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Original Contribution

Association of Obesity-related Genetic Variants With Endometrial Cancer Risk: A Report From the Shanghai Endometrial Cancer Genetics Study

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Obesity is a well-established risk factor for endometrial cancer, the most common gynecologic malignancy. Recent genome-wide association studies (GWAS) have identified multiple genetic markers for obesity. The authors evaluated the association of obesity-related single nucleotide polymorphisms (SNPs) with endometrial cancer using GWAS data from their recently completed study, the Shanghai Endometrial Cancer Genetics Study, which comprised 832 endometrial cancer cases and 2,049 controls (1996–2005). Thirty-five SNPs previously associated with obesity or body mass index (BMI; weight (kg)/height $(m)^2$) at a minimum significance level of $\leq 5 \times 10^{-7}$ in the US National Human Genome Research Institute's GWAS catalog (http://genome.gov/gwastudies) and representing 26 unique loci were evaluated by either direct genotyping or imputation. The authors found that for 22 of the 26 unique loci tested (84.6%), the BMI-associated risk variants were present at a higher frequency in cases than in population controls ($P = 0.0003$). Multiple regression analysis showed that 9 of 35 BMI-associated variants, representing 7 loci, were significantly associated ($P \leq 0.05$) with the risk of endometrial cancer; for all but 1 SNP, the direction of association was consistent with that found for BMI. For consistent SNPs, the allelic odds ratios ranged from 1.15 to 1.29. These 7 loci are in the *SEC16B/RASAL*, *TMEM18*, *MSRA*, *SOX6*, *MTCH2*, *FTO*, and *MC4R* genes. The associations persisted after adjustment for BMI, suggesting that genetic markers of obesity provide value in addition to BMI in predicting endometrial cancer risk.

body mass index; endometrial neoplasms; genetics; genome-wide association study; obesity; risk factors

Abbreviations: BMI, body mass index; CI, confidence interval; GRS, genetic risk score; GWAS, genome-wide association study(ies); NHGRI, National Human Genome Research Institute; OR, odds ratio; SNP, single nucleotide polymorphism.

Endometrial cancer is one of the most common gynecologic malignancies in the United States and many other countries. Although endometrial cancer is relatively uncommon among Chinese women, its incidence has been increasing at an alarming rate. For example, incidence of endometrial cancer among Chinese women in urban Shanghai has increased 90% over the last 2 decades, from 4.0 per 100,000 in 1987 (1) to 7.62 per 100,000 in 2007 (2). Obesity, typically defined as a body mass index (BMI; weight (kg)/height $(m)^2$) of 30 or higher, is a well established risk factor for endometrial cancer, as summarized by the World Cancer Research Fund (3). Obese persons have a 4.5–6.25 times' higher risk of endometrial cancer compared with nonobese persons (4, 5). The increase in obesity prevalence worldwide over the past few decades (6) may have contributed to the increased incidence of endometrial cancer. In China, the obesity rate reached 7.1% in 2004, a 97% increase compared with the rate in 1992 (7). The contribution of obesity to endometrial cancer risk among Chinese women has been demonstrated previously (8–10).

Although environmental factors are major determinants of obesity risk, genetic susceptibility to obesity is also well recognized. The genetic architecture of BMI and obesity has recently been investigated through the use of genome-wide association studies (GWAS) (11–13). To date, 18 studies have identified 96 single nucleotide polymorphisms (SNPs),

representing approximately 75 loci, associated with high BMI and/or obesity. While some loci (e.g., *FTO*, *MC4R*) have been verified in multiple studies, others have been reported only in discovery samples. Findings have been replicated in other studies for only 13 loci.

The heritability of BMI is estimated to be 0.3–0.7 (14–17), which is comparable to that of endometrial cancer (approximately 0.5). The strong relation between BMI and endometrial cancer and the availability of GWAS-identified risk variants for obesity motivated us to evaluate the association of BMI-related GWAS markers with endometrial cancer. To our knowledge, this is the first study to systematically test the hypothesis that endometrial cancer and measures of obesity share a common genetic architecture. We accomplished this using GWAS data from our recently completed study, the Shanghai Endometrial Cancer Genetics Study. We further evaluated whether associations between these variants and endometrial cancer were mediated by BMI.

MATERIALS AND METHODS

Study population

In the Shanghai Endometrial Cancer Genetics Study, we recruited incident endometrial cancer cases from the Shanghai Endometrial Cancer Study and controls from the Shanghai Breast Cancer Study. Both the Shanghai Endometrial Cancer Study and the Shanghai Breast Cancer Study were population-based case-control studies. The study design has been described in detail elsewhere (18). Briefly, through Shanghai's population-based tumor registry, we identified 1,449 female residents of Shanghai aged 30–69 years who were newly diagnosed with endometrial cancer (and had no prior history of cancer) between 1997 and 2003. Of these 1,449 women, 1,199 (83%) were successfully recruited. DNA samples from 839 cases who donated a blood sample for the study were genotyped using the Affymetrix 6.0 platform (Affymetrix, Santa Clara, California). Controls came from the Shanghai Breast Cancer Study, which was carried out during approximately the same time period (1996–2005) using a study protocol identical to that of the Shanghai Endometrial Cancer Study (19). Controls without a history of cancer were randomly selected from the general population using the Shanghai Resident Registry in 2 phases. The overall response rate for controls was 91% for phase I and 74% for phase II. DNA samples from 2,049 controls were genotyped using the Affymetrix 6.0 platform. Women with a prior hysterectomy were excluded from this study.

Participants completed a detailed in-person interview at the time of enrollment and provided a blood or buccal cell sample. Trained interviewers, who were retired medical professionals, conducted in-person interviews using a structured questionnaire and took anthropometric measurements, including height, weight, and waist and hip circumferences, according to a standard protocol. Indicators of energy balance (i.e., exercise participation and total energy intake) were derived from the questionnaire data (20). This study was approved by the relevant committees for the use of human subjects at all participating institutions, and all study participants provided written informed consent.

Candidate SNP selection

Our SNP selection scheme is shown in Figure 1. The US National Human Genome Resource Institute (NHGRI) GWAS catalog (21) was used to identify SNPs previously associated with high BMI and/or obesity. We selected the traits obesity, BMI, weight, waist circumference, and adiposity (or ''anthropometric'' or ''quantitative'' traits that included these) to identify SNPs. By using this approach, we found 96 SNPs previously associated with the above traits by GWAS. We used the following criteria to select SNPs: 1) a P value less than or equal to 5×10^{-7} in the initial GWAS ($n = 41$) and 2) SNPs for which the obesity-associated allele was known or could be determined ($n = 38$). For the remaining 3 SNPs, the obesity-increasing risk allele (e.g., A or G) was not reported in the original publication.

Genotyping, quality control, and imputation

Genotyping was performed using the Affymetrix 6.0 array, which includes 906,602 SNPs. The Birdseed algorithm

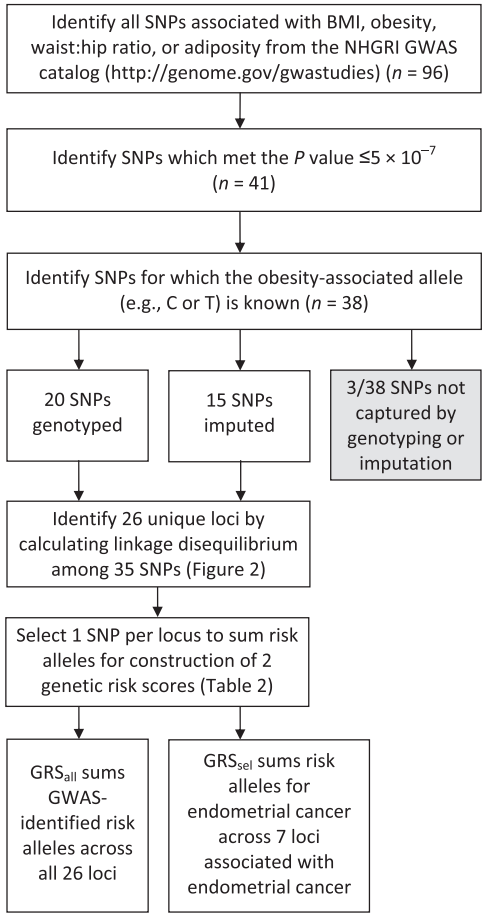

Figure 1. Scheme used for selection of single nucleotide polymorphisms (SNPs) and identification of loci used for genetic risk score (GRS) calculation, Shanghai Endometrial Cancer Genetics Study, Shanghai, China, 2010. (BMI, body mass index; GWAS, genome-wide association study; NHGRI, National Human Genome Research Institute).

Table 1. Demographic and Other Characteristics Associated With Endometrial Cancer in the Shanghai Endometrial Cancer Genetics Study, Shanghai, China, 1996–2005

	Controls (n = 2,049)		Cases (n = 832)		Odds Ratio[a]	95% Confidence Interval
	%	Mean (SD)	%	Mean (SD)		
Age, years						
<40	9.4		4.1		1	Reference
40–49	47.4		28.0		1.60	1.07, 2.39
50–59	26.8		35.7		3.22	2.16, 4.81
≥60	16.4		32.2		5.33	3.50, 8.12
Income, yuan/year						
<10,000	32.2		12.5		1	Reference
10,000–19,999	37.2		44.0		3.29	2.56, 4.24
20,000–29,999	18.5		20.3		3.66	2.73, 4.90
≥30,000	12.2		23.2		6.76	4.98, 9.17
Education						
None	5.2		9.3		1	Reference
Elementary school	8.5		14.9		1.11	0.76, 1.64
Middle school	42.4		38.9		1.15	0.80, 1.65
High school	34.4		24.2		0.82	0.56, 1.20
College/post-high-school	9.5		12.7		0.88	0.58, 1.34
Waist:hip ratio						
<0.77	23.9		8.4		1	Reference
0.77–<0.81	28.0		19.1		1.91	1.39, 2.62
0.81–<0.84	22.1		19.7		2.23	1.61, 3.08
≥0.84	26.0		52.8		4.89	3.63, 6.59
Body mass index[b]						
<21.7	33.4		14.0		1	Reference
21.7–24.5	33.4		28.3		1.68	1.30, 2.18
>24.5	33.3		57.7		3.13	2.44, 4.01
Physical activity participation						
Median or more	15.3		13.4		1	Reference
Less than median	14.9		15.6		1.52	1.10, 2.10
None	69.7		71.0		2.03	1.56, 2.65
Energy intake, kcal						
<1,460	25.0		23.3		1	Reference
1,460–<1,701	25.0		23.8		0.95	0.74, 1.22
1,701–<1,983	24.9		23.2		0.95	0.74, 1.22
≥1,983	25.0		29.7		1.22	0.96, 1.55
Age at menarche, years						
<13	8.4		11.5		1	Reference
13–<15	39.7		40.0		0.68	0.50, 0.93
15–<16	19.1		20.0		0.66	0.47, 0.92
≥16	32.8		28.5		0.50	0.37, 0.69
Age at menopause, years						
<47	24.0		12.7		1	Reference
47–<49	20.2		16.7		1.34	0.88, 2.04
49–<51	26.8		30.9		1.72	1.17, 2.52
≥51	29.0		39.8		1.81	1.25, 2.62
Reproductive years		31.1 (5.2)		34.6 (4.9)	1.68	1.09, 1.14
No. of pregnancies		2.54 (1.33)		2.64 (1.57)	0.82	0.76, 0.88
Family history of cancer	26.7		34.5		1.38	1.14, 1.66
Family history of endometrial or colorectal cancer	2.1		5.2		2.68	1.68, 4.28

Abbreviation: SD, standard deviation.

[a] Odds ratios were adjusted for age, income, and education.

[b] Weight (kg)/height $(m)^2$.

Table 2. Obesity-related Single Nucleotide Polymorphisms Identified in Genome-wide Association Studies and Their Associations With Body Mass Index, Shanghai Endometrial Cancer Genetics Study, Shanghai, China, 1996–2005

Locus	dbSNP Identification No.	Chr	Position	Nearby Gene(s)	Initial GWAS Report				SECGS (n = 2,371 Persons)				
					Trait	PMID	Reference P Value[a]	GWAS Risk Allele[b]	β[c]	95% Confidence Interval	P Value[d]	Typing	GRS_{all}[e]
1	rs2568958	1	72537704	*NEGR1*	BMI	19079260	1.0×10^{-11}	A	−0.20	−0.54, 0.15	0.2583	I	
1	rs2815752	1	72585028	*NEGR1*	BMI	19079261	6.0×10^{-08}	A	−0.21	−0.55, 0.14	0.2381	T	Yes
2	rs10913469	1	176180142	*SEC16B*, *RASAL2*	BMI	19079260	6.0×10^{-08}	C	0.39	0.15, 0.63	0.0014	I	Yes
3	rs2605100	1	217710847	*LYPLAL1*	Adiposity	19557161	3.0×10^{-08}	G	−0.11	−0.34, 0.12	0.3471	T	Yes
4	rs6429082	1	233666752	*TBCE*	Adiposity	19557161	3.0×10^{-07}	C	−0.01	−0.20, 0.18	0.9197	T	Yes
5	rs6548238	2	624905	*TMEM18*	BMI	19079261	1.0×10^{-18}	C	0.18	−0.12, 0.49	0.2425	T	Yes
5	rs7561317	2	634953	*TMEM18*	BMI	19079260	4.0×10^{-17}	G	0.19	−0.12, 0.50	0.2386	I	
6	rs1260326	2	27584444	*GCKR*	WC	18454146	4.0×10^{-08}	T	0.08	−0.13, 0.29	0.4611	I	Yes
7	rs7647305	3	187316984	*SFRS10*, *ETV5*, *DGKG*	BMI	19079260	7.0×10^{-11}	C	−0.16	−0.60, 0.28	0.4745	I	Yes
8	rs10938397	4	44877284	*GNPDA2*	BMI	19079261	3.0×10^{-16}	G	0.03	−0.17, 0.23	0.7801	I	Yes
9	rs12517906	5	180103425	*MGAT1*	Weight	19851299	7.0×10^{-08}	T	−0.04	−0.35, 0.28	0.8215	T	Yes
10	rs2844479	6	31680935	*AIF1*, *NCR3*	Weight	19079260	2.0×10^{-08}	A	0.15	−0.04, 0.34	0.1302	I	Yes
11	rs987237	6	50911009	*TFAP2B*	Adiposity	19557161	2.0×10^{-11}	G	0.10	−0.15, 0.34	0.4404	T	Yes
12	rs545854	8	9897490	*MSRA*	Adiposity	19557161	9.0×10^{-09}	C	0.10	−0.08, 0.28	0.2867	T	Yes
13	rs7832552	8	110184852	*TRHR*	Lean body mass	19268274	4.0×10^{-10}	T	0.20	0.01, 0.38	0.0377	T	Yes
14	rs297325	11	16346170	*SOX6*	Obesity	19714249	4.0×10^{-07}	C	−0.06	−0.25, 0.13	0.5366	T	Yes
15	rs925946	11	27623778	*BDNF*	BMI	19079260	9.0×10^{-10}	T	0.09	−0.39, 0.57	0.7054	I	Yes
16	rs6265	11	27636492	*BDNF*	BMI	19079260	5.0×10^{-10}	C	0.14	−0.04, 0.32	0.1352	T	Yes
17	rs10838738	11	47619625	*MTCH2*	BMI	19079261	5.0×10^{-09}	G	0.04	−0.15, 0.23	0.6806	I	Yes
18	rs7138803	12	48533735	*BCDIN3D*, *FAIM2*	BMI	19079260	1.0×10^{-07}	A	−0.02	−0.22, 0.18	0.8464	T	Yes
19	rs7498665	16	28790742	*SH2B1*, *ATP2A1*	BMI	19079261	5.0×10^{-11}	G	0.02	−0.26, 0.31	0.8845	I	Yes
20	rs6499640	16	52327178	*FTO*	BMI	19079260	4.0×10^{-13}	A	−0.01	−0.25, 0.24	0.9676	I	Yes
21	rs1421085	16	52358455	*FTO*	Obesity	19151714	1.0×10^{-28}	C	0.41	0.13, 0.69	0.0036	T	
21	rs1558902	16	52361075	*FTO*	WC	19557197	5.0×10^{-19}	A	0.40	0.13, 0.68	0.0041	I	
21	rs1121980	16	52366748	*FTO*	BMI	18159244	1.0×10^{-07}	A	0.31	0.07, 0.55	0.0107	T	
21	rs8050136	16	52373776	*FTO*	BMI/weight	19079260	1.0×10^{-47}	A	0.42	0.15, 0.69	0.0027	T	Yes
21	rs9939609	16	52378028	*FTO*	BMI	17434869	2.0×10^{-20}	A	0.42	0.14, 0.69	0.0029	T	
21	rs9941349	16	52382989	*FTO*	Obesity (extreme)	19553259	6.0×10^{-12}	T	0.32	0.08, 0.56	0.0101	T	
22	rs1424233	16	78240252	*MAF*	Obesity	19151714	4.0×10^{-13}	T	0.03	−0.17, 0.22	0.7973	I	Yes

23	rs1805081	18	19394430	*NPC1*	Obesity	19151714	3.0×10^{-07}	T	0.09	−0.15, 0.33	0.4453	I	Yes
24	rs1840440	18	21511184	*NR*	Weight	19851299	3.0×10^{-07}	C	0.10	−0.08, 0.28	0.2934	T	Yes
25	rs17782313	18	56002077	*MC4R*	BMI	18454148	3.0×10^{-15}	C	0.33	0.11, 0.55	0.0039	T	Yes
25	rs12970134	18	56035730	*MC4R*	WC	18454146	2.0×10^{-09}	A	0.25	0.02, 0.48	0.0300	T	
26	rs29941	19	39001372	*KCTD15, CHST8*	BMI	19079260	7.0×10^{-12}	G	0.10	−0.12, 0.32	0.3751	I	
26	rs11084753	19	39013977	*KCTD15*	BMI	19079261	2.0×10^{-08}	G	0.09	−0.1, 0.28	0.3712	T	Yes

Abbreviations: BMI, body mass index; Chr, chromosome; dbSNP, Database of Single Nucleotide Polymorphisms; GRS, genetic risk score; GWAS, genome-wide association study; I, imputed; PMID, PubMed identification number; SECGS, Shanghai Endometrial Cancer Genetics Study; T, typed; WC, waist circumference.

[a] *P* value for the trait in the referenced PMID.

[b] BMI- or obesity-increasing risk allele identified in the associated PMID and GWAS.

[c] Mean difference in BMI (weight (kg)/height $(m)^2$) per allele, adjusted for age, income, and education. Positive β's indicate that the BMI risk allele was the same between the GWAS and the SECGS.

[d] *P* value for association with BMI in the SECGS.

[e] One single nucleotide polymorphism was selected per locus to be used in the calculation of GRS_{all} (see Materials and Methods).

(version 2; http://www.broad.mit.edu/mpg/birdsuite/) was used to call genotypes. Quality control procedures included removal of SNPs with minor allele frequencies less than 0.01, Hardy-Weinberg *P* values less than 0.00001, and samples with more than 5% of genotypes missing. In addition, we included a number of other quality control measures to verify the integrity of our genotyping. Three sets of SNPs on the Affymetrix SNP Array 6.0 were previously genotyped using different platforms, including: 1) 669 SNPs genotyped by the Affymetrix Targeted Genotyping System, 17 SNPs genotyped by TaqMan, and 56 SNPs genotyped by Sequenom (Sequenom, Inc., San Diego, California). These SNP sets served for cross-platform sample verification. The mean concordance rates were 99.4%, 98.2%, and 98.8% for the Affymetrix Targeted Genotyping System, TaqMan, and Sequenom, respectively, when compared with the Affymetrix SNP Array 6.0. Additionally, we included 1 negative control (water) and 3 positive quality control samples (NA15510, NA10851, and NA18505) purchased from the Coriell Cell Repositories (Coriell Institute, Camden, New Jersey; http://ccr.coriell.org/) in each of the 96-well plates genotyped to assess batch-to-batch validation. The average concordance rate between the quality control samples was 99.8% (median, 100%). Of the 38 BMI-associated variants selected for this study, 20 were directly genotyped with high quality, while the remainder were imputed as described below.

We used the hidden Markov model as implemented in MACH 1.0 (http://www.sph.umich.edu/csg/abecasis/MaCH/) to impute the genotype for variants of interest that were not directly genotyped. Of the remaining 18 selected SNPs that were not directly genotyped, 15 showed high imputation quality, as measured by an *Rsq* value (an estimate of the squared correlation between imputed and true genotypes) greater than 0.3. Our average *Rsq* was 0.95. Thus, through either genotyping or imputation, we were able to evaluate the majority (35/38; 92.1%) of selected variants. To determine the number of unique loci these 35 SNPs represented, we used the SNAP (SNP Annotation and Proxy Search) server (Broad Institute, Cambridge, Massachusetts; http://www.broadinstitute.org/mpg/snap/ldsearch.php) to identify variants with $r^2 > 0.3$ (in CEU or CHB + JPT populations). HapMap Phase II data were used as the reference, since these data contain a greater selection of SNPs. Any 2 SNPs with $r^2 > 0.3$ in the HapMap sample were considered to be in sufficient linkage disequilibrium to represent the same locus (i.e., they were not sufficiently independent to warrant artificially weighting the locus). In total, the 35 selected SNPs of interest were found to represent 26 distinct loci (Figure 1).

Statistical analysis

Statistical analysis was carried out using SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina). Unconditional logistic regression was used to calculate odds ratios and 95% confidence intervals for associations between genotypes and endometrial cancer risk, with adjustment for age, income, and education. Income and education were categorized into 4 and 5 strata, respectively, while age was a continuous variable.

We derived 2 genetic risk scores (GRSs) by summing the number of risk alleles. For imputed SNPs, we used dosage

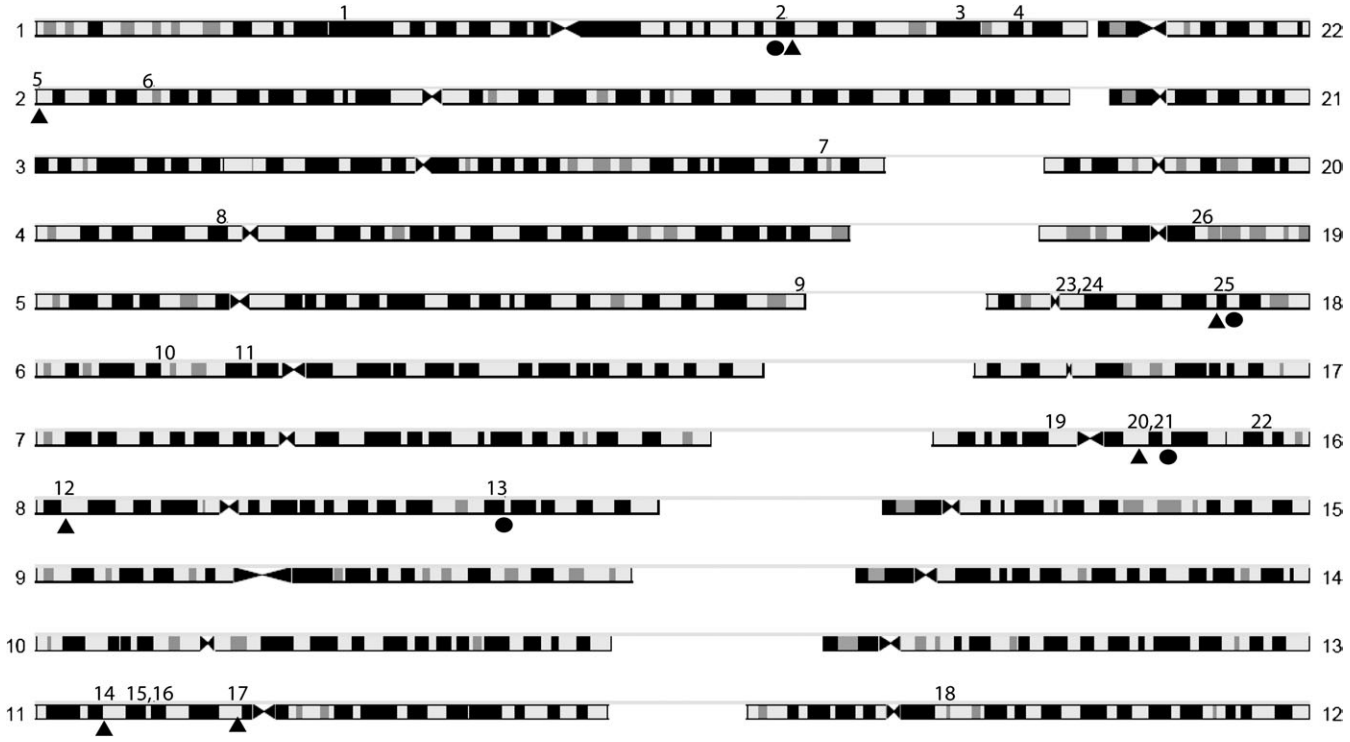

Figure 2. Associations of selected genetic loci with body mass index and/or endometrial cancer, Shanghai Endometrial Cancer Genetics Study, Shanghai, China, 2010. The chromosome number is indicated on the left side of chromosomes 1–11 and on the right side of chromosomes 12–22. Locus numbers corresponding to the text and Tables 2 and 3 are shown above their chromosome positions. Black circles indicate loci associated with body mass index; black triangles indicate loci associated with endometrial cancer. All associations marked were significant at $P \leq 0.05$.

data to capture the probability of a given genotype. For variants that were directly genotyped or found by linkage disequilibrium to represent nonindependent loci, only 1 SNP per locus was included in the GRS calculations. The choice of which SNPs to include per locus was determined first by data source, selecting genotyped variants over imputed variants, and second by the significance of *P* values for BMI- or obesity-related traits as reported in the NHGRI GWAS catalog. GRS_{all} was defined by summing the risk alleles, according to the original BMI GWAS report, of 26 SNPs that represented all BMI-selected loci. GRS_{sel} was defined by summing the 7 selected variants that were significantly associated with endometrial cancer ($P \leq 0.05$) in our study. The SNPs selected were a subset of those used for the calculation of GRS_{all}, selecting 1 SNP per locus and summing the alleles associated with endometrial cancer. GRSs were analyzed both continuously and by categorizing them into quartiles based on the distributions among controls. Relations between GRS and BMI were evaluated by linear regression, whereas relations between GRS and endometrial cancer were evaluated by logistic regression. We evaluated joint effects and tested for the presence of multiplicative interactions of GRS_{sel} with 3 major indicators of energy balance: BMI, exercise participation, and total energy intake.

The probability that an endometrial cancer risk allele and a BMI risk allele have the same direction of effect or the probability of observing a larger number of significant associations ($P \leq 0.05$) than would be expected by chance is a function of the binomial distribution (12). We conducted a global test for the hypothesis that the risk alleles for BMI- or obesity-related SNPs would have a higher frequency among endometrial cancer cases than among controls based on the probability of deviation from the binomial distribution, as well as a test evaluating whether the number of significant associations with endometrial cancer ($P \leq 0.05$) was greater than expected for the number of loci tested.

All statistical tests were based on 2-sided probabilities, with significance determined by $P \leq 0.05$.

RESULTS

Associations of selected demographic characteristics and known risk factors with endometrial cancer are shown in Table 1. As expected, cases and controls differed in regards to age, income, education, BMI, waist:hip ratio, and other traditional risk factors for endometrial cancer.

Table 2 presents the associations of GWAS-identified obesity-related SNPs with BMI in our study population. Ten variants in 4 gene regions (*SEC16B*, *TRHR*, *FTO*, and *MC4R*) were significantly associated with BMI (Figure 2). The probability of observing 4 of 26 loci with significant associations with BMI (at $P \leq 0.05$) was significantly greater than expected by chance ($P = 0.039$). Further, 26 of 35 SNPs associated with BMI traits by GWAS showed a consistent direction

of association (as indicated by positive beta coefficients) with BMI in our study population (i.e., the BMI risk allele was the same as in the GWAS from which it was selected). For loci with more than 1 SNP identified in the NHGRI GWAS catalog, we selected 1 SNP to represent each locus (see Materials and Methods), resulting in a total of 26 unique loci. On this per-locus basis, 19 of 26 loci had consistent directions of association for BMI in both prior GWAS and our study population (binomial sign test: $P = 0.01$). For all 10 SNPs in the 4 loci (2, 13, 21, and 25) that were significantly associated with BMI in our study ($P \leq 0.05$), the directions of association were consistent with prior GWAS.

With regard to endometrial cancer, for 22 of the 26 loci (84.6%), the obesity risk allele showed a higher frequency among cases than among controls ($P = 0.0003$). In addition, 9 of 35 SNPs (25.7%) were significantly associated with endometrial cancer ($P \leq 0.05$) (Table 3). For 8 of these 9 SNPs, the directions of association with endometrial cancer were consistent with reported associations for obesity (i.e., the obesity-related allele was the same as the one that increased the risk of endometrial cancer). These 9 SNPs represent 7 of the 26 loci evaluated. The probability of observing this number of significant results at $P \leq 0.05$, based on the binomial distribution under the null hypothesis, was 0.0002. Two of the 4 loci associated with BMI in our population were also associated with endometrial cancer (locus 2, *SEC16B/RASAL2* and locus 25, *MC4R*). Since these 2 loci were associated with both BMI and endometrial cancer, we examined the extent to which the inclusion of BMI in the regression analysis changed the resultant odds ratio for the SNPs at these loci. No significant differences were observed. In the only gene spanning more than 1 locus, *FTO*, 1 locus was associated with BMI (locus 21), and an independent locus within this gene (locus 20) was associated with endometrial cancer.

GRS_{all}, based on 26 SNPs in unique loci, and GRS_{sel}, based on 7 SNPs significantly associated with endometrial cancer in unique loci, were evaluated. Risk alleles were defined by previously reported BMI GWAS results for all variants included in GRS_{all}. For GRS_{sel}, risk alleles were those associated with endometrial cancer. In 6 of 7 loci, the endometrial cancer risk allele was identical to the BMI risk allele in the source GWAS from which it was selected. Both GRS_{all} and GRS_{sel} were positively correlated with BMI in our study (Table 4), with beta coefficients of 0.07 and 0.04, respectively. Further, both types of GRS had stronger associations with BMI among controls than among cases, whether analyzed continuously or in quartiles based on distributions among controls.

The associations of GRS_{all} and GRS_{sel} with endometrial cancer were evaluated by logistic regression. Both GRS_{all} (odds ratio (OR) = 1.05, 95% confidence interval (CI): 1.02, 1.08) and GRS_{sel} (OR = 1.21, 95% CI: 1.14, 1.28) were significantly associated with endometrial cancer risk. With adjustment for BMI, these associations were somewhat attenuated, but they remained significant ($OR_{GRSall} = 1.04$, 95% CI: 1.01, 1.07; $OR_{GRSsel} = 1.20$, 95% CI: 1.13, 1.27). Categorical analysis showed that odds ratios across the 4 quartiles (lowest to highest) were 1.00, 1.25, 1.13, and 1.50 for GRS_{all} and 1.00, 1.15, 1.31, and 1.96 for GRS_{sel}. Additional adjustment for BMI did not appreciably alter these results.

The joint effect of energy balance-related variables (including BMI, energy intake, and exercise participation) and GRS_{sel} on endometrial cancer risk was evaluated (Table 5). Although there were no statistically significant interactions between energy balance-related variables and GRS_{sel}, we found that persons who were in the higher categories of GRS_{sel} and BMI or who did not exercise had higher odds ratios for endometrial cancer compared with persons in the lowest categories. For example, women in the highest quantiles of both GRS_{sel} and BMI were 8 times more likely to have endometrial cancer than controls (OR = 8.03, 95% CI: 4.78, 13.51), in comparison with women in the lowest quantiles.

DISCUSSION

To our knowledge, this is the first study to have systematically evaluated the shared genetic architecture between measures of obesity and endometrial cancer risk. Of the 35 GWAS-identified SNPs that are associated with high BMI, obesity, weight, or waist:hip ratio, associations with endometrial cancer were found for 9 SNPs ($P \leq 0.05$), representing 7 loci (*FTO*, *MC4R*, *MSRA*, *MTCH2*, *SEC16B*, *SOX6*, and *TMEM18*). The number of endometrial cancer associations among BMI-related variants was significantly higher than would be expected by chance on the basis of the binomial distribution test, indicating that genetic variants associated with BMI are also involved in endometrial cancer. In addition, the direction of association with endometrial cancer for the majority of the variants evaluated (84.6%) was in agreement with the direction of association with BMI found by other GWAS. The binomial distribution test was highly significant, indicating that additional BMI-associated variants may be associated with endometrial cancer, even if they were not found to be significant in the current analysis. Our findings are in agreement with a recent report by Elks et al. (22), in which 4 loci (i.e., *FTO*, *SEC16B*, *TMEM18*, and *MTCH2*) were also associated with age at menarche, a phenotype that is strongly related to both endometrial cancer risk and BMI. Notably, in our study, adjustment for BMI had little impact on these results, indicating that these SNPs capture more information on endometrial cancer risk than does current BMI alone.

Associations with both endometrial cancer and BMI were found for genetic variants at 2 loci: locus 2, near the *SEC16B* and *RASAL* genes, and locus 25, near the *MC4R* gene. In addition, locus 21 was associated with BMI and locus 20 was associated with endometrial cancer; both of these loci are near the *FTO* gene. The 2 strongest associations with endometrial cancer in this study were for loci in the *FTO* gene (locus 20, SNP rs6499640; $P = 0.0045$) and near the *MC4R* gene (locus 25, rs17782313; $P = 0.0007$). These 2 genes have been the subject of multiple reports of associations with BMI (12, 16, 17). *FTO*, the fat mass and obesity-associated gene, has been detected as a locus affecting BMI in 13 independent GWAS (12, 23). In addition, the *FTO* gene has been associated with diabetes in 5 independent GWAS (24). *FTO* has 7 SNPs, of which 6 are within 1 locus by linkage disequilibrium, while the other is independent. The current study included the 6 single-locus SNPs, and the direction of

Table 3. Association Between Obesity-related Single Nucleotide Polymorphisms Identified in Genome-wide Association Studies and Endometrial Cancer Risk, Shanghai Endometrial Cancer Genetics Study, Shanghai, China, 1996–2005

Locus	dbSNP Identification No.	Nearby Gene(s)	GWAS Risk Allele Frequency[a]	GWAS Risk Allele[b]	Other Allele	Odds Ratio[c]	95% Confidence Interval[c]	SECGS *P* Value[d]	Typing	GRS_{sel}[e]
1	rs2568958	*NEGR1*	0.925	A	G	1.08	0.86, 1.36	0.5200	I	
1	rs2815752	*NEGR1*	0.923	A	G	1.06	0.84, 1.34	0.6176	T	
2	rs10913469	*SEC16B*, *RASAL2*	0.216	C	T	1.21	1.04, 1.41	0.0145	I	Yes
3	rs2605100	*LYPLAL1*	0.794	G	A	1.06	0.91, 1.23	0.4741	T	
4	rs6429082	*TBCE*	0.666	C	T	0.94	0.82, 1.06	0.3082	T	
5	rs6548238	*TMEM18*	0.902	C	T	1.28	1.04, 1.59	0.0215	T	Yes
5	rs7561317	*TMEM18*	0.909	G	A	1.25	1.01, 1.56	0.0395	I	
6	rs1260326	*GCKR*	0.528	T	C	1.08	0.95, 1.24	0.2430	I	
7	rs7647305	*SFRS10*, *ETV5*, *DGKG*	0.946	C	T	1.05	0.78, 1.41	0.7540	I	
8	rs10938397	*GNPDA2*	0.298	G	A	1.01	0.89, 1.16	0.8540	I	
9	rs12517906	*MGAT1*	0.095	T	C	0.93	0.75, 1.16	0.5241	T	
10	rs2844479	*AIF1*, *NCR3*	0.563	A	C	0.97	0.85, 1.10	0.6405	I	
11	rs987237	*TFAP2B*	0.159	G	A	1.04	0.88, 1.23	0.6421	T	
12	rs545854	*MSRA*	0.583	C	G	1.19	1.05, 1.35	0.0068	T	Yes
13	rs7832552	*TRHR*	0.478	T	C	1.01	0.89, 1.15	0.8313	T	
14	rs297325	*SOX6*	0.336	C	T	1.15	1.01, 1.30	0.0348	T	Yes
15	rs925946	*BDNF*	0.044	T	G	1.09	0.80, 1.48	0.5839	I	
16	rs6265	*BDNF*	0.510	C	T	1.06	0.93, 1.19	0.3820	T	
17	rs10838738	*MTCH2*	0.328	G	A	0.84	0.73, 0.96	0.0094	I	Yes
18	rs7138803	*BCDIN3D*, *FAIM2*	0.283	A	G	1.01	0.88, 1.16	0.9249	T	
19	rs7498665	*SH2B1*, *ATP2A1*	0.115	G	A	1.06	0.88, 1.27	0.5643	I	
20	rs6499640	*FTO*	0.164	A	G	1.26	1.08, 1.48	0.0045	I	Yes
21	rs1421085	*FTO*	0.122	C	T	1.01	0.84, 1.22	0.9238	T	
21	rs1558902	*FTO*	0.117	A	T	1.05	0.87, 1.26	0.6130	I	
21	rs1121980	*FTO*	0.171	A	G	1.05	0.89, 1.23	0.5700	T	
21	rs8050136	*FTO*	0.123	A	C	1.08	0.90, 1.30	0.4085	T	
21	rs9939609	*FTO*	0.123	A	T	1.07	0.89, 1.29	0.4731	T	
21	rs9941349	*FTO*	0.172	T	C	1.05	0.89, 1.23	0.5840	T	
22	rs1424233	*MAF*	0.673	T	C	1.07	0.94, 1.22	0.3306	I	
23	rs1805081	*NPC1*	0.772	T	C	1.10	0.95, 1.29	0.2135	I	
24	rs1840440	*NR*	0.490	C	T	1.08	0.95, 1.22	0.2324	T	
25	rs17782313	*MC4R*	0.216	C	T	1.29	1.11, 1.50	0.0007	T	Yes
25	rs12970134	*MC4R*	0.207	A	G	1.19	1.03, 1.38	0.0208	T	
26	rs29941	*KCTD15*, *CHST8*	0.231	G	A	0.96	0.83, 1.11	0.5607	I	
26	rs11084753	*KCTD15*	0.356	G	A	1.00	0.88, 1.14	0.9783	T	

Abbreviations: BMI, body mass index; dbSNP, Database of Single Nucleotide Polymorphisms; GRS, genetic risk score; GWAS, genome-wide association study; I, imputed; SECGS, Shanghai Endometrial Cancer Genetics Study; T, typed.

[a] Frequency (proportion) of the GWAS risk allele in cases and controls.

[b] BMI- or obesity-increasing risk allele identified in a prior GWAS (see Table 2 for study identification).

[c] Odds ratio and 95% confidence interval for association with endometrial cancer, adjusted for age, income, and education. Positive values indicate that the BMI risk allele was the same between the GWAS and the SECGS.

[d] *P* value for association with endometrial cancer in cases and controls.

[e] "Yes" indicates that the single nucleotide polymorphism was used in the calculation of GRS_{sel} (see Materials and Methods).

Table 4. Association of Genetic Risk Scores With Body Mass Index and the Risk of Endometrial Cancer, Shanghai Endometrial Cancer Genetics Study, Shanghai, China, 1996–2005

	Linear Regression of GRS and BMI[a]									Association of GRS and Endometrial Cancer (n = 2,881)					
	Total (n = 2,881)			Cases (n = 832)			Controls (n = 2,049)			OR_1[b]	95% CI	P Value[c]	OR_2[d]	95% CI	P Value[e]
	β[f]	95% CI	P Value[g]	β[h]	95% CI	P Value[g]	β[h]	95% CI	P Value[g]						
GRS_{all}[i]															
Q1	0	Reference		0	Reference		0	Reference		1	Reference		1	Reference	
Q2	0.12	−0.24, 0.48	0.508	0.18	−0.63, 0.99	0.661	0.08	−0.31, 0.47	0.676	1.25	0.99, 1.60	0.065	1.38	1.07, 1.80	0.015
Q3	0.33	−0.03, 0.69	0.075	0.15	−0.67, 0.98	0.715	0.41	0.02, 0.8	0.04	1.13	0.88, 1.45	0.315	1.25	0.96, 1.63	0.105
Q4	0.42	0.06, 0.77	0.022	0.48	−0.31, 1.27	0.233	0.39	0.00, 0.78	0.051	1.50	1.18, 1.92	0.001	1.51	1.17, 1.95	0.002
Continuous	0.07	0.02, 0.11	0.002	0.05	−0.04, 0.14	0.242	0.07	0.03, 0.12	0.002	1.05	1.02, 1.08	0.001	1.04	1.01, 1.07	0.009
GRS_{sel}[j]															
Q1	0	Reference		0	Reference		0	Reference		1	Reference		1	Reference	
Q2	0.06	−0.30, 0.43	0.732	−0.19	−1.04, 0.65	0.653	0.08	−0.31, 0.47	0.679	1.15	0.88, 1.49	0.303	1.15	0.88, 1.51	0.300
Q3	0.08	−0.27, 0.43	0.651	−0.14	−0.93, 0.66	0.732	0.10	−0.28, 0.48	0.615	1.31	1.02, 1.67	0.035	1.32	1.02, 1.70	0.035
Q4	0.24	−0.11, 0.59	0.177	−0.25	−1.01, 0.5	0.507	0.41	0.03, 0.79	0.035	1.96	1.54, 2.5	<0.001	1.91	1.49, 2.45	<0.001
Continuous	0.04	−0.04, 0.12	0.329	−0.08	−0.32, −0.69	0.531	0.13	0.01, 0.25	0.041	1.21	1.14, 1.280	<0.001	1.20	1.13, 1.27	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; GRS, genetic risk score; OR, odds ratio; Q, quartile; SNP, single nucleotide polymorphism.

[a] Weight (kg)/height (m)^2.

[b] Odds ratio was adjusted for age, income, and education.

[c] P value for logistic regression for endometrial cancer, adjusted for age, income, and education.

[d] Odds ratio was adjusted for age, income, education, and BMI.

[e] P value for logistic regression for endometrial cancer, adjusted for age, income, education, and BMI.

[f] Mean difference in BMI, adjusted for age, income, education, and case-control status.

[g] P value from linear regression, adjusted for age, income, and education.

[h] Mean difference in BMI, adjusted for age, income, and education.

[i] GRS_{all} was calculated using the 26 SNPs indicated in Table 2 for which the BMI-associated allele was known and was adjusted for age, income, and education.

[j] GRS_{sel} was calculated using the 7 SNPs indicated in Table 3 and was adjusted for age, income, and education.

Table 5. Joint Associations of Indicators of Energy Balance (Body Mass Index, Exercise, and Energy Intake) and Genetic Risk Score With Risk of Endometrial Cancer, Shanghai Endometrial Cancer Genetics Study, Shanghai, China, 1996–2005

Indicator and Category	Quartile of GRS_{sel}[a]								OR for Indicator	95% CI	*P* for Interaction
	1		2		3		4				
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI			
Body mass index[b]											0.26
T1	1	Reference	1.72	0.91, 3.26	1.37	0.72, 2.59	3.79	2.11, 6.81	1	Reference	
T2	2.19	1.23, 3.91	3.33	1.89, 5.85	3.05	1.75, 5.32	3.41	1.98, 5.89	1.63	1.26, 2.12	
T3	4.56	2.68, 7.75	3.94	2.28, 6.80	5.99	3.53, 10.16	8.03	4.78, 13.51	3.08	2.40, 3.96	
GRS_{sel} OR			1.18	0.90, 1.55	1.35	1.04, 1.74	1.94	1.51, 2.49			
Exercise participation											0.92
Yes, median or more	1	Reference	0.89	0.44, 1.80	1.43	0.74, 2.76	2.17	1.14, 4.13	1	Reference	
Yes, less than median	1.77	0.91, 3.44	2.01	1.04, 3.90	1.83	0.96, 3.53	2.44	1.30, 4.59	1.50	1.09, 2.08	
No	1.89	1.11, 3.22	2.35	1.37, 4.01	2.58	1.53, 4.37	4.00	2.37, 6.73	1.99	1.52, 2.60	
GRS_{sel} OR			1.17	0.90, 1.52	1.32	1.02, 1.69	1.98	1.55, 2.53			
Total energy intake											0.67
T1	1	Reference	1.10	0.68, 1.78	1.29	0.84, 1.99	1.76	1.15, 2.70	1	Reference	
T2	0.83	0.53, 1.31	0.89	0.56, 1.41	1.04	0.66, 1.64	2.11	1.38, 3.23	0.91	0.73, 1.14	
T3	1.11	0.71, 1.72	1.41	0.91, 2.19	1.52	0.99, 2.32	1.95	1.29, 2.93	1.16	0.94, 1.43	
GRS_{sel} OR			1.15	0.89, 1.50	1.31	1.02, 1.69	1.97	1.54, 2.51			

Abbreviations: CI, confidence interval; GRS, genetic risk score; OR, odds ratio; T, tertile.
[a] Logistic regression odds ratios adjusted for age, income, and education.
[b] Weight (kg)/height $(m)^2$.

the association with BMI was consistent between our study and previous GWAS. The seventh and independent SNP in the *FTO* gene, rs6499640, was not associated with BMI in our population but was strongly associated with endometrial cancer. This suggests that *FTO* may be involved in endometrial cancer via mechanisms other than obesity. *MC4R*, the melanocortin 4 receptor gene, has been associated with BMI and related body measurements in 8 independent GWAS and across multiple ethnic groups (25, 26). In our study, 2 SNPs at this locus showed an association with endometrial cancer, with the strongest signal coming from rs17782313 ($P = 0.0007$; OR = 1.29, 95% CI: 1.11, 1.50). *MC4R* has been linked to both obesity and reproductive dysfunction (26–30). A SNP near *SEC16B/RASAL*, rs10913469, was also associated with both BMI and endometrial cancer in our study. This locus was also recently associated with early age at menarche (22), a strong risk factor for endometrial cancer (12).

In our study population of Chinese women, other loci that were associated with endometrial cancer but had no statistically significant association with BMI included *TMEM18*, *MSRA*, *SOX6*, and *MTCH2*. Aside from rs10838738 at *MTCH2*, all other SNPs showed an association with endometrial cancer that was consistent with the directions of association with BMI reported in previous GWAS.

The GRS provides a measure of the combined genetic effect of obesity-associated loci on endometrial cancer risk. The GRS calculated in this study was associated with both BMI and endometrial cancer. The effect of the GRS on BMI is somewhat paradoxical: The accumulation of risk alleles as measured by GRS_{all} showed that the positive correlation with BMI is driven chiefly by controls but modestly or significantly attenuated among cases. Two explanations seem plausible. First, these genetic variants may increase the risk of obesity initially, but then the disease itself, or its treatment, attenuates the effects among cases. Several common treatments for endometrial cancer may result in weight loss. These include hysterectomy (31), radiation therapy (32), and several common chemotherapeutic agents (33). The second possibility is that the risk alleles comprising the GRS may influence the risk of endometrial cancer through mechanisms other than those related to obesity alone. The persistent significance of associations of the GRS with endometrial cancer risk after adjustment for BMI supports this explanation. It is noteworthy that although no statistically significant interactions were observed between the GRS and factors related to energy balance in our study, we did find that women with a high GRS and high BMI or no exercise participation were at substantially increased risk of developing endometrial cancer. These findings suggest the potential value of using genetic markers to identify populations at high risk of endometrial cancer for targeted prevention.

One limitation of our study is that it relied on the NHGRI GWAS catalog for identification of SNPs for inclusion. Because the threshold for entry of SNPs into the GWAS

catalog is higher than that used for most association studies, a number of potentially interesting loci may have been missed. A further limitation is that data were not available for all originally selected SNPs, although the majority were captured (92.1%). In addition, BMI was measured at the time of interview for cases, which may not reflect women's prediagnosis weight due to the effects of either illness or treatment. Further, this study was carried out in a Chinese population with an average BMI of 23.4 in controls and 25.7 in cases. The results may not be directly generalizable to non-Chinese populations. However, almost all of the risk factors for endometrial cancer found in this Chinese population were identical to those found in populations of European ancestry. Because the majority of GWAS-identified SNPs associated with BMI were identified in populations of European ancestry, associations between BMI-associated SNPs and endometrial cancer may be even stronger in those discovery populations. Nevertheless, our study also had many strengths. To our knowledge, this was the first population-based epidemiologic study to comprehensively evaluate GWAS-identified obesity markers in association with endometrial cancer risk. The vast majority of persons in our study population were of a single ethnic group, reducing the potential effects of population stratification. The relatively large sample size and the detailed exposure information allowed us to evaluate the joint effect of obesity-related genetic markers and energy balance measures on endometrial cancer risk.

In summary, our study found strong evidence linking obesity and endometrial cancer at the genetic level. We also found that relations between BMI-associated variants and endometrial cancer risk appear to be independent of BMI, suggesting that genetic markers of obesity have value themselves, in addition to BMI, for defining women who may be at higher risk of endometrial cancer.

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