Adiposity and Cancer

Mendelian randomization study of adiposity-related traits and risk of breast, ovarian, prostate, lung and colorectal cancer

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Abstract

Background: Adiposity traits have been associated with risk of many cancers in observational studies, but whether these associations are causal is unclear. Mendelian randomization (MR) uses genetic predictors of risk factors as instrumental variables to eliminate reverse causation and reduce confounding bias. We performed MR analyses to assess the possible causal relationship of birthweight, childhood and adult body mass index (BMI), and waist-hip ratio (WHR) on the risks of breast, ovarian, prostate, colorectal and lung cancers.

Methods: We tested the association between genetic risk scores and each trait using summary statistics from published genome-wide association studies (GWAS) and from 51 537 cancer cases and 61 600 controls in the Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium.

Results: We found an inverse association between the genetic score for childhood BMI and risk of breast cancer [odds ratio (OR) = 0.71 per standard deviation (s.d.) increase in childhood BMI; 95% confidence interval (CI): 0.60, 0.80; $P = 6.5 \times 10^{-5}$). We also found the genetic score for adult BMI to be inversely associated with breast cancer risk (OR = 0.66 per s.d. increase in BMI; 95% CI: 0.57, 0.77; $P = 2.5 \times 10^{-7}$), and positively associated with ovarian cancer (OR = 1.35; 95% CI: 1.05, 1.72; $P = 0.017$), lung cancer (OR = 1.27; 95% CI: 1.09, 1.49; $P = 2.9 \times 10^{-3}$) and colorectal cancer (OR = 1.39; 95% CI: 1.06, 1.82, $P = 0.016$). The inverse association between genetically predicted adult BMI and breast cancer risk remained even after adjusting for directional pleiotropy via MR-Egger regression.

Conclusions: Findings from this study provide additional understandings of the complex relationship between adiposity and cancer risks. Our results for breast and lung cancer are particularly interesting, given previous reports of effect heterogeneity by menopausal status and smoking status.

Key words: Cancer risk, body mass index, waist-to-hip ratio, Mendelian randomization, post-GWAS study

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Key Messages

- Adiposity traits have been associated with risk of many cancers in observational studies, but whether these associations are causal is unclear.
- We performed Mendelian randomization analyses to assess the possible causal relationship of birthweight, childhood and adult body mass index (BMI), and waist-hip ratio on the risks of breast, ovarian, prostate, colorectal and lung cancers.
- We found that genetic score for higher adult BMI is associated with decreased risk of breast cancer and increased risk of ovarian, lung and colorectal cancer. We also observed an inverse association between genetically predicted childhood BMI and risk of breast cancer.
- These results provide additional understanding of the complex relationship between adiposity and cancer risks.

Introduction

Obesity influences risk for many chronic diseases such as cancer, cardiovascular disease and diabetes.[1,2] Observational studies have found associations between body mass index (BMI) and various cancer types including increasing risk of postmenopausal breast,[3] colorectal,[4] endometrial[5] and pancreatic cancer,[6,7] and decreasing risk of lung cancer and premenopausal breast cancer.[8]

However, the mechanisms underlying the contribution of obesity to cancer risk remains poorly understood. It is also unclear whether these associations between obesity and cancer in observational studies are causal. For instance, the observed increased risk of lung cancer among individuals with low BMI may be due to residual confounding by smoking or weight loss resulting from chronic lung disease.[9]

Recent studies have also found time-dependent associations between assessment of adiposity and subsequent cancer risk. Higher adiposity at young ages is inversely associated with both pre- and postmenopausal breast cancer.[10] In contrast, higher adult BMI is positively associated with postmenopausal breast cancer risk.[3,11,12] Evidence also suggests that childhood obesity may be associated with ovarian cancer independent of adult BMI.[13] These findings demonstrate a dynamic relationship between adiposity and cancer development during different time frames of life, which requires a deeper investigation.

Elevated waist-to-hip ratio (WHR), representing a higher abdominal fat distribution, is associated with multiple hormonal and metabolic changes including insulin resistance and hyperinsulinaemia which may increase risk of chronic disease such as cancer.[14–16] Previous studies examining WHR and breast cancer risk indicated a positive association which remained positive after adjusting for BMI.[12,17] Some studies also suggest that measures of abdominal adiposity are more predictive of colorectal cancer than BMI.[18,19] Thus, further investigations on the contribution of WHR to cancer risk may improve our understanding of the relationship between body fat distribution, obesity and cancerogenesis.

Mendelian randomization (MR) is a technique that uses genetic predictors of risk factors as instrumental variables to assess the possible causal associations between risk factors and diseases.[20] As genetic variants are fixed at conception and are generally independent of confounders, such an approach seeks to eliminate potential reverse causality and reduce confounding bias.[21,22] To our knowledge, there has not been any large-scale MR study assessing the potential causal relationship between obesity across different life stages and risk of multiple cancers.

In this study, we performed MR analysis to estimate the causal relationship between adiposity at different life stages (birthweight, childhood BMI, adult BMI and WHR) and risk of breast, ovarian, prostate, colorectal and lung cancers. We leveraged the results of recently published large-scale genome-wide association studies (GWAS) of adiposity-related traits to define a genetic score for each trait. We then assessed the associations between these scores and risks of five cancers from the Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium, which include 51 537 cancer cases and 61 600 controls from 32 participating studies.

Materials and Methods

The GAME-ON post-GWAS initiative

The Genetic Associations and Mechanisms in Oncology (GAME-ON) Initiative is a network of cancer-specific consortia engaged in GWAS and post-GWAS research. It includes five cancer-specific consortia: DRIVE (breast), CORECT (colorectal), ELLIPSE (prostate), FOCI (ovarian) and TRICL (lung) (Table 1). GWAS data from 32 studies (all European ancestry) contributing to the GAME-ON consortium were imputed using the 1000 Genomes reference panel (phase I version 3). Studies contributed summary statistics only to cancer-specific meta-analyses. Further information regarding imputation and analyses can be found in Fehringer *et al.*[23] and Zhang *et al.*[24]

Identification of single nucleotide polymorphisms associated with birthweight, childhood obesity and adult BMI and WHR

To calculate the genetic scores, we considered single nucleotide polymorphisms (SNPs) that were genome-wide significant ($P < 5 \times 10^{-8}$) in the largest GWAS to date for each trait as follows: (i) 7 SNPs of birthweight from Horikoshi *et al.*;[25] (ii) 15 SNPs of childhood BMI from Felix *et al.*;[26] (iii) 77 SNPs of adult BMI from Locke *et al.* (SNPs from primary meta-analysis of European-descents only);[27] and (iv) 14 SNPs of adult WHR from Heid *et al.*[28] All GWAS were restricted to individuals of European ancestry. For all identified SNPs, we obtained the chromosome and position, the nearest gene, the risk allele and trait-specific association estimates and standard errors reported in the papers above. For each SNP, we also extracted cancer-specific effect estimates and *P*-values from the GAME-ON consortium (Supplementary Table 1, available as Supplementary data at *IJE* online).

Several SNPs associated with birthweight, childhood BMI, adult BMI and WHR were not found in GAME-ON

Table 1. Participants and studies included in the Genetic Associations and Mechanisms in Oncology (GAME-ON) consortium by cancer site and subtype

Cancer type	Cancer subtype	Cases	Controls	GWAS studies
Breast	All	15748	18084	11
	ER-negative	4939	13128	8
Colorectal	All	5100	4831	6
Lung	All	12160	16838	6
	Adenocarcinoma	3718	15871	6
	Squamous	3422	16015	6
Ovarian	All	4369	9123	3
	Clear-cell	356	9123	3
	Endometrioid	715	9123	3
	Serous	2556	9123	3
Prostate	All	14160	12724	6
	Aggressive	4450	12724	6
Total	All	51537	61600	32

data for ovarian endometrioid cancer subtype, lung cancer or colorectal cancer. For these SNPs, proxy SNPs ($r^2 > 0.9$, 1000 Genomes Northern and Western European population) were used in the analysis instead (Supplementary Table 2, available as Supplementary data at *IJE* online) There were no overlaps (lead SNPs within 250 kb) among the GWAS-identified loci for different adiposity-related traits except childhood BMI and adult BMI, for which we found 10 overlap regions: *SEC16B, TNNI3K, FTO, MC4R, TMEM18, TFAP2B, OLFM4, ADCY3, GPR61/ GNAT2* and *GNPDA2* (Supplementary Figure 1, available as Supplementary data at *IJE* online).

Statistical analysis

We conducted MR analyses to estimate the association between adiposity-related traits and cancer using summary genetic association statistics, as described in Burgess *et al.*[29] Specifically, the ratio estimate ($\hat{\beta}$) of the effect of a risk factor (X) on disease outcome (Y) using genetic variants $k = 1, \ldots, K$ can be calculated as:

$$\hat{\beta} = \frac{\sum_k X_k Y_k \sigma_{Y_k}^{-2}}{\sum_k X_k^2 \sigma_{Y_k}^{-2}}$$

where x_k is the per-allele effect of SNP k with the risk factor, Y_k is the per-allele change in the log odds ratio for the cancer being tested and σ_{Yk}^2 is the standard error for Y_k. The summary statistics X_k, Y_k and σ_{Yk}^2 are taken from the GWAS for the risk factor and for cancer, respectively. The standard error of $\hat{\beta}$ is given by: $se(\hat{\beta}) = \sqrt{\frac{1}{\sum_k X_k^2 \sigma_k^{-2}}}$.[16, 21]Under certain assumptions,[30] the ratio estimate $\hat{\beta}$ can be interpreted as the causal log odds ratio of cancer risk associated with one unit change in the adiposity-related traits (birthweight, childhood BMI, adult BMI and WHR).

Since some cancers demonstrate aetiological heterogeneity by histological subtype or clinical characteristics, we also conducted the following cancer-specific subgroup analyses: estrogen receptor-negative (ER-) breast cancer; clear cell, endometrioid and serous ovarian cancer; adenocarcinoma and squamous lung cancer; and aggressive prostate cancer (defined as a Gleason score of $\geq$ 8, a disease stage of 'distant', a prostate-specific antigen level of > 100 ng/ml or death from prostate cancer.[31] In addition, sensitivity analyses were performed excluding the overlap loci between childhood BMI and adult BMI. One key assumption for MR analysis is no pleiotropic effect. Thus, Egger regression was performed to evaluate directional pleotropic effect for adult and childhood BMI[32] to provide effect estimates after adjusting for potential pleiotropic effects. The

intercept from Egger regression provides a test for directional pleiotropy (the average direct effects of adiposity-increasing variants increase [or decrease] cancer risk). Under the assumption that the SNPs' direct effects on cancer risk are independent of their association with body mass index, Egger regression provides an unbiased estimate of the causal effect of genetically predicted BMI on cancer. Unless otherwise noted, all *P*-values are unadjusted for multiple testing.

Results

We estimated the associations between adiposity-related genetic scores and risk of five cancers (Table 1). Figures comparing results across cancers are shown in Supplementary Figure 2 (available as Supplementary data at *IJE* online).

Breast cancer

The risk of breast cancer decreased with increasing genetic score for childhood BMI [odds ratio (OR) = 0.71 per standard deviation (s.d.) increase in childhood BMI; 95% confidence interval (CI): 0.60, 0.80; $P = 6.5 \times 10^{-5}$] and also with increasing genetic score for adult BMI (OR = 0.66 per s.d. increase in adult BMI; 95% CI: 0.57, 0.77; $P = 2.5 \times 10^{-7}$) (Table 2). Similar associations were found for ER-negative breast cancer (OR = 0.69; 95% CI: 0.53, 0.98, $P = 5.8 \times 10^{-3}$ for childhood BMI; OR = 0.59; 95% CI: 0.46, 0.75; $P = 2.0 \times 10^{-5}$ for adult BMI). We did not observe an association between the genetic score for birthweight and breast cancer and observed an inverse association between the genetic score for WHR and breast cancer risk (OR = 0.73; 95% CI: 0.54, 1.00; $P = 0.05$).

Ovarian cancer

The estimated association between the genetic scores for higher adult BMI is associated with increased risk of overall ovarian cancer. One standard deviation increase in genetically predicted adult BMI was associated with 35% increased risk of ovarian cancer (OR = 1.35; 95% CI: 1.05, 1.72; $P = 0.017$). We did not find strong evidence of associations between genetically predicted birthweight, childhood BMI or WHR and ovarian cancer risk.

Lung cancer

We observed a positive association between genetically predicted adult BMI and overall lung cancer (OR = 1.27; 95% CI: 1.09, 1.49; *P*-value = 2.9×10^{-3}) (Table 2). This

Table 2. Mendelian randomization odds ratios of birthweight, childhood BMI, adult BMI, and waist-hip ratio across five different cancer types obtained using summary data from GAME-ON consortium

Cancer type		Birthweight		Childhood BMI		Adult BMI		Waist-hip ratio	
		OR	*P*-value	OR	*P*-value	OR	*P*-value	OR	*P*-value
		(95% CI)		(95% CI)		(95% CI)		(95% CI)	
Breast cancer	All	1.22	0.15	0.71	6.5×10^{-5}	0.66	2.5×10^{-7}*	0.73	0.051
		(0.93, 1.60)		(0.60, 0.80)		(0.57, 0.77)		(0.53, 1.00)	
	ER-negative	1.01	0.98	0.69	0.0058	0.59	2.0×10^{-5}*	0.74	0.23
		(0.66, 1.53)		(0.53, 0.98)		(0.46, 0.75)		(0.45, 1.21)	
Ovarian cancer	All	1.07	0.75	1.07	0.62	1.35	0.017	1.19	0.50
		(0.69, 1.65)		(0.82, 1.39)		(1.05, 1.72)		(0.73, 1.94)	
	Clear-cell	2.75	0.10	1.45	0.34	1.68	0.14	1.31	0.71
		(0.82, 9.30)		(0.68, 3.09)		(0.84, 3.36)		(0.32, 5.30)	
	Endometrioid	0.79	0.60	1.47	0.16	1.34	0.26	1.03	0.95
		(0.33, 1.92)		(0.86, 2.52)		(0.80, 2.26)		(0.38, 2.84)	
	Serous	0.85	0.56	0.91	0.56	1.30	0.089	1.34	0.34
		(0.50, 1.45)		(0.65, 1.26)		(0.97, 1.76)		(0.73, 2.46)	
Prostate cancer	All	1.33	0.082	1.01	0.91	1.01	0.97	1.02	0.90
		(0.96, 1.82)		(0.83, 1.22)		(0.84, 1.21)		(0.72, 1.46)	
	Aggressive	1.63	0.037	1.10	0.49	1.11	0.44	1.19	0.51
		(1.03, 2.57)		(0.83, 1.45)		(0.85, 1.44)		(0.71, 1.98)	
Lung cancer	All	0.93	0.64	1.01	0.90	1.27	2.9×10^{-3}	1.15	0.46
		(0.70, 1.23)		(0.85, 1.2)		(1.09, 1.49)		(0.80, 1.66)	
	Adenocarcinoma	0.95	0.83	0.90	0.47	0.93	0.59	0.90	0.71
		(0.62, 1.46)		(0.69, 1.19)		(0.73, 1.19)		(0.51, 1.58)	
	Squamous	0.99	0.94	1.08	0.57	1.54	6.6×10^{-4}*	1.33	0.33
		(0.64, 1.52)		(0.82, 1.43)		(1.20, 1.96)		(0.75, 2.36)	
Colorectal cancer	All	0.69	0.12	1.20	0.21	1.39	0.016	1.29	0.35
		(0.44, 1.10)		(0.90, 1.59)		(1.06, 1.82)		(0.75, 2.22)	

BMI SNP rs12016871 has been merged into rs9581854 and thus rs9581854 was used for analysis instead.

*Denotes analyses that have $P < 0.001$ after Bonferroni correction for 48 tests.

association appeared restricted to squamous cell lung cancer (OR = 1.54; 95% CI: 1.20, 1.96; $P = 6.6 \times 10^{-4}$), as we found no strong evidence for association with lung adenocarcinoma (OR = 0.93; 95% CI: 0.73, 1.19, $P = 0.59$). We also did not find strong evidence for association between either genetically predicted birthweight or childhood BMI and lung cancer risk.

Prostate cancer

We found a positive association between the genetic score for birthweight and aggressive prostate cancer (OR = 1.63 per s.d. unit increase in birthweight; 95% CI: 1.03, 2.57; $P = 0.037$). No strong evidence was found for associations between prostate cancer and any other adiposity measures.

Colorectal cancer

We found an increase in risk of colorectal cancer per s.d. increase of genetically predicted adult BMI (OR = 1.39; 95% CI: 1.06, 1.82; $P = 0.016$). No associations were

found between birthweight, childhood BMI or waist-hip-ratio and colorectal cancer risk.

Overlap in adiposity SNP scores

None of the pairs of adiposity-trait SNP scores overlap (within 250 kb) except childhood BMI and adult BMI, which overlap at 10 loci: *SEC16B, TNNI3K, FTO, MC4R, TMEM18, TFAP2B, OLFM4, ADCY3, GPR61/GNAT2* and *GNPDA2*. To assess the specificity of the observed associations between childhood and adult BMI and cancer risk, we repeated the analyses after removing the SNPs from the overlapping loci. The associations remained between adult BMI and breast and lung cancer, whereas the associations between childhood BMI and breast were attenuated after removing the overlapping loci (Table 3).

Egger regression

With the possible exception of genetically predicted childhood BMI and breast cancer risk, the Egger regression did

Table 3. Mendelian randomization odds ratios of childhood BMI and adult BMI across five different cancer types obtained using summary data from GAME-ON consortium, excluding overlap loci (*SEC16B, TNNI3K, FTO, MC4R, TMEM18, TFAP2B, GNAT2, OLFM4, ADCY3, GNPDA2*)

		Childhood BMI		Adult BMI	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Breast cancer	All	1.05 (0.74, 1.48)	0.80	0.75 (0.62, 0.92)	4.7×10^{-3}*
	ER-negative	1.17 (0.68, 2.03)	0.57	0.66 (0.49, 0.91)	0.011
Ovarian cancer	All	0.58 (0.34, 1.01)	0.053	1.26 (0.93, 1.72)	0.14
	Clear-cell	0.70 (0.15, 3.25)	0.69	1.44 (0.60, 3, 43)	0.42
	Endometrioid	0.67 (0.22, 2.03)	0.47	0.84 (0.43, 1.64)	0.61
	Serous	0.54 (0.27, 1.06)	0.07	1.43 (0.98, 2.10)	0.062
Prostate cancer	All	1.29 (0.88, 1.87)	0.19	1.09 (0.86, 1.37)	0.48
	Aggressive	1.32 (0.77, 2.29)	0.32	1.24 (0.89, 1.73)	0.20
Lung cancer	All	0.90 (0.63, 1.28)	0.55	1.41 (1.16, 1.73)	6.8×10^{-4}*
	Adenocarcinoma	1.06 (0.62, 1.83)	0.83	1.00 (0.74, 1.36)	0.99
	Squamous	0.66 (0.38, 1.14)	0.13	1.73 (1.27, 2.38)	5.3×10^{-4}*
Colorectal cancer	All	0.85 (0.48, 1.50)	0.57	1.36 (0.96, 1.92	0.08

*Denotes analyses that have $P < 0.001$ after Bonferroni correction for 48 tests.

not reveal any strong directional pleiotropic effect on the risk estimation of genetically predicted adult BMI/childhood BMI/WHR/birthweight on various cancers (Table 4). All estimated intercepts from the Egger regression are near zero. The effect estimates from the Egger regression are generally in the same direction as the estimates from the MR analysis and larger in magnitude, except for lung cancer. We detect no strong pleiotropic effect on the risk estimation of genetically predicted adult BMI and lung cancer (intercept = 0.011; $P = 0.057$) but found no positive association between the BMI score on lung cancer in the Egger regression analysis (OR = 0.90; 95% CI: 0.51, 1.29; $P = 0.59$).

Associations between individual adiposity-related SNPs and cancer risk

Figure 1 illustrates SNP-specific associations with risk of breast (top left), ovarian (top right), colorectal (bottom left) and lung cancer (bottom right) versus the documented associations between each SNP and adult BMI. After excluding potential outliers (rs1558902 and rs17024393 for breast and ovarian cancer; rs17105752 for lung cancer), the MR analysis still shows strong evidence for association between predicted adult BMI and cancer (for breast cancer, OR = 0.69 per s.d. increase in BMI; 95% CI: 0.58, 0.82; $P = 3.0 \times 10^{-5}$; for ovarian cancer, OR = 1.32 per s.d. increase in BMI; 95% CI: 1.01, 1.74; $P = 0.041$; for lung cancer, OR = 1.30 per s.d. increase in BMI; 95% CI: 1.10, 1.52; $P = 1.5 \times 10^{-3}$).

Discussion

In this study, we found an inverse association between the genetic scores for childhood BMI and adult BMI and risk of both overall and ER-negative breast cancer. Further, the genetic score for adult BMI was associated with increased risk of ovarian, lung, squamous lung and colorectal cancer.

Consistent with our results, observational studies have shown an inverse association between higher childhood

Table 4. Effect estimates from Egger regression for adult BMI, childhood BMI, birthweight and WHR

Adult BMI	MR OR	Egger regression					
		Intercept	Standard error	*P*	OR Egger	Standard error	*P*
Breast cancer	0.66 (0.57, 0.77)	0.0035	0.0056	0.53	0.59	0.20	0.0076
Ovarian cancer	1.35 (1.05, 1.72)	−0.0093	0.0088	0.29	1.80	0.31	0.054
Prostate cancer	1.01 (0.84, 1.21)	0.0096	0.0066	0.15	0.74	0.23	0.19
Lung cancer	1.27 (1.09, 1.49)	0.011	0.0057	0.057	0.90	0.20	0.59
Colorectal cancer	1.39 (1.06, 1.82)	0.0082	0.0098	0.40	1.08	0.33	0.82

Childhood BMI	MR OR	Egger regression					
		Intercept	Standard error	*P*	OR Egger	Standard error	*P*
Breast cancer	0.71 (0.60, 0.80)	0.048	0.027	0.026	0.34	0.21	0.0017
Ovarian cancer	1.07 (0.82, 1.39)	−0.053	0.044	0.12	2.44	0.33	0.10
Prostate cancer	1.01 (0.83, 1.22)	−0.020	0.033	0.42	1.38	0.25	0.42
Lung cancer	1.01 (0.85, 1.2)	−0.0015	0.088	0.95	1.04	0.21	0.92
Colorectal cancer	1.20 (0.90, 1.59)	−0.020	0.15	0.41	1.63	0.35	0.22

WHR	MR OR	Egger regression					
		Intercept	Standard error	*P*	OR Egger	Standard error	*P*
Breast cancer	0.73 (0.53, 1.00)	0.0048	0.026	0.85	0.63	0.83	0.58
Ovarian cancer	1.19 (0.73, 1.94)	−0.037	0.042	0.38	3.67	1.32	0.32
Prostate cancer	1.02 (0.72, 1.46)	0.046	0.031	0.14	0.25	0.97	0.15
Lung cancer	1.15 (0.80, 1.66)	−0.017	0.032	0.60	1.97	1.04	0.52
Colorectal cancer	1.29 (0.75, 2.22)	−0.068	0.046	0.14	10.38	1.43	0.10

Birthweight	MR OR	Egger regression					
		Intercept	Standard error	*P*	OR Egger	Standard error	*P*
Breast cancer	1.22 (0.93, 1.60)	0.040	0.030	0.18	1.75	0.59	0.34
Ovarian cancer	1.07 (0.69, 1.65)	0.069	0.048	0.15	3.46	0.93	0.18
Prostate cancer	1.33 (0.96, 1.82)	0.0043	0.035	0.90	0.82	0.69	0.77
Lung cancer	0.93 (0.70, 1.23)	0.0011	0.031	0.97	1.10	0.60	0.88
Colorectal cancer	0.69 (0.44, 1.10)	−0.026	0.051	0.96	1.38	0.100	0.75
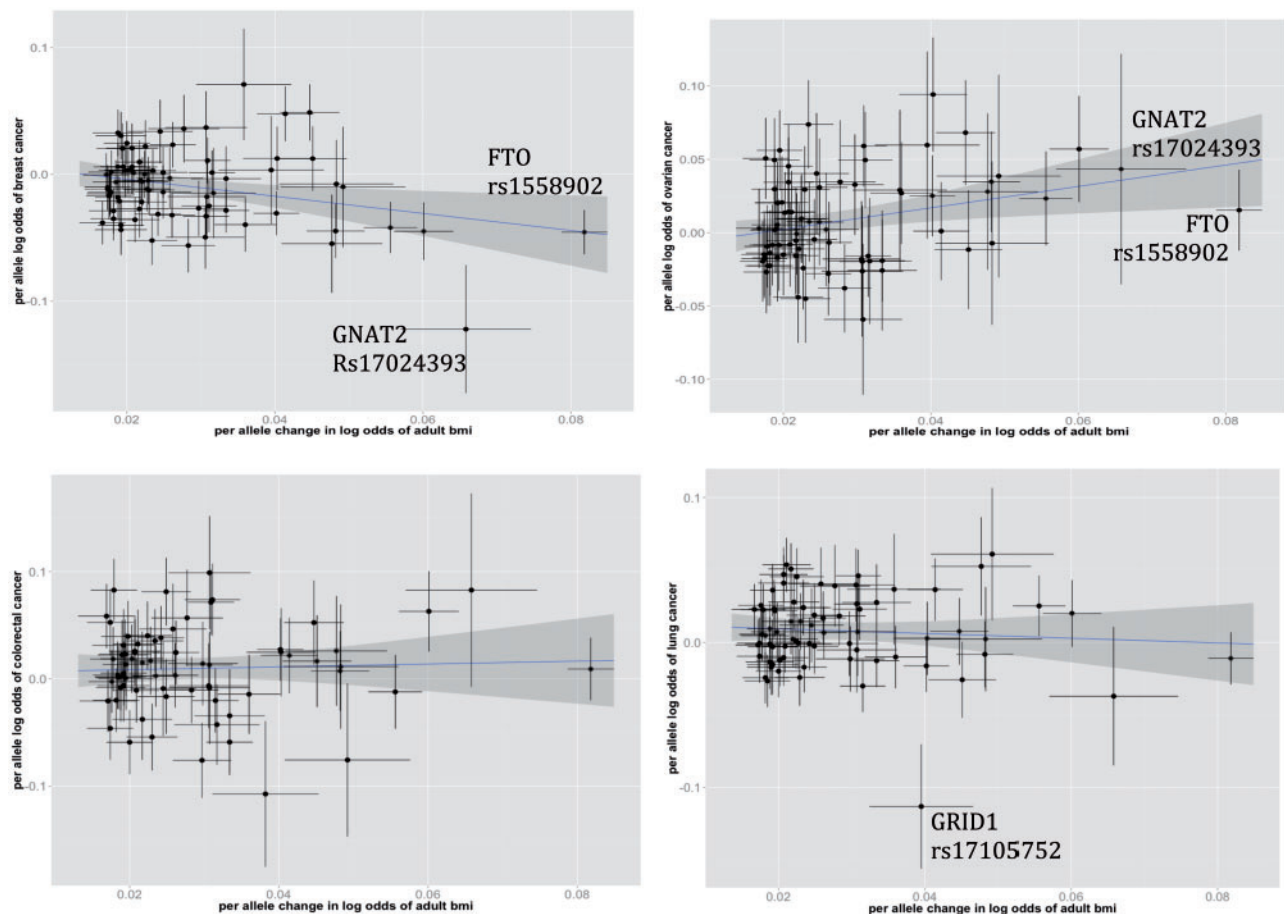
Figure 1. Scatterplot of SNP-specific effects for the associations with adult BMI and a) breast cancer(top left), b) ovarian cancer risk(top right), c) colorectal cancer(bottom left), d) lung cancer(bottom right) for all 77 BMI-associated SNPs. SNP-specific vertical and horizontal bars correspond to standard errors for the breast/ovarian/colorectal/lung cancer association and BMI association respectively. The shaded region corresponds to 95%CI of the association between BMI and cancer risk.

BMI and both premenopausal and postmenopausal breast cancer.[10,33,34] In contrast to our findings, observational studies have found that higher adult BMI was positively associated with postmenopausal breast cancer;[35,36] this includes a recent instrumental variables analysis using offspring BMI as an instrument for parental BMI.[37] However, we found decreased risk of breast cancer with higher adult BMI genetic score, even though the majority of women who contributed to our analysis were postmenopausal (62%). We did not have access to summary statistics stratified by menopausal status, but findings from a recent MR analysis of a large data set from the Collaborative Oncological Gene-Environment Study (COGS) are consistent with our study. The MR estimate from that study for 5kg/m^2 increase in BMI was 0.65 (95% CI: 0.56, -0.75; $P = 3.3\ 2 \times 10^{-10}$) for overall breast cancer. This inverse association was consistent across both pre- and postmenopausal women: OR = 0.44; 95% CI: 0.31, 0.62; $P = 9.91 \times 10^{-8}$ for premenopausal women, and OR = 0.57; 95% CI: 0.46, 0.71; $P = 1.88 \times 10^{-6}$ for postmenopausal women.[38]

Thus, at first sight, our results might suggest that increasing adult BMI is associated with reduced postmenopausal breast cancer risk, contradicting the epidemiological evidence. There are several possible explanations for this discrepancy. One hypothesis to explain this is illustrated in the causal graph in Figure 2. The positive association between observed adult BMI and postmenopausal breast cancer in observational studies may be driven by adult weight gain, which has been linked to increased postmenopausal breast cancer risk.[39] This weight gain could be due to environmental factors that are not captured by genetic risk scores.[40]. The effects of the BMI-associated SNPs on breast cancer risk may be mediated through their effects on BMI in childhood and young adulthood, which have been shown to be inversely associated with postmenopausal breast cancer risk (as shown in Figure 2 by a negative sign).[10,33,34] It is also possible that the adult BMI genetic score is a stronger instrumental variable for early life BMI as compared with later life BMI that is largely determined by environment, and that the inverse association of early life BMI with breast cancer may counterbalance the association with BMI later in life.
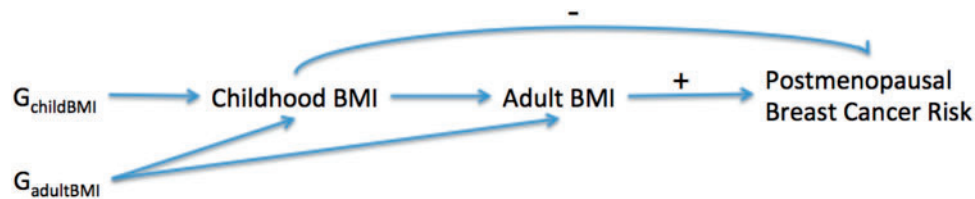
Figure 2. DAG demonstrating one potential explanation of how genetic variants influence postmenopausal breast cancer risk.

Consistent with our hypothesis, an observational study examining the association between weight change across the life course and breast cancer risk in the Nurses Health Study (77 232 women from 1980 to 2012) found that weight at age 18 was inversely associated with both pre- and postmenopausal incidence of breast cancer. In contrast, adult weight gain was positively associated with both pre and postmenopausal breast cancer risks (B. Rosner, personal communication).

Three of the four strongest (largest effect size) adult BMI SNPs are also associated with childhood BMI. In sensitivity analyses excluding overlapping loci from the adult and childhood BMI scores, we still observed an inverse association with breast cancer for the genetic score for adult BMI (OR = 0.75, 95% CI: 0.62, 0.92; $P = 4.7 \times 10^{-3}$); but the association between childhood BMI score and breast cancer was attenuated (Table 3). However, we found the genetic instrument for adult BMI was associated with childhood BMI (and vice versa, Supplementary Table 5, available as Supplementary data at *IJE* online) even after removing the overlapping loci. This suggests that care is required when interpreting these results. The association between predicted adult BMI and breast cancer risk may reflect effects on a pathway distinct from childhood BMI, or it may simply reflect the shared genetics of early- and later-life BMI.

We found that a genetic risk score predicting higher BMI was associated with increased risk of lung cancer overall and lung squamous carcinoma in particular. Studies have found obesity to be associated with high insulin resistance[41] which is positively associated with lung cancer risk,[42] suggesting that the observed positive associations may be mediated by insulin resistance. Multiple studies have reported an inverse relationship between BMI and lung cancer among smokers but no or a weakened association among never smokers.[8,43–45] These results may be due to residual confounding, reverse causation or effect modification by smoking.[9,44,45] We did not have access to individual-level genetic and smoking data for this study, so our Mendelian randomization estimate of the effect of body mass index on cancer risk should be interpreted with care: it represents an average of the effects across smoking status (83% of the participants in the lung cancer GWAS were ever smokers). Future work in the large OncoArray Network will be able to perform stratified analysis by smoking status.[46]

Another concern with our MR analyses on adult BMI and lung cancer risk is that some BMI-associated SNPs are associated with neurological response and stress-related behaviour that affect smoking.[27,47,48] To assess whether our results were driven by pleiotropic effects, we performed additional analysis excluding SNPs that are associated with smoking initiation or schizophrenia (rs1191560, rs11030104[27]). We still observe a positive association between genetically predicted adult BMI and lung cancer (OR = 1.25; 95% CI: 1.07,1.47; $P = 6.0 \times 10^{-3}$). It is also worth noting that, although we detect limited directional pleiotropy for the association between predicted adult BMI and lung cancer risk, we found inverse association between the genetically predicted adult BMI and lung cancer risk in the MR Egger regression analysis ($P = 0.59$). This could be due to bias caused by other type of pleiotropy or lack of statistical power.

Our MR results showed an increased risk in ovarian cancer with increasing adiposity measures across different life stages; this is consistent with previous observational studies.[49,50] Obesity in adolescence is associated with increased risk of ovulatory infertility that may increase risk of ovarian cancer.[51] In addition, obesity is also associated with an increased level of insulin-like growth factor 1 (IGF-1) which increases cell proliferation and modulates synthesis and bioavailability of sex steroids hormones that are involved in ovarian cancer aetiology.[52,53] The opposite risk profiles between breast and ovarian cancer also suggest that adiposity determined by genetic variants has different underlying mechanisms in relation to breast versus ovarian cancer carcinogenesis.

Our analyses suggest that adult BMI is associated with increased risk of colorectal cancer, consistent with the published epidemiological literature. Keimling *et al.* found a 14% increase in colorectal cancer risk per s.d. increase in BMI.[54] A recently published MR study also found that genetically influenced BMI was associated with higher risk of colorectal cancer (OR = 1.50 per 5 kg/m^2 increase; 95% CI: 1.13, 2.01).[55] The mechanisms linking adiposity and colorectal cancer are not yet fully understood. One possible explanation is that obese individuals have higher leptin secretion from the white adipose tissue, and the binding of leptin to its receptor in the colon epithelium activates biological pathways implicated with colorectal cancer.[56]

Although there is evidence that genetically predicted BMI is associated with breast and lung cancer, the underlying mechanisms remain unknown. There are many factors that can influence both adiposity and cancer risks such as physical activity, mental stress, insulin resistance and exposure to hormones secreted by adipose tissue. Further studies incorporating these factors might provide a better understanding of the mechanism underlying the relationship between adiposity and cancer risk. As data on SNP-specific function emerge, future studies can also carefully categorize SNPs by their functionality, and perform MR analysis for different groups of SNPs. This will allow us to parse out specific sets of SNPs and further evaluate which pathway(s) are of importance in the adiposity-cancer association. In addition, gene-environmental interaction can also provide additional insights in understanding the mechanism underlying adiposity and cancer risk. Although not feasible in the GAME-ON data, in the newly completed OncoArray data, where we have individual data on menopausal status, hormone therapy, reproductive factors for breast cancer and smoking status for lung cancer, we will be able to perform gene-environment interaction analysis in the near future.[46]

Our study has several limitations. The summary-level statistics approach does not allow us to perform analyses stratified by covariates such as menopausal or smoking status. The summary statistics also did not permit us to explore the non-linearity of the association between obesity and cancer risk, which has been observed in a previous study.[8] We note that non-linearity does not invalidate the test of association, although it may complicate the interpretation of the effect estimate.[57] Finally, the statistical power is limited by both the proportion of the adiposity risk factors explained by the genetic instruments, and the sample size in the cancer genetic association studies,[58] and this is particularly an issue for analyses of rare cancer subtypes.

MR analyses are only valid under a few strong assumptions:[30,59] (i) valid association between SNPs and risk factors; (ii) SNPs are not associated with other confounders of the risk factors and outcome; and (iii) SNPs only affect the outcome through their effect on the risk factors (no pleiotropic effects). The second and third assumptions are the most concerning and require careful interpretation. For (ii), population stratification may be a source of confounding but the original studies saw little evidence for such bias and all have appropriately controlled for it. Assumption (iii) raises the most concern, especially for relationship between genetically predicted adult BMI and breast cancer risk. As noted before, the association between the genetic instrument for adult BMI and childhood BMI (and vice versa) makes the associations between these instruments and breast cancer difficult to distinguish. This is a situation where the

InSIDE (Instrument Strength Independent of Direct Effects) assumption—the direct effect of an SNP on cancer risk is uncorrelated with its association with trait of interest—does not hold.[32] There are other reasons why assumption (iii) might not hold. For example, two SNPs known to be associated with breast cancer are near the *FTO* gene, raising the possibility that obesity-related variants may affect cancer risk through other pathways.[60] To test for and correct for bias due to pleiotropy where the InSIDE assumption holds, we performed Egger regression for all traits investigated (Table 4 and Supplementary Table 4, available as Supplementary data at *IJE* online). Egger regression shows limited evidence for any directional pleiotropic effects influencing associations between genetically predicted adiposity traits and the cancer studied here.

Despite these issues, our study also has several important strengths. Many studies examining BMI and cancer risk in the past were susceptible for recall bias, confounding and reverse causation,[61] none of which are concerns of MR studies. In addition, we used summary statistics from the largest meta-analyses of primary GWAS of these cancer types to date, which improves our power of detecting real causal effects. Moreover, by comparing results across cancer types, we are able to demonstrate specificity of the association between genetic markers of adiposity and particular cancers.

In summary, we found associations between genetic scores for higher adult BMI and increased risk of lung, colorectal and ovarian cancers. Additionally, we observed an inverse association of both genetically predicted childhood BMI and adult BMI with breast cancer. Given the strength of the epidemiological and biological studies linking obesity after menopause with increased risk of breast cancer, this highlights the need for caution when interpreting the results of MR analyses. Our study supports the hypothesis of dynamic relationships between genetic variation underlying obesity and different cancer risks throughout life. To better interpret the complexity of the relationship between adiposity and breast cancer, future investigations that effectively distinguish childhood versus adulthood obesity need to be undertaken. In addition, MR studies stratifying by menopausal status or smoking status can add additional insight in understanding the relationship between adiposity and breast or lung cancer risk.

Supplementary Data

Supplementary data are available at *IJE* online.

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Commentary: Two-sample Mendelian randomization: opportunities and challenges

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Introduction

In this volume of the *IJE*, Gao and colleagues explore the causal effect of adiposity on several cancers using two-sample Mendelian randomization (MR), and find some evidence that greater adult body mass index (BMI) causally reduces the risk of breast cancer while increasing ovarian, lung and colorectal cancer.[1] The authors conclude that the