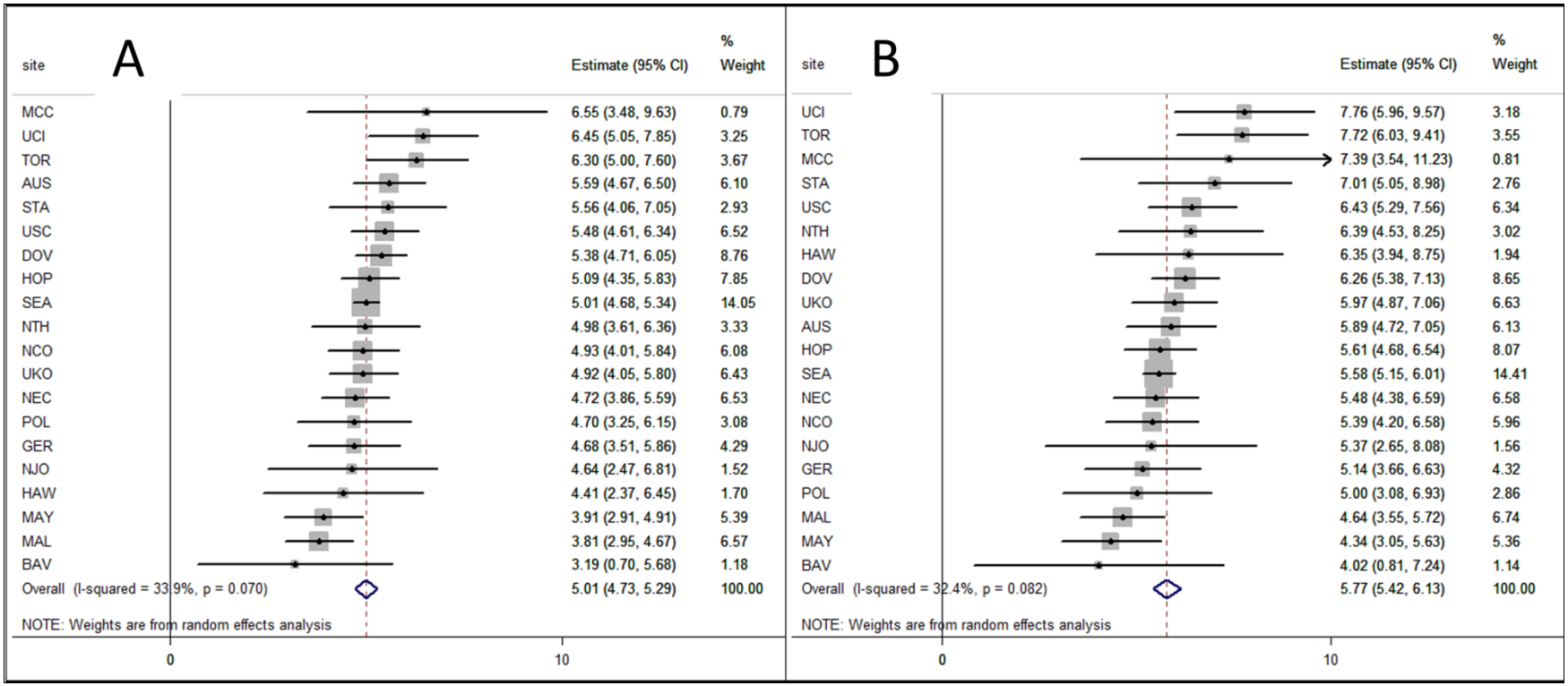
SNPs (rs numbers)	GRS-609	GRS-363	GRS-377	GRS-92
rs11799609, rs3814333, rs6694089, rs6696239, rs991967, rs3791679, rs780094, rs9309101, rs13088462, rs2581830, rs3915129, rs9841435, rs9880211, rs1996422, rs2302580, rs955748, rs26024, rs4624820, rs820848, rs314263, rs7740107, rs1055144, rs273945, rs42039, rs1036821, rs2956605, rs3763631, rs7033487, rs11049611, rs11612228, rs2306694, rs3825199, rs8756, rs11618507, rs5742915, rs975210, rs1659127, rs217181, rs8052560, rs3760318, rs3923086, rs9217, rs2074977, rs2682587, rs1326023, rs4812586, rs6061231, rs9977276	✓	✓	✓	✓
rs17163588, rs3767627, rs12329133, rs7561273, rs7605699, rs992157, rs2240919, rs6762606, rs7633464, rs1812175, rs868489, rs7731703, rs9327705, rs1341278, rs1415701, rs3020418, rs3800461, rs4713902, rs12533079, rs10958476, rs17088184, rs2737220, rs4448343, rs11198820, rs11599750, rs1815314, rs17659078, rs2735469, rs2915404, rs4320932, rs4357716, rs10492364, rs1861908, rs2164968, rs12863103, rs7334755, rs129963, rs2377058, rs2070776, rs6504389, rs8067165, rs8073177, rs1535466, rs6020202	✓	✓		✓
rs10779751, rs10863936, rs12120956, rs12855, rs1544196, rs212524, rs2275325, rs2811594, rs425277, rs564914, rs6600365, rs7517682, rs7544462, rs7551732, rs9428104, rs11684404, rs11687941, rs12470505, rs12474201, rs12693589, rs354196, rs4953951, rs6714546, rs6761041, rs7567851, rs7568069, rs897080, rs1546391, rs1658351, rs17806888, rs1797625, rs2633761, rs4686904, rs4974480, rs724016, rs936339, rs9835332, rs9858528, rs12513181, rs12639764, rs13113518, rs17081935, rs17556750, rs2306596, rs3958122, rs6813055, rs6838153, rs7692995, rs13177718, rs1582931, rs17410035, rs2662027, rs301901, rs32855, rs3812040, rs39623, rs422421, rs6894139, rs7701414, rs7716219, rs7733195, rs9291926, rs10948222, rs11156098, rs1155939, rs12214804, rs2145357, rs2748483, rs2763273, rs486359, rs4896582, rs6902771, rs6911389, rs6920372, rs7743622, rs9392918, rs9395264, rs12538407, rs3807931, rs552707, rs6949739, rs6952113, rs6955948, rs6974574, rs798497, rs929637, rs11783655, rs1550162, rs1599473, rs3812423, rs4733724, rs4735677, rs4875421, rs6988484, rs7007200, rs1571892, rs1576900, rs181338, rs2149163, rs7033940, rs7849585, rs7853235, rs10794175, rs10995319, rs10997979, rs12779328, rs1614303, rs1923367, rs2631676, rs291979, rs6584575, rs7069985, rs7899004, rs10767838, rs1461503, rs1945237, rs3782089, rs7112925, rs10877030, rs10880969, rs11047239, rs11616067, rs12228415, rs1420023, rs2164747, rs2856321, rs2888893, rs497273, rs7980687, rs12323101, rs12871822, rs3118905, rs3818416, rs7319045, rs7985356, rs11624136, rs1980850, rs2093210, rs7154721, rs10152739, rs16964211, rs16968242, rs316618, rs4548838, rs7162825, rs11642612, rs2326458, rs3790086, rs4785393, rs6420435, rs8058684, rs10083886, rs11867479, rs199515, rs2079795, rs2117563, rs4605213, rs8069300, rs870183, rs9766, rs11152213, rs4369779, rs11880992, rs2059877, rs4802134, rs7253628, rs7259684, rs8103992, rs1074683, rs2425163, rs2211866, rs2829941, rs2834442	✓	✓	✓	
rs1014987, rs12125882, rs12144094, rs1321666, rs1409156, rs17369123, rs2219320, rs4652773, rs926438, rs1367226, rs17032525, rs1864439, rs2343240, rs3791673, rs4973429, rs6751657, rs6754426, rs711245, rs994533, rs2300921, rs2596831, rs4325879, rs509035, rs7646824, rs17777628, rs6829680, rs867245, rs1004202, rs11950938, rs12153391, rs1529701, rs33852, rs4868645, rs6594336, rs6596075, rs7712162, rs12204421, rs1265097, rs17603945, rs3957165, rs648831, rs6899744, rs6919534, rs6921207, rs7774834, rs806794, rs9405356, rs2390151, rs2888877, rs7782764, rs4273857, rs6577717, rs894343, rs10119624, rs10759774, rs10962832, rs10990303, rs1742829, rs3812591, rs7870753, rs902143, rs9409082, rs11245515, rs703985, rs10766065, rs3750972, rs7126398, rs10843390, rs10859567, rs11057552, rs12820411, rs1809889, rs833706, rs1753637, rs6563199, rs1190545, rs10152591, rs10744956, rs11633371, rs2238300, rs4337252, rs7162542, rs7170986, rs731874, rs782930, rs11861084, rs12597498, rs11867943, rs1625895, rs2044124, rs2072153, rs2378870, rs8073371, rs9889755, rs10401193, rs11880124, rs17721822, rs6137287	✓	✓		

SNPs (rs numbers)	GRS-609	GRS-363	GRS-377	GRS-92
rs12137162, rs1325596, rs16834765, rs17113369, rs17391694, rs1935157, rs2284746, rs2298265, rs2806561, rs2815379, rs4656220, rs567401, rs6540834, rs6658763, rs6688100, rs9434723, rs11683207, rs12621643, rs12987566, rs13006748, rs13388725, rs13416119, rs2120335, rs2289195, rs2345835, rs3116168, rs4425077, rs540652, rs6435143, rs6746356, rs749234, rs7567288, rs12330322, rs2034172, rs2175513, rs2597513, rs6441170, rs6794009, rs720390, rs7652177, rs9816693, rs9825951, rs1562975, rs763318, rs7659107, rs996743, rs9993613, rs11750568, rs12186664, rs165189, rs17574650, rs2247870, rs2961830, rs2974438, rs34651, rs526896, rs7727731, rs9292468, rs12190423, rs12209223, rs1405212, rs16895130, rs17330192, rs1832871, rs310421, rs4141885, rs761391, rs932445, rs991946, rs1113765, rs17250196, rs17807185, rs2715094, rs4725061, rs6462432, rs6962887, rs6971575, rs822531, rs11779459, rs2013265, rs429433, rs568610, rs7834383, rs8180991, rs9650315, rs3132297, rs3739707, rs7027110, rs7043114, rs7466269, rs817300, rs953199, rs989393, rs10883563, rs1171615, rs4332428, rs4350272, rs915506, rs1681630, rs2237886, rs2272566, rs2510396, rs3802758, rs632124, rs6485978, rs757081, rs10748128, rs11835818, rs17122659, rs17783015, rs7971536, rs11616380, rs4883972, rs12882130, rs1950500, rs2058092, rs2781373, rs8017130, rs862034, rs11855014, rs12904334, rs17349981, rs2257011, rs2871865, rs7177711, rs7181724, rs1966913, rs2023693, rs26868, rs4843367, rs1552173, rs2072268, rs2338115, rs2854207, rs318095, rs3809790, rs4640244, rs4986172, rs584828, rs11659752, rs14062, rs692964, rs9967417, rs2123731, rs4803468, rs8102380, rs8103068, rs891088, rs17450430, rs1884897, rs2224538, rs6080830, rs7261425, rs11090631, rs7284476, rs738288	✓		✓	
rs10495098, rs12119525, rs12411277, rs17387330, rs2046158, rs2421992, rs4428898, rs956796, rs10048625, rs11677466, rs16859517, rs17181956, rs2278483, rs2305833, rs4344931, rs4674354, rs6544089, rs749052, rs11708412, rs13078528, rs1533269, rs16860216, rs4256170, rs11731978, rs13133465, rs16994718, rs17499117, rs4240326, rs4834927, rs6845999, rs7654571, rs961014, rs11745439, rs12055154, rs13183624, rs17075869, rs4620037, rs6887276, rs1040941, rs3828760, rs389663, rs479744, rs4895801, rs6903448, rs7745166, rs9328445, rs9443804, rs1007358, rs2188177, rs16939034, rs6999671, rs7823327, rs10820814, rs12344396, rs12347744, rs1257763, rs1329393, rs2451948, rs3927536, rs11244750, rs4746769, rs7097701, rs11236294, rs2099745, rs11107062, rs11175992, rs4326884, rs4767473, rs7299326, rs2687950, rs10140101, rs4901537, rs6571772, rs11634405, rs1348002, rs2573625, rs4246302, rs8028843, rs8042424, rs2531992, rs300039, rs3748394, rs11661645, rs12454567, rs12458127, rs2337143, rs1346490, rs6511689, rs143384, rs5757318	✓			

GIANT, Genetic Investigation of ANthropometric Traits consortium; GRS, genetic risk score; SNP, single nucleotide polymorphism.

[a] In our controls, minor allele frequencies for the 609 SNPs included in the GRS were consistent with those reported by GIANT.

[b] 88 SNPs identified by GIANT had an imputation quality score (r^2, estimated correlation between imputed and true genotype) of <0.6 in our data and were not included in any scores (rs4601530, rs209918, rs3014219, rs6691924, rs12731056, rs7534365, rs1244981, rs17038954, rs3885668, rs10460566, rs17511102, rs12615742, rs2166898, rs833152, rs6733349, rs2679184, rs13393800, rs6439168, rs11714558, rs11722554, rs6446315, rs2167645, rs11100790, rs13150868, rs3811958, rs10059761, rs12519505, rs4868126, rs1368380, rs6879260, rs163071, rs4246079, rs1047014, rs1233627, rs9404952, rs6457374, rs2857693, rs3129254, rs9456307, rs17140875, rs12669267, rs10283100, rs10972628, rs11144688, rs958225, rs10780910, rs999599, rs10817960, rs2509133, rs606452, rs10790381, rs11221442, rs10770705, rs1199734, rs6561319, rs17792664, rs12435366, rs10131337, rs8006657, rs1036477, rs17264185, rs12914466, rs16942341, rs2280470, rs3817428, rs11648796, rs2014467, rs12926008, rs1053996, rs960006, rs9929889, rs11640018, rs4243206, rs2028067, rs3169906, rs227724, rs1401795, rs1478610, rs4239020, rs888403, rs8097893, rs4072910, rs7273787, rs6085662, rs8117259, rs2057291, rs3026499, rs2413143).



Supplementary Figure 1. Association between two genetic risk score (GRS) versions and height, by study.
(A) GRS comprising 609 SNPs. (B) GRS comprising 363 SNPs with imputation quality scores ≥0·9.

Supplementary Table 3. Association between potential confounders and adult height and the height genetic risk score, among controls [a]

Characteristic	Adult height, cm (Mean [SD])	*P*-value[b]	GRS-609 Mean (SD)	*P*-value[b]
Age at diagnosis				
<40	1.66 (0.07)		17.2 (0.4)	
40-49	1.64 (0.07)		17.2 (0.5)	
50-59	1.64 (0.06)		17.2 (0.5)	
60-69	1.62 (0.06)		17.2 (0.5)	
≥70	1.61 (0.07)	<0.0001	17.2 (0.5)	0.2
Number of full-term pregnancies[c]				
0	1.64 (0.07)		17.2 (0.5)	
≥1	1.63 (0.07)	<0.0001	17.2 (0.5)	0.3
Oral contraceptive use				
Never	1.62 (0.07)		17.2 (0.5)	
Ever	1.64 (0.07)	<0.0001	17.2 (0.5)	0.95
<5 years	*1.64 (0.07)*		*17.2 (0.5)*	
≥ 5 years	*1.64 (0.07)*	*<0.0001*	*17.2 (0.5)*	*0.2*
Attained education				
High school or lower	1.63 (0.07)		17.3 (0.5)	
Trade/college/higher education	1.64 (0.07)	<0.0001	17.2 (0.5)	0.6
Age at menarche				
<10	1.61 (0.07)		17.2 (0.5)	
10-12	1.63 (0.07)		17.2 (0.5)	
13-15	1.63 (0.07)		17.2 (0.5)	
≥16	1.64 (0.07)	<0.0001	17.3 (0.5)	0.03

GRS, genetic risk score; NA, not applicable; SD, standard deviation.

[a.] Data are summarised for case-control studies where >50% participants had data available. Height data are for a maximum of 20 studies; GRS data are for a maximum of 39 studies. We used χ^2 statistics or analysis of variance stratified by study.

[b.] *P*-values are from comparisons adjusting for study. *P*-values for age (at menarche and at diagnosis) use continuous age.

[c.] Defined as longer than 6 months.

Supplementary Table 4. Association between increasing height, and between increasing genetically-predicted height, per 5 cm, and risk of ovarian cancer, among women with height and confounder data.

		Odds Ratios (95% CI)[a]	
Histologic subtype[b]	**N studies**	**from conventional analysis[c]**	**from MR analysis[d]**
Primary outcomes			
All ovarian cancers	16	1.01 (0.99-1.04)	1.06 (1.00-1.13)
Invasive	16	1.00 (0.98-1.03)	1.06 (1.00-1.14)
Borderline	10	1.08 (1.02-1.14)	1.13 (0.99-1.29)
Secondary outcomes, by histologic subtype and behaviour			
Serous			
High-grade	16	0.98 (0.95-1.01)	1.03 (0.95-1.11)
Invasive low-grade & borderline	14	1.04 (0.98-1.10)	1.17 (1.02-1.35)
Mucinous (invasive & borderline)	16	1.08 (1.02-1.15)	1.20 (1.04-1.39)
Endometrioid (invasive)	16	1.02 (0.97-1.08)	1.10 (0.96-1.25)
Clear cell (invasive)	15	1.10 (1.02-1.19)	1.17 (0.97-1.42)

CI, confidence interval.

a. Odds ratios were stratified by study.

b. Includes studies with >5 cases.

c. Conventional epidemiological analysis modelled case-control status on height. Models were adjusted for parity, oral contraceptive use, education, and age at menarche, and stratified by study and 5-year age group.

d. Height predicted by a weighted 609-locus genetic risk score.

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