Circulating adipokine concentrations and risk of five obesity-related cancers: A Mendelian randomization study

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Abbreviations: BMI, body mass index; CCFR, Colon Cancer Family Registry; CI, confidence interval; CORECT, ColoRectal Transdisciplinary Study; EPIC, European Prospective Investigation into Cancer and Nutrition; GECCO, Genetics and Epidemiology of Colorectal Cancer; GWAS, genome-wide association studies; HPFS, Health Professional Follow-up; IVW, inverse-variance weighted; LD, linkage disequilibrium; MR, Mendelian randomization; OR, odds ratio; PAI-1, plasminogen activator inhibitor-1; PCs, principal components; PPARG, Peroxisome Proliferator Activated Receptor Gamma; RCC, renal cell carcinoma; sOB-R, soluble leptin receptor; WHI, Women's Health Initiative.

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Abstract

Obesity is considered a chronic inflammatory state characterized by continued secretion of adipokines and cytokines. Experimental and epidemiological evidence indicates that circulating adipokines may be associated with the development of obesity-related cancers, but it is unclear if these associations are causal or confounded. We examined potential causal associations of specific adipokines (adiponectin, leptin, soluble leptin receptor [sOB-R] and plasminogen activator inhibitor-1 [PAI-1]) with five obesity-related cancers (colorectal, pancreatic, renal cell carcinoma [RCC], ovarian and endometrial) using Mendelian randomization (MR) methods. We used summary-level data from large genetic consortia for 114 530 cancer cases and 245 284 controls. We constructed genetic instruments using 18 genetic variants for adiponectin, 2 for leptin and 4 for both sOB-R and PAI-1 (P value for inclusion $< 5 \times 10^{-8}$). Causal estimates were obtained using two-sample MR methods. In the inverse-variance weighted models, we found an inverse association between adiponectin and risk of colorectal cancer (odds ratio per 1 $\mu\text{g/mL}$ increment in adiponectin concentration: 0.90 [95% confidence interval = 0.84–0.97]; $P = .01$); but, evidence of horizontal pleiotropy was detected and the association was not present when this was taken into consideration. No association was found for adiponectin and risks of pancreatic cancer, RCC, ovarian cancer and endometrial cancer. Leptin, sOB-R and PAI-1 were also similarly unrelated to risk of obesity-related cancers. Despite the large sample size, our MR analyses do not support causal effects of circulating adiponectin, leptin, sOB-R and PAI-1 concentrations on the development of five obesity-related cancers.

KEYWORDS

adiponectin, cancer, leptin, Mendelian randomization, plasminogen activator inhibitor, soluble leptin receptor

1 | INTRODUCTION

A substantial body of evidence has shown that excess adiposity is associated with a greater risk of developing many common cancers.^{1,2} The biological pathways linking adiposity with cancer development are incompletely understood, but likely involve alterations in insulin signaling, sex hormone pathways and adipose tissue-derived inflammation.^{3,4} Obesity is considered as a chronic inflammatory state characterized by continued infiltration of adipose tissue by macrophages and other immune cells leading to increased or decreased adipose secretion of adipokines (such as adiponectin, leptin and plasminogen activator inhibitor-1 [PAI-1]) that may be linked to cancer development.

Adiponectin lowers secretion of inflammatory cytokines, improves insulin sensitivity and inhibits cell growth and angiogenesis, but is downregulated in obesity.^{5,6} Multiple epidemiological studies

What's new?

Chronic inflammation attributed to obesity may influence cancer development. However, little is known about the relationship between oncogenesis and changes in adipokine secretion stemming from immune cell infiltration in adipose tissue. Here, large-scale Mendelian randomization analysis was used to assess possible causal associations of adipokine concentrations influenced by genetic variation and risk of five obesity-related cancers, including renal cell carcinoma and colorectal, pancreatic, ovarian and endometrial cancer. In general, no association was detected between adipokines and the five malignancies, suggesting that adipokine levels have no causal influence on these cancers.

have investigated the association between circulating adiponectin concentration and cancer risk with inverse relationships sometimes reported for endometrial, colorectal, renal cell carcinoma (RCC) and pancreatic cancer.^{3,7-10} Epidemiological studies that examined the association between circulating leptin concentration, which has pro-inflammatory effects, and obesity-related cancers have yielded inconsistent results.^{9,11,12} It is unclear if these mixed results were due to most studies failing to measure soluble leptin receptor (sOB-R) concentrations, which may regulate the biological effects of circulating leptin concentration. Within the European Prospective Investigation into Cancer and Nutrition (EPIC) study, circulating concentration of sOB-R was inversely associated with colorectal cancer, even after statistical adjustment for leptin concentrations, suggesting that sOB-R may have an independent role in colorectal cancer development.¹¹ It is currently unknown if sOB-R is similarly associated with other obesity-related cancers as these studies have not been conducted. In addition, few studies have examined the association between circulating PAI-1 concentration (elevated in obesity) and cancer outcomes, although positive associations were found for colorectal cancer in the EPIC-Italy and Women's Health Initiative (WHI) studies.^{9,13}

These previous observational epidemiological studies are vulnerable to residual confounding and reverse causality which make causal inference challenging. An alternative approach is Mendelian randomization (MR) that uses genetic variants robustly associated with the exposure of interest as instrumental variables to allow causal inference for the effect of an exposure on an outcome.¹⁴ MR analyses are largely free of conventional confounding and reverse causality as genetic variants are randomly assigned, and fixed, at conception.

We used a two-sample MR framework to examine the associations of specific adipokines (ie, adiponectin, leptin, sOB-R and PAI-1) with five obesity-related cancers using genetic variants associated with adipokines concentrations from published genome-wide association studies (GWAS).¹⁵⁻¹⁹ We investigated the associations of these genetic variants with risks of colorectal cancer (58 221 cases and 67 694 controls), pancreatic cancer (7110 cases and 7264 controls), RCC (10 784 cases and 20 406 controls), ovarian cancer (25 509 cases and 40 941 controls) and endometrial cancer (12 906 cases and 108 979 controls).

2 | METHODS

2.1 | Adipokines data

We selected genetic variants for the MR analysis on the basis of a genome-wide significant association with circulating adipokine concentrations (ie, *P* value threshold for inclusion at $<5 \times 10^{-8}$). For adiponectin, we used 18 variants in linkage disequilibrium (LD) below 1% (ie, rs2791552, rs2943641, rs2276853, rs3087866, rs13303, rs17366568, rs13133548, rs2925979, rs10282707, rs3735080, rs7134375, rs10861661, rs11057405, rs11057353, rs4311394, rs3865188, rs145119400, rs4805885) reported in a recent largest GWAS involving 67 739 individuals that were adjusted for age, sex, body mass index (BMI) and principal components (PCs) to account for

possible population stratification.²⁰ For leptin, two variants were incorporated (rs10487505 and rs6071166) adjusted for age² BMI and PCs¹⁷ excluding rs780093 in the GCKR gene due to potential pleiotropy with several other traits (eg, urate concentrations, triglycerides, Crohn's disease, breast size).^{21,22} We constructed an instrument for sOB-R using four variants in the *LEPR* gene (rs17415296, rs4655537, rs17412403 and rs7535099), with low LD ($R^2 \leq 10\%$) to avoid underpowered MR analyses, that were adjusted for age, sex and BMI.¹⁹ In addition, we excluded rs3790438 yielding genome-wide significance for sOB-R since it was in almost perfect LD (ie, $R^2 = 0.96$) with rs17415296.²³ Finally, performing LD pruning ($R^2 \leq 1\%$) resulted in four variants for PAI-1 (rs11128603, rs2227631, rs6976053 and rs6486122) adjusted for age, sex and PCs.¹⁶ The variance explained in circulating adipokine concentration by the genetic instruments was 3%, 0.2%, 5% and 0.7% for adiponectin, leptin, sOB-R and PAI-1, respectively (Table S1).

2.2 | Cancer data

Summary data for the associations of adipokine variants with colorectal cancer were obtained from a meta-analysis of 125 915 participants (58 221 cases and 67 694 controls) within the ColoRectal Transdisciplinary Study (CORECT), the Colon Cancer Family Registry (CCFR) and the Genetics and Epidemiology of Colorectal Cancer (GECCO) consortia.²⁴ GWAS data from pancreatic cancer samples (7110 cases and 7264 controls) were obtained from the PanScan and PanC4 consortia through the National Center for Biotechnology Information database of Genotypes and Phenotypes (dbGaP).²⁵⁻²⁷ Summary data for RCC (10 784 cases and 20 406 controls) were obtained from a recent GWAS.²⁸ For ovarian cancer, summary data were obtained from a GWAS of 25 509 cases and 40 941 controls from the Ovarian Cancer Association Consortium (OCAC).²⁹ For endometrial cancer, we obtained data from a GWAS of 12 906 cases and 108 979 controls from the Endometrial Cancer Association Consortium.³⁰

2.3 | Statistical power

Power calculations were performed based on the method suggested by Brion et al.³¹ We fixed the type-I error rate at 0.05. Based on the aforementioned cancer case and control numbers, and assuming an R^2 of 3.0% (variance explained by the selected variants for circulating adiponectin), our study had 80% power to detect an odds ratio (OR) of 0.914/1.094 for colorectal cancer, 0.766/1.306 for pancreatic cancer, 0.831/1.204 for RCC, 0.881/1.135 for ovarian cancer and 0.870/1.150 for endometrial cancer. Power calculations by cancer subsite, subtype and by sex for various R^2 values are presented in Table 1.

2.4 | Statistical analysis

We employed a fixed-effects inverse-variance weighted (IVW) MR method.³² For causal estimates from MR studies to be valid, three

TABLE 1 Number of cancer cases and controls and statistical power in Mendelian randomization study of adipokines and risk of cancer

Cancer type	Cases	Controls	Total	Proportion of cases	Minimum detectable odds ratio				
					R ² = 0.01	R ² = 0.02	R ² = 0.03	R ² = 0.04	R ² = 0.05
Colorectal cancer									
Overall	58 221	67 694	125 915	0.46	0.855/1.170	0.894/1.118	0.914/1.094	0.924/1.082	0.932/1.073
Overall (men)	31 288	34 527	65 815	0.48	0.806/1.241	0.858/1.166	0.882/1.134	0.897/1.115	0.907/1.102
Overall (women)	26 843	32 820	59 663	0.45	0.797/1.255	0.850/1.176	0.876/1.141	0.892/1.121	0.903/1.108
Colon	31 083	67 694	98 777	0.31	0.831/1.203	0.873/1.145	0.897/1.115	0.910/1.099	0.918/1.089
Rectal	15 775	67 694	83 469	0.19	0.796/1.257	0.847/1.180	0.873/1.146	0.888/1.126	0.898/1.113
Pancreatic cancer									
Overall	7110	7264	14 374	0.49	0.632/1.582	0.722/1.386	0.766/1.306	0.793/1.261	0.831/1.230
Overall (men)	3861	4056	7917	0.49	0.542/1.845	0.646/1.549	0.696/1.437	0.733/1.365	0.757/1.321
Overall (women)	3252	3268	6520	0.50	0.508/1.968	0.617/1.621	0.672/1.489	0.709/1.410	0.735/1.360
Renal cell carcinoma									
Overall	10 784	20 406	31 190	0.35	0.730/1.369	0.798/1.253	0.831/1.204	0.851/1.175	0.865/1.156
Ovarian									
Overall	25 509	40 941	66 450	0.38	0.805/1.242	0.857/1.167	0.881/1.135	0.896/1.116	0.906/1.104
Serous	16 003	40 941	56 944	0.28	0.782/1.279	0.838/1.193	0.864/1.157	0.881/1.135	0.893/1.120
Clear-cell	1366	40 941	42 307	0.03	0.554/1.806	0.638/1.568	0.683/1.464	0.714/1.401	0.736/1.358
Endometrioid	2810	40 941	43 751	0.06	0.635/1.575	0.712/1.405	0.752/1.329	0.778/1.285	0.797/1.254
Endometrial cancer									
Overall	12 906	108 979	121 885	0.11	0.792/1.262	0.845/1.184	0.870/1.150	0.885/1.130	0.896/1.116

Note: Minimum detectable odds ratio: assume 80% power, 5% alpha level and that 1% to 5% of adipokines heritability is explained by the variants used in this article.

main assumptions must be satisfied: (a) the selected genetic variants used in the instrument are robustly associated with adipokine concentrations, (b) the genetic variants are not associated with any confounder of the adipokines and cancer relationship and (c) the genetic instrument should not affect the outcome independently of its effect on adipokine concentration. Assumption 1 was likely to be satisfied as only variants associated with adipokines at a genome-wide significance level were used. For assumption 2, we acquired information for the association of the selected variants used in the instruments with other traits from the Phenoscanner.³³ A series of statistical tests were performed to investigate the potential violation of MR assumption 3 and to assess the possible influence of horizontal pleiotropy on the causal estimates. We estimated the Cochran's Q statistic that quantifies the heterogeneity in effect sizes attributed to the selected genetic variants. When there was evidence for heterogeneity, we performed a random effects IVW approach in order to take into account this source of uncertainty.³⁴ MR-Egger regression was also used³⁵ and the estimator from the weighted median approach.³⁶ We conducted sensitivity analyses with variants associated with adiposity measures or insulin resistance excluded. We also restricted our analyses to *cis*-acting variants. For adiponectin, we used rs17366568 variant in the *ADIPOQ* gene; for leptin, we used rs10487505 variant in the *LEP* gene; for PAI-1, we used rs2227631 variant in the *SERPINE1* gene; while for sOB-R, all four

genetic variants (ie, rs17415296, rs4655537, rs17412403 and rs7535099) used are located in the *LEPR* gene.

For adiponectin and leptin, in sensitivity analyses, we also conducted analyses using selected variants unadjusted for BMI, to examine if collider bias may have influenced our results. In this scenario, we also accounted for pleiotropic effects acting via BMI using data from a recent GWAS of the GIANT consortium and the UK-Biobank³⁷ in a multivariable MR framework.³⁸

3 | RESULTS

3.1 | Adiponectin

In the IVW models, we found an inverse association between adiponectin and risks of colorectal cancer (OR per 1 µg/mL increment in adiponectin concentrations: 0.90 (95% confidence interval [CI] = 0.84–0.97); $P = .01$), with similar association found for men and women, colon cancer and rectal cancer (Figure 1 and Table S2). Near identical results were found when we used summary estimates of adiponectin unadjusted for BMI (Table S3). However, evidence of pleiotropy was detected and using robust MR methods (ie, MR-Egger and Weighted median test) results were attenuated toward the null for all models

FIGURE 1 Mendelian randomization estimates between (A) adiponectin, (B) leptin, (C) soluble leptin receptor and (D) plasminogen activator inhibitor-1 concentrations and cancer risk using the inverse-variance weighted method. CI, confidence interval; OR, odds ratio; PAI-1, plasminogen activator inhibitor-1; RCC, renal cell carcinoma; sOB-R, soluble leptin receptor

except for colorectal cancer in women, for which weak evidence of an inverse effect was suggested by the MR-Egger method (OR = 0.80 [95% CI = 0.62-1.03]) (Table S2). The effect estimates for adiponectin and colorectal cancer were also slightly attenuated after the exclusion of variants associated with adiposity measures/insulin [overall colorectal cancer (OR = 0.92 [95% CI = 0.84-1.01]; $P = .09$) (data not shown) or in a multivariable MR analysis accounting for BMI (overall colorectal cancer; OR = 0.92 [95% CI = 0.84-1.01]; $P = .1$) (Table S3). Similar results were obtained when a *cis*-acting variant was used as the genetic instrument (ie, rs17366568 in *ADIPOQ* gene) (overall colorectal cancer; OR = 0.92 [95% CI = 0.82-1.03]; $P = .16$) (Table S2).

No association was found between adiponectin and pancreatic cancer (OR = 1.10 [95% CI = 0.91-1.34]; $P = .32$), RCC (OR = 0.93 [95% CI = 0.79-1.08]; $P = .33$), ovarian cancer (OR = 1.07 [95% CI = 0.96-1.19]; $P = .22$) and endometrial cancer (OR = 1.02 [95% CI = 0.89-1.17]; $P = .75$). Similar null results were found for the weighted median, MR-Egger analyses, and when variants associated with obesity or insulin resistance were excluded from the instrument (Table S7).

3.2 | Leptin and soluble leptin receptor

Leptin concentration was unrelated to risk of colorectal cancer (IVW OR per 1 ng/mL increase in log-transformed leptin concentration:

0.99 [95% CI = 0.62-1.57]; $P = .96$), pancreatic cancer (OR = 0.39 [95% CI = 0.11-1.37]; $P = .14$), RCC (OR = 0.93 [95% CI = 0.35-2.44]; $P = .88$), ovarian cancer (OR = 1.78 [95% CI = 0.93-3.38]; $P = .08$) and endometrial cancer (OR = 1.46 [95% CI = 0.69-3.06]; $P = .32$) (Figure 1 and Table S4). Similar results were found when analyses were restricted to the rs10487505 variant in the *LEP* gene (Table S4). No associations were also found for sOB-R with any cancer type (Figure 1 and Table S5). For both leptin and sOB-R, similar results were generally found by cancer subsite, subtype and sex, and no evidence of heterogeneity or pleiotropy was detected.

3.3 | Plasminogen activator inhibitor-1

PAI-1 concentration was positively associated with endometrial cancer risk in the IVW models (OR = 1.38 [95% CI = 1.04-1.82]; $P = 0.03$). This association was driven solely by the variant rs11128603 that is also associated with type-2 diabetes, adiposity and body size traits; when this variant was excluded the association was attenuated toward the null (OR = 1.17 [95% CI = 0.86-1.59]; $P = .33$). PAI-1 concentration was not associated with risks of colorectal cancer (IVW OR per 1 ng/mL increase in log-transformed PAI-1 concentration: 1.01 [95% CI = 0.86-1.19]; $P = .92$), pancreatic cancer (OR = 1.13 [95% CI = 0.73-1.76]; $P = .58$), RCC (OR = 1.09 [95% CI = 0.78-1.52];

$P = 0.62$) and ovarian cancer (OR = 1.22 [95% CI = 0.95-1.55]; $P = .11$) (Figure 1 and Table S6). There was no association between genetically predicted circulating PAI-1 concentration and any of the cancers when rs2227631 variant in the *SERPINE1* gene was used as the genetic instrument (Table S6). Similar results were generally found by cancer subsite, subtype and sex, and no evidence of heterogeneity or pleiotropy was detected.

4 | DISCUSSION

In this large-scale MR analysis, we found no evidence to support causal associations of genetically determined concentrations of adipokines and risk of five obesity-related cancers. These results, together with the generally inconsistent observational epidemiological evidence, suggest that adiponectin, leptin, sOB-R and PAI-1 may not play a major role in the development of these five malignancies.

Adiponectin is predominantly secreted by visceral adipose tissue and is the most abundant adipokine, with circulating concentrations inversely correlated with adiposity. Numerous epidemiological studies have investigated the circulating adiponectin and cancer relationship, with inverse associations generally observed.^{8,30} For colorectal cancer, higher circulating adiponectin concentrations have been associated with lower risk within the EPIC, Women's Health Initiative (WHI) and Health Professional Follow-up (HPFS) studies, with these associations usually attenuated after BMI adjustment.^{7,9,10} In our MR analysis, we found an inverse association between genetically determined adiponectin concentration and colorectal cancer, which was not robust in the MR-Egger and Weighted median approach, which suggests that horizontal pleiotropy may have influenced this result. Additionally, the inverse association was attenuated toward the null after removing variants that were associated with adiposity. Collectively, these results do not support adiponectin having a causal effect on colorectal cancer risk.

For the other cancers, our results indicate that circulating adiponectin is unlikely to be causally related to tumorigenesis. Epidemiological studies examining the adiponectin and pancreatic risk association have reported mixed results. A nested case-control study of five cohorts in the United States reported that higher circulating adiponectin concentrations were associated with lower pancreatic cancer risk (OR for highest vs compared with lowest quintile 0.66 [95% CI = 0.44-0.97]),³⁹ whereas a null result was found between adiponectin and pancreatic cancer in an analysis of the EPIC study.⁴⁰ The evidence of circulating adiponectin concentration and risks of RCC and endometrial cancer from prospective epidemiological studies is mixed, with inverse associations reported by some⁴¹⁻⁴³ studies, but not by others.^{44,45} It is possible that this inconsistency in results is a consequence of measurement error, residual confounding and reverse causality inherent to observational epidemiology influencing these analyses to varying degrees. In contrast, our MR analyses should be largely free of conventional confounding and reverse causality which allows causal inference.

Our MR analyses for colorectal cancer and all other obesity-related cancers considered found no associations with genetically determined leptin and sOB-R concentrations. Multiple epidemiological studies have investigated the association between circulating leptin and risks of obesity-related cancers. Circulating concentrations of leptin were positively associated with colon cancer risk in a Norwegian nested case-control study (OR comparing the highest vs the lowest quartile 2.72 [95% CI = 1.44-5.12]).¹² Similarly, in a WHI case-cohort study, a positive association between serum leptin concentration and colorectal cancer risk was found, even after adjustment for insulin concentrations.⁹ An analysis in the EPIC study found no association for circulating leptin, but did observe an inverse association for sOB-R with colorectal cancer.¹¹ The null results we found for leptin and sOB-R are largely consistent with previous epidemiological evidence for pancreatic cancer,⁴⁶ but inconsistent for RCC and endometrial cancer, for which the few prospective studies conducted have generally found positive associations for circulating leptin concentration.^{43,47}

We found no association between genetically determined PAI-I concentration and risks of colorectal, pancreatic, renal cell and ovarian cancer. Few epidemiological studies have investigated the relationship between circulating PAI-1 concentration and obesity-related cancers. For colorectal cancer, analyses in the EPIC-Italy and WHI studies found positive association for circulating PAI-1,^{9,13} although the WHI positive association were attenuated toward the null after adjusting for circulating insulin concentration.⁹ Few epidemiological studies have examined the association of PAI-1 with risks of pancreatic, RCC, ovarian cancer and endometrial cancer. Limited data exist for PAI-1 and RCC, with some evidence of an association between PAI-1 with angiogenesis of tumors in clear cell RCC.⁴⁸ For endometrial cancer, our MR analysis yielded a positive association with PAI-I. However, this association was driven solely by one variant (rs11128603) in the Peroxisome Proliferator Activated Receptor Gamma (*PPARG*) gene, which is also associated with type-2 diabetes, adiposity and body size traits.

A large body of epidemiological research has investigated the relationships between circulating concentrations of adipokines and cancer development, with inconsistent results found. We conducted the largest and most comprehensive MR study investigating potential causal associations between genetically determined circulating adipokines concentrations and risks of five obesity-related cancers. Our results are consistent with the findings of a recent MR study that showed no association between adiponectin, sOB-R and PAI-1 concentrations and breast cancer risk.⁴⁹ Though it is not possible to prove the validity of some of the MR assumptions with summarized data, we performed various sensitivity analyses and investigated potential associations with secondary phenotypes of interest, including BMI and insulin resistance. Importantly, our results were similar when we restricted the genetic instruments to include *cis*-acting variants, suggesting that pleiotropy did not markedly influence our findings. Power calculations indicated that our analyses were adequately powered to detect effect sizes comparable with prior observational

studies that reported associations between adipokine concentrations and these cancers,^{7,11-13,43,47} with the exception of some of the pancreatic cancer and cancer subtype models for which GWAS case-control numbers were relatively low.³⁹ A further limitation was that the GWAS for adipokine concentrations included largely middle-aged individuals; therefore, it is unknown to what extent these data capture early life exposures which may be of relevance for the development of these cancers. In addition, the summary level data that we used did not allow for stratified analyses by covariates of interest, such as menopausal status, circulating insulin concentration, family history of cancer, physical activity, smoking and alcohol. Further, for sOB-R and PAI-1, sex-specific GWAS estimates were unavailable so we used the sex-combined estimates for all analyses. The data that we retrieved for adiponectin, leptin and sOB-R were adjusted for BMI and this may have introduced collider bias into these analyses; however, in the GWAS for adiponectin, it was estimated that any bias resulting from adjusting for BMI was minimal.²⁰ This was further corroborated by our sensitivity analysis using the estimates unadjusted for BMI for adiponectin and leptin that resulted in similar effect estimates. Finally, results from a recent empirical study suggest that using covariate adjusted GWAS summary estimates is unlikely to markedly influence MR effect estimates.⁵⁰

In summary, using a MR analytical framework, our results do not support causal effects of circulating adipokines on risk of five obesity-related cancers. Although we cannot rule out the existence of weak associations for specific cancer subtypes for which our analyses were possibly underpowered, or undetected violations to the MR assumptions for causal inference, our results suggest that adiponectin, leptin, sOB-R and PAI-1 do not play a causal role in cancer development.

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The authors declare no potential conflict of interest.

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REFERENCES

1. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer—viewpoint of the IARC Working Group. *N Engl J Med*. 2016; 375:794-798.
2. Research WCRF/AICR. *Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. A Summary of the Third Expert Report*. London, England: World Cancer Research Fund/American Institute for Cancer Research; 2018.
3. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. *Nat Rev Cancer*. 2015;15: 484-498.

4. Murphy N, Jenab M, Gunter MJ. Adiposity and gastrointestinal cancers: epidemiology, mechanisms and future directions. *Nat Rev Gastroenterol Hepatol*. 2018;15:659-670.
5. Kant P, Hull MA. Excess body weight and obesity—the link with gastrointestinal and hepatobiliary cancer. *Nat Rev Gastroenterol Hepatol*. 2011;8:224-238.
6. Vaiopoulos AG, Marinou K, Christodoulides C, Koutsilieris M. The role of adiponectin in human vascular physiology. *Int J Cardiol*. 2012;155:188-193.
7. Aleksandrova K, Boeing H, Jenab M, et al. Total and high-molecular weight adiponectin and risk of colorectal cancer: the European Prospective Investigation into Cancer and Nutrition Study. *Carcinogenesis*. 2012;33:1211-1218.
8. Dalamaga M, Diakopoulos KN, Mantzoros CS. The role of adiponectin in cancer: a review of current evidence. *Endocr Rev*. 2012;33:547-594.
9. Ho GY, Wang T, Gunter MJ, et al. Adipokines linking obesity with colorectal cancer risk in postmenopausal women. *Cancer Res*. 2012;72:3029-3037.
10. Song M, Zhang X, Wu K, et al. Plasma adiponectin and soluble leptin receptor and risk of colorectal cancer: a prospective study. *Cancer Prev Res*. 2013;6:875-885.
11. Aleksandrova K, Boeing H, Jenab M, et al. Leptin and soluble leptin receptor in risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition Cohort. *Cancer Res*. 2012;72:5328-5337.
12. Stattin P, Lukanova A, Biessy C, et al. Obesity and colon cancer: does leptin provide a link? *Int J Cancer*. 2004;109:149-152.
13. Iacoviello L, Agnoli C, De Curtis A, et al. Type 1 plasminogen activator inhibitor as a common risk factor for cancer and ischaemic vascular disease: the EPICOR study. *BMJ Open*. 2013;3:e003725.
14. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32:1-22.
15. Dastani Z, Hivert MF, Timpson N, et al. Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals. *PLoS Genet*. 2012;8:e1002607.
16. Huang J, Sabater-Lleal M, Asselbergs FW, et al. Genome-wide association study for circulating levels of PAI-1 provides novel insights into its regulation. *Blood*. 2012;120:4873-4881.
17. Kilpelainen TO, Carli JF, Skowronski AA, et al. Genome-wide meta-analysis uncovers novel loci influencing circulating leptin levels. *Nat Commun*. 2016;7:10494.
18. Richards JB, Waterworth D, O'Rahilly S, et al. A genome-wide association study reveals variants in ARL15 that influence adiponectin levels. *PLoS Genet*. 2009;5:e1000768.
19. Suhre K, Arnold M, Bhagwat AM, et al. Connecting genetic risk to disease end points through the human blood plasma proteome. *Nat Commun*. 2017;8:14357.
20. Spracklen CN, Karaderi T, Yaghootkar H, et al. Exome-derived adiponectin-associated variants implicate obesity and lipid biology. *Am J Hum Genet*. 2019;105:15-28.
21. Below JE, Parra EJ, Gamazon ER, et al. Meta-analysis of lipid-traits in hispanics identifies novel loci, population-specific effects, and tissue-specific enrichment of eQTLs. *Sci Rep*. 2016;6:19429.
22. Eriksson N, Benton GM, Do CB, et al. Genetic variants associated with breast size also influence breast cancer risk. *BMC Med Genet*. 2012;13:53.
23. Sun BB, Maranville JC, Peters JE, et al. Genomic atlas of the human plasma proteome. *Nature*. 2018;558:73-79.
24. Huyghe JR, Bien SA, Harrison TA, et al. Discovery of common and rare genetic risk variants for colorectal cancer. *Nat Genet*. 2019;51:76-87.
25. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. *Nat Genet*. 2009;41:986-990.
26. Childs EJ, Mocci E, Campa D, et al. Common variation at 2p13.3, 3q29, 7p13 and 17q25.1 associated with susceptibility to pancreatic cancer. *Nat Genet*. 2015;47:911-916.
27. Petersen GM, Amundadottir L, Fuchs CS, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. *Nat Genet*. 2010;42:224-228.
28. Scelo G, Purdue MP, Brown KM, et al. Genome-wide association study identifies multiple risk loci for renal cell carcinoma. *Nat Commun*. 2017;8:15724.
29. Phelan CM, Kuchenbaecker KB, Tyrer JP, et al. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. *Nat Genet*. 2017;49:680-691.
30. O'Mara TA, Glubb DM, Amant F, et al. Identification of nine new susceptibility loci for endometrial cancer. *Nat Commun*. 2018;9:3166.
31. Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. *Int J Epidemiol*. 2013;42:1497-1501.
32. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37:658-665.
33. Staley JR, Blackshaw J, Kamat MA, et al. PhenoScanner: a database of human genotype-phenotype associations. *Bioinformatics*. 2016;32:3207-3209.
34. Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med*. 2017;36:1783-1802.
35. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44:512-525.
36. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40:304-314.
37. Yengo L, Sidorenko J, Kemper KE, et al. Meta-analysis of genome-wide association studies for height and body mass index in approximately 700000 individuals of European ancestry. *Hum Mol Genet*. 2018;27:3641-3649.
38. Burgess S, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. *Am J Epidemiol*. 2015;181:251-260.
39. Bao Y, Giovannucci EL, Kraft P, et al. A prospective study of plasma adiponectin and pancreatic cancer risk in five US cohorts. *J Natl Cancer Inst*. 2013;105:95-103.
40. Grote VA, Rohrmann S, Dossus L, et al. The association of circulating adiponectin levels with pancreatic cancer risk: a study within the prospective EPIC cohort. *Int J Cancer*. 2012;130:2428-2437.
41. Cust AE, Kaaks R, Friedenreich C, et al. Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. *J Clin Endocrinol Metab*. 2007;92:255-263.
42. Liao LM, Weinstein SJ, Pollak M, et al. Prediagnostic circulating adipokine concentrations and risk of renal cell carcinoma in male smokers. *Carcinogenesis*. 2013;34:109-112.
43. Luhn P, Dallal CM, Weiss JM, et al. Circulating adipokine levels and endometrial cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev*. 2013;22:1304-1312.
44. Liao LM, Hofmann JN, Cho E, Pollak MN, Chow WH, Purdue MP. Circulating levels of obesity-related markers and risk of renal cell carcinoma in the PLCO cancer screening trial. *Cancer Causes Control*. 2017;28:801-807.

45. Soliman PT, Cui X, Zhang Q, Hankinson SE, Lu KH. Circulating adiponectin levels and risk of endometrial cancer: the prospective Nurses' Health Study. *Am J Obstet Gynecol.* 2011;204:167.e1-167.e5.
46. Stolzenberg-Solomon RZ, Newton CC, Silverman DT, et al. Circulating leptin and risk of pancreatic cancer: a pooled analysis from 3 cohorts. *Am J Epidemiol.* 2015;182:187-197.
47. Liao LM, Schwartz K, Pollak M, et al. Serum leptin and adiponectin levels and risk of renal cell carcinoma. *Obesity.* 2013;21:1478-1485.
48. Zubac DP, Wentzel-Larsen T, Seidal T, Bostad L. Type 1 plasminogen activator inhibitor (PAI-1) in clear cell renal cell carcinoma (CCRCC) and its impact on angiogenesis, progression and patient survival after radical nephrectomy. *BMC Urol.* 2010;10:20.
49. Robinson T, Martin RM, Yarmolinsky J. Mendelian randomisation analysis of circulating adipokines and C-reactive protein on breast cancer risk. *Int J Cancer.* 2020;147:1597-1603.
50. Walker V, Harrison S, Carter A, Gill D, Tzoulaki I, Davies N. The consequences of adjustment, correction and selection in genome-wide

association studies used for two-sample Mendelian randomization. medRxiv; 2020.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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