Effect Modification by Levels of Sex Hormones in the Association between Adiposity and Cancer Incidence in the UK Biobank

LeeAnn Lucas[1], Yujia Lu[1], Edward Giovannucci[1,2], and Mingyang Song[1,2,3]

ABSTRACT

The role of sex hormones in the sex difference between adiposity and cancer risk remains unclear. We examined body mass index (BMI) and visceral adipose tissue (VAT) estimated using a validated equation in relation to cancer incidence according to serum sex hormone–binding globulin (SHBG), testosterone, and estradiol among 451,500 UK Biobank participants. For cancers showing a sex-specific adiposity association, we used Cox regression to calculate multivariable HRs per increase between the 10th and 90th percentiles of adiposity according to low versus high sex hormone levels. We documented 42,949 cancers over a median follow-up of 13.1 years. BMI and VAT were more strongly associated with a higher risk of esophageal, liver, and colorectal cancers in males than in females. In males, BMI showed a stronger association with esophageal (HR for high vs. low SHBG = 2.38 vs. 1.62; $P_{interaction} = 0.04$) and liver cancers (HR = 3.24 vs. 1.96; $P_{interaction} = 0.03$) among those with high versus low SHBG, whereas an opposite pattern was observed for colorectal cancer (HR = 1.12 vs. 1.47; $P_{interaction} = 0.03$). Among females, BMI was associated with a higher esophageal cancer risk in those with low (HR = 1.68) but not high SHBG (HR = 0.64; $P_{interaction} = 0.025$); for liver cancer, results were similar but statistically nonsignificant. No interaction by estradiol or testosterone was detected. Similar results were observed for VAT. SHBG may be an important factor underlying the sex difference in adiposity-associated risk for colorectal, esophageal, and liver cancers.

Prevention Relevance: Understanding the interactions between sex hormones and adiposity can help explain sex differences in cancer risk associated with body fat. Our findings suggest that SHBG may be a promising target for future research on strategies to reduce the risk of colorectal, esophageal, and liver cancers in individuals with excess adiposity.

Introduction

Adiposity is associated with increased risk of 13 cancer types, with an estimated 4% to 8% of cancer cases globally attributed to adiposity (1). The effects of adiposity are stronger in males than in females for some cancer types including colorectal, esophageal, and liver cancers, although the reasons for these differences are not fully understood (2). As the prevalence of obesity continues to increase worldwide in both sexes, studies to examine how obesity affects cancer incidence differentially in males and females are warranted (3).

The sex differences found in the adiposity and cancer relationship may stem from several factors, either independently or in combination, such as differences in the distribution of fat deposition in the body, differences in sex hormone levels, and differences in the role of sex chromosomes (4). Distributions of fat differ between males and females, as males store a higher percentage of their body fat in the abdomen as visceral adipose tissue (VAT), whereas females tend to have a higher percentage of subcutaneous fat located around the arms and legs. Excess VAT surrounding vital organs increases insulin resistance and inflammation, creating a protumorigenic environment (5). Alterations in the metabolism of sex hormones, such as changes in estradiol, testosterone, and sex hormone–binding globulin (SHBG), have been hypothesized as a potential mechanism linking adiposity and cancer (6). Under this theory, androgenic precursors are converted at a higher rate to estradiol through aromatization when adiposity is present, elevating cancer risk (6). Additionally, animal studies have shown that estrogen depletion is associated with increased abdominal fat, providing a link between sex hormones and fat distributions (7). Although the sex hormone hypothesis has been primarily examined in sex-specific cancers, prospective data on effect modification and interaction between adiposity and sex hormones with multiple cancers in nonreproductive organs are sparse. In addition, few large-scale cohort studies have assessed body composition using metrics beyond body mass index (BMI) and waist circumference.

[1]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [2]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [3]Division of Gastroenterology, Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Mingyang Song, Department of Epidemiology, Harvard T.H. Chan School of Public Health, 655 Huntington Avenue, Boston, MA 02115. E-mail: msong@hsph.harvard.edu

Cancer Prev Res 2025;18:735–44

doi: 10.1158/1940-6207.CAPR-25-0246

Our study sought to characterize how adiposity affects cancer incidence differently in males and females by leveraging the sex hormone data available in the entire UK Biobank. We integrate information on BMI, as well as a measure of VAT estimated from a newly developed model (8). We hypothesized that sex hormones are important modifiers and may partly explain the sex difference in the obesity–cancer incidence relationship. Among cancers with a stronger association between obesity and cancer in males than females, we hypothesized that the association between obesity and incidence will be attenuated in males with higher estradiol, lower testosterone, or higher SHBG levels (i.e., levels more like those in females). Confirmation of this hypothesis would suggest that variations in sex hormone levels may play a role in the observed sex differences of obesity–cancer associations in nonreproductive organs and could provide a mechanism to target for prevention and treatment.

Materials and Methods

Study population and design

The UK Biobank is a prospective cohort study that enrolled 502,336 participants from across the United Kingdom between 2006 and 2010 and has been described in detail previously (9). Briefly, numerous data elements were collected at participant's recruitment visit through blood sampling, physical measurements, and touchscreen self-completed questionnaires. Individuals were then followed, with cancer diagnosis ascertained using the 10th Revision of the International Classification of Diseases (ICD-10) codes from cancer registry linkage.

Our study excluded individuals who had a history of cancer (except nonmelanoma skin cancer) at enrollment ($N = 23{,}774$); had missing data on all sex hormones, BMI, or estimators of VAT at baseline ($N = 25{,}290$); and had less than 6 months of follow-up to prevent reverse causation ($N = 1{,}772$; Supplementary Fig. S1). All individuals provided consent for participation in the UK Biobank. The UK Biobank has been ethically approved as a Research Tissue Bank by the North West Multi-centre Research Ethics Committee.

Anthropometric exposures

Anthropometric measures were collected at baseline visits using standardized procedures (10). Participant's BMI was calculated as weight divided by height squared (kg/m^2). VAT was estimated using baseline measures of height, weight, hip circumference, waist circumference, and the participant's age at the time of assessment (8). This equation was developed in the UK Biobank and validated externally in the National Health and Nutrition Examination Survey, with a Spearman correlation coefficient with measured VAT in the National Health and Nutrition Examination Survey of 0.81 for males and 0.86 for females. In joint analyses, BMI and estimated VAT were classified as high and low using the median value in each sex as the cutoff point.

Sex hormone levels

Serum sex hormone levels were measured in the blood at baseline on a Beckman Coulter Unicel Dxl 800 system. Estradiol was measured using a two-step competitive immunoassay analysis [coefficient of variation (CV) for low = 15.3%, for medium = 8.7%, and for high concentrations = 6.5%; limit of detection (LOD) = 175 pmol/L], testosterone by a one-step competitive immunoassay analysis (CV for low = 8.3%, for medium = 3.7%, and for high concentrations = 4.2%; LOD = 0.35 nmol/L), and SHBG by a two-step sandwich immunoassay analysis (CV for low = 5.7%, for medium = 5.3%, and for high concentrations = 5.2%; LOD = 0.33 nmol/L; ref. 11). Because of the similarity in distributions of SHBG between males and females, SHBG levels were classified as high or low using the median value among all participants of 45 nmol/L as a cutoff point. Testosterone levels were classified as high and low based on the median value of testosterone for males (11.64 nmol/L) and females (1.01 nmol/L) separately (Supplementary Fig. S2). Because many participants (82%) had estradiol measurements that fell below the detection limit, we considered estradiol levels below the detection limit as low whereas detectable measurements were considered high to match previous analyses (12, 13). Low levels of estradiol were expected as most of the participants in the UK Biobank are males or postmenopausal females.

Covariates

We selected covariates *a priori* that are known to be associated with adiposity and cancer incidence but are likely not a consequence of adiposity, in line with the previous work in the UK Biobank (8). Covariates for our analysis were assessed at baseline using a touchscreen questionnaire. Covariates included age, educational attainment (at least a college degree or less than a college degree), race (White or non-White), height (m), physical activity (MET hours per week), smoking status (never, previous, current and less than 15 pack-years, or current and more than 15 pack-years), alcohol intake (never, previous, or current using frequency), aspirin use (yes or no), processed meat intake (never, less than once per week, 2–4 times per week, 5–6 times per week, or once or more daily), vegetable intake (pieces per day), fruit intake (pieces per day), serum 25(OH) vitamin D level (nmol/L), cereal intake (servings per week), family history of cancer (yes or no), and past bowel cancer screening (yes or no). Missing continuous covariate data were imputed using the median value, whereas a missing indicator variable was used for categorical variables.

Outcome

Cancer incidence was ascertained through cancer registry linkage using the ICD-10 codes. Cancer case ascertainment from the English cancer registries has been previously reported as 98% to 99% complete (14). For this analysis, we examined total cancer, total cancer excluding nonfatal prostate cancer (prostate cancer defined as ICD = C61 and no primary

cause of death as prostate cancer), and nonreproductive cancers known to be associated with adiposity or with large case numbers in the UK Biobank. The cancers included in our analysis were bladder (ICD = C67), colorectal (ICD = C18–20), esophageal (ICD = C15), gallbladder (ICD = C23), kidney (ICD = C64–65), liver (ICD = C22), lung (ICD = C34), pancreatic (ICD = C25), stomach (ICD = C16), and thyroid (ICD = C73) cancers.

Statistical analysis

We calculated Spearman correlation coefficients between adiposity and sex hormone levels adjusting for age within each sex. We used multivariable Cox regression to calculate HRs and 95% confidence intervals (CI) for cancer incidence per unit increase from the 10th to 90th percentile of adiposity (BMI or estimated VAT). Individuals contributed person-time to our study from the date of enrollment until the earliest of a diagnosis of cancer, death, lost to follow-up, or the study end date of June 1, 2022, and age was used as the timescale in our model. A multiplicative interaction term between sex and adiposity measurement was included to assess the sex difference. For cancer types that showed statistically significant sex differences ($P < 0.05$) in the adiposity–cancer relationship, we further assessed interaction by high versus low hormone level in males and females separately by including a multiplicative interaction term between adiposity measurement and sex hormone level in the Cox regression model. To correct for multiple testing, adjusted P values were calculated using the Benjamini–Hochberg method to control the FDR. Adjusted P values less than 0.05 were considered statistically significant. We also conducted a three-way joint association analysis by classifying individuals according to the combination of sex, sex hormone level, and adiposity status. In separate sensitivity analyses, we assessed multiplicative interaction by hormone level (1) excluding premenopausal females and females below 55 years with unknown menopausal status to assess interaction among postmenopausal females only, the majority of females in the UK Biobank, due to large differences in hormone levels based on menopausal status, (2) restricting our study population to never smokers to limit residual confounding by smoking status, and (3) starting follow-up at 1 and 5 years from baseline to prevent reverse causation, in which adiposity or hormone levels may be affected by preclinical cancer. All analyses were conducted using R statistical software version 4.3.0 (RRID: SCR_001905).

Results

A total of 451,500 participants were included in our analysis (Supplementary Fig. S1). Most individuals were White (94.2%) with a median age of 57 (IQR = 13) upon study entry. In general, females tended to have less physical activity, lower aspirin use, less consumption of meat, and were less likely to smoke compared with males. Among females, the median BMI was 26.1 kg/m^2 (IQR = 6.3), with a median estimated VAT of 2.5 L (IQR = 1.8), whereas males had a slightly higher median BMI of 27.3 kg/m^2 (IQR = 5.1) and a median estimated VAT approximately twice that of females, at 5.0 L (IQR = 2.7; **Table 1**).

Correlation between adiposity and serum sex hormone levels

BMI and estimated VAT were negatively correlated with SHBG levels in both males (BMI: r = −0.33; VAT: r = −0.34) and females (BMI: r = −0.46; VAT: r = −0.50), adjusting for age. In males, higher BMI (r = −0.31) and estimated VAT (r = −0.32) were correlated with lower testosterone levels, whereas in females both adiposity measures had a weak positive correlation with testosterone (BMI: r = 0.10; VAT: r = 0.09). Estradiol levels were weakly correlated with BMI and estimated VAT in males and exhibited a slightly stronger negative correlation in females (BMI: r = −0.06; VAT: r = −0.07). The correlation coefficients among females were relatively unchanged after restricting to only postmenopausal females (**Table 2**).

Sex differences in the association between adiposity and cancer

During a median follow-up time of 13.1 years, 22,867 incident cancers were documented among 207,436 males and 20,082 incident cancers among 244,064 females. The association between BMI and cancer was stronger in males than females for colorectal (males: HR = 1.36; 95% CI, 1.25–1.48 and females: HR = 1.06; 95% CI, 0.96–1.18), esophageal (males: HR = 1.76; 95% CI, 1.49–2.07 and females: HR = 0.84; 95% CI, 0.61–1.16), and liver cancers (males: HR = 2.13; 95% CI, 1.74–2.61 and females: HR = 1.40; 95% CI, 1.00–1.94; **Table 3**). Wald tests for interaction between sex and estimated VAT yielded similar results to the Wald tests for interaction between sex and BMI, except in liver cancer, in which the sex difference was more pronounced using estimated VAT ($P_{\text{interaction}} = 0.02$) compared with BMI ($P_{\text{interaction}} = 0.09$). Models comparing the 90th with 10th percentile of VAT yielded generally stronger associations with cancer than the models comparing the 90th with 10th percentile of BMI. Based on these results, we focused on colorectal, esophageal, and liver cancers in the subsequent analysis for the effect modification by sex hormone level.

Effect modification by hormone level

The associations between BMI and cancer differed by SHBG levels among males for colorectal (P adjusted = 0.027) and liver cancers (adjusted P value = 0.027) and among both sexes for esophageal cancer (P adjusted in males = 0.038 and P adjusted in females = 0.025; **Fig. 1**). BMI was more strongly associated with esophageal and liver cancers among males with high versus low baseline SHBG levels (esophageal: HR = 2.38; 95% CI, 1.77–3.21 vs. HR = 1.62; 95% CI, 1.29–2.03; liver: HR = 3.24; 95% CI, 2.48–4.22 vs. HR = 1.96; 95% CI, 1.40–2.74) but more strongly associated in low versus high SHBG levels with colorectal cancer (HR = 1.47;

Table 1. Characteristics of UK Biobank participants at baseline by sex.

Characteristic	Female, *N* = 244064, mean (SD) or *N* (%)	Male, *N* = 207436, mean (SD) or *N* (%)
Age	56 (± 8.0)	57 (± 8.2)
Weight (kg)	71 (± 14)	86 (± 14)
Height (cm)	160 (± 6.3)	180 (± 6.8)
BMI (kg/m^2)	27 (± 5.2)	28 (± 4.2)
Waist circumference (cm)	85 (± 13)	97 (± 11)
Hip circumference (cm)	100 (± 10)	100 (± 7.6)
Estradiol		
Below LOD	166,578 (68.3%)	173,047 (83.4%)
Above LOD	56,513 (23.2%)	17,661 (8.5%)
Missing	20,973 (8.6%)	16,728 (8.1%)
SHBG (nmol/L)	62 (± 31)	39 (± 17)
Missing	28,878 (11.8%)	19,937 (9.6%)
Testosterone (nmol/L)	1.1 (± 0.65)	12 (± 3.7)
Missing	44,031 (18.0%)	4,678 (2.3%)
Race		
White	229,922 (94.2%)	195,180 (94.1%)
Non-White	13,151 (5.4%)	11,099 (5.4%)
Missing	991 (0.4%)	1,157 (0.6%)
Education		
No college	163,560 (67.0%)	133,482 (64.3%)
College	75,809 (31.1%)	69,777 (33.6%)
Missing	4,695 (1.9%)	4,177 (2.0%)
MET hours per week	39 (± 37)	44 (± 46)
Smoking status		
Never	145,299 (59.5%)	101,591 (49.0%)
Previous	75,749 (31.0%)	78,778 (38.0%)
Current	21,824 (8.9%)	26,003 (12.5%)
Missing	1,192 (0.5%)	1,064 (0.5%)
Alcohol status		
Daily or almost daily	39,211 (16.1%)	52,437 (25.3%)
Three or four times a week	50,184 (20.6%)	54,253 (26.2%)
Once or twice a week	62,806 (25.7%)	53,728 (25.9%)
One to three times a month	31,857 (13.1%)	18,448 (8.9%)
Special occasions only	36,514 (15.0%)	15,124 (7.3%)
Never	22,984 (9.4%)	12,959 (6.2%)
Missing	508 (0.2%)	487 (0.2%)
Aspirin use		
No	215,583 (88.3%)	164,457 (79.3%)
Yes	23,779 (9.7%)	38,347 (18.5%)
Missing	4,702 (1.9%)	4,632 (2.2%)
Processed meat consumption		
Never	30,720 (12.6%)	11,215 (5.4%)
Less than once a week	92,622 (37.9%)	44,264 (21.3%)
Once a week	69,660 (28.5%)	61,577 (29.7%)
2–4 times a week	45,770 (18.8%)	76,106 (36.7%)
5–6 times a week	3,528 (1.4%)	10,672 (5.1%)
Once or more daily	917 (0.4%)	2,799 (1.3%)
Missing	847 (0.4%)	803 (0.4%)
Bowel cancer screening		
No	169,720 (69.5%)	137,807 (66.4%)
Yes	71,234 (29.2%)	64,449 (31.1%)
Missing	3,110 (1.3%)	5,180 (2.5%)
Family history of cancer		
No	152,491 (62.5%)	122,970 (59.3%)
Yes	67,456 (27.6%)	56,755 (27.4%)
Missing	24,117 (9.9%)	27,711 (13.4%)
Vegetable consumption (pieces/day)	5.1 (± 3.2)	4.6 (± 3.5)
Fruit consumption (pieces/day)	2.4 (± 1.6)	2.0 (± 1.6)
Cereal consumption (servings/week)	4.5 (± 2.8)	4.4 (± 2.9)
25(OH) vitamin D level (nmol/L)	49 (± 20)	48 (± 21)

Abbreviations: BMI, body mass index; LOD, limit of detection.

Table 2. Spearman correlation coefficients between adiposity measures and serum sex hormone level adjusted for age, by sex.

Adiposity measure	SHBG, r (*P* value)	Testosterone, r (*P* value)	Estradiol, r (*P* value)
BMI			
Females (all)	−0.46 (< 0.001)	0.10 (< 0.001)	−0.06 (< 0.001)
Postmenopause	−0.46 (< 0.001)	0.10 (< 0.001)	−0.07 (< 0.001)
Males	−0.33 (< 0.001)	−0.31 (< 0.001)	0.02 (0.016)
VAT			
Females (all)	−0.50 (< 0.001)	0.09 (< 0.001)	−0.07 (< 0.001)
Postmenopause	−0.50 (< 0.001)	0.09 (< 0.001)	−0.07 (< 0.001)
Males	−0.34 (< 0.001)	−0.32 (< 0.001)	0.02 (0.006)

r: Spearman correlation coefficient.

95% CI, 1.31–1.64 vs. HR = 1.12; 95% CI, 0.94–1.33). As with BMI, the associations between VAT and colorectal, esophageal, and liver cancers among males differed by SHBG level in the same direction but were less pronounced and statistically insignificant. Among females, SHBG was a modifier in the association between VAT and esophageal cancer (low SHBG: HR = 2.10; 95% CI, 1.16–3.80 and high SHBG: HR = 0.82; 95% CI, 0.49–1.37). No effect modification by estradiol or testosterone was observed.

When conducting a joint association analysis stratifying by sex, SHBG level, and adiposity, the HR for liver cancer comparing males with high SHBG levels and high BMI levels was 14.8 (95% CI, 6.4–34.2) and those with high estimated VAT levels was 8.9 (95% CI, 4.9–16.3) compared with females with low SHBG levels and low adiposity (**Fig. 2**). In esophageal cancer, no additive effect modification by SHBG was observed between groups of the same sex and adiposity, such that among males with high BMI, HRs were similar among both levels of SHBG (low SHBG: HR = 3.90; 95% CI, 2.36–6.44 and high SHBG: HR = 4.46; 95% CI, 2.65–7.50). Among males with a high BMI, high SHBG levels were associated with a lower HR of colorectal cancer (HR = 1.38; 95% CI, 1.14–1.66) than males with low SHBG levels (HR = 1.51; 95% CI, 1.28–1.79).

Sensitivity analyses

For this sensitivity analysis, 175,338 postmenopausal females were included to assess sex hormone levels representing 72% of the full female cohort. Baseline SHBG, testosterone, and estradiol levels did not modify the relationship between either BMI or estimated VAT and cancer incidence among postmenopausal females (Supplementary Table S1). The directionality of the associations and the interaction patterns remained the same as the analysis of the full female cohort.

Table 3. Multivariable associations between adiposity and cancer risk by sex, UK Biobank.

	BMI					Estimated VAT				
	Female		Male			Female		Male		
Cancer type	HR[a] (95% CI)	*P* value	HR[a] (95% CI)	*P* value	Adjusted $P_{interaction}$[b]	HR[a] (95% CI)	*P* value	HR[a] (95% CI)	*P* value	Adjusted $P_{interaction}$[b]
Total cancer	1.25 (1.21, 1.29)	<0.001	1.08 (1.05, 1.12)	<0.001	<0.001	1.25 (1.21, 1.29)	<0.001	1.16 (1.12, 1.20)	<0.001	0.007
Total cancer excluding nonfatal prostate	-	-	1.23 (1.18, 1.28)	<0.001	-	-	-	1.35 (1.29, 1.41)	<0.001	-
Bladder	1.56 (1.14, 2.12)	0.005	1.17 (0.97, 1.40)	0.10	0.28	1.70 (1.22, 2.37)	0.002	1.24 (1.02, 1.52)	0.03	0.23
Brain	0.89 (0.67, 1.20)	0.46	0.95 (0.75, 1.21)	0.71	0.88	0.96 (0.71, 1.30)	0.80	0.94 (0.72, 1.21)	0.62	0.92
Colorectal	1.06 (0.96, 1.18)	0.26	1.36 (1.25, 1.48)	<0.001	0.001	1.10 (0.98, 1.22)	0.10	1.49 (1.36, 1.65)	<0.001	<0.001
Esophageal	0.84 (0.61, 1.16)	0.29	1.76 (1.49, 2.07)	<0.001	<0.001	1 (0.72, 1.38)	0.98	2.10 (1.72, 2.56)	<0.001	0.001
Gallbladder	1.78 (1.04, 3.02)	0.03	2.41 (1.36, 4.27)	0.003	0.80	2.15 (1.2, 3.84)	0.01	2.99 (1.4, 6.38)	0.005	0.89
Kidney	1.87 (1.54, 2.27)	<0.001	1.72 (1.49, 2.00)	<0.001	0.83	2.10 (1.70, 2.60)	<0.001	2.01 (1.69, 2.39)	<0.001	0.92
Liver	1.40 (1.00, 1.94)	0.05	2.13 (1.74, 2.61)	<0.001	0.09	1.54 (1.08, 2.20)	0.02	2.75 (2.13, 3.57)	<0.001	0.02
Lung	0.80 (0.71, 0.90)	<0.001	0.82 (0.73, 0.92)	0.001	0.88	0.93 (0.82, 1.05)	0.23	0.91 (0.80, 1.02)	0.12	0.92
Pancreatic	1.50 (1.22, 1.83)	<0.001	1.45 (1.21, 1.75)	<0.001	0.88	1.57 (1.27, 1.95)	<0.001	1.59 (1.29, 1.97)	<0.001	0.92
Stomach	1.38 (1.00, 1.90)	0.05	1.43 (1.16, 1.78)	0.001	0.88	1.55 (1.10, 2.18)	0.01	1.69 (1.32, 2.17)	<0.001	0.92
Thyroid	1.52 (1.17, 1.98)	0.002	1.19 (0.75, 1.88)	0.46	0.77	1.57 (1.18, 2.09)	0.002	1.43 (0.87, 2.35)	0.16	0.92

[a]HRs with 95% CI of cancer risk per one unit increase from the 10th to 90th percentile in BMI or estimated VAT, adjusted for age, education level, race, height, MET hours per week, smoking status, alcohol intake, aspirin usage, processed meat consumption, previous bowel cancer screening, family history of cancer, vegetable intake (pieces/day), fruit intake (pieces/day), vitamin D in blood, and cereal intake (servings/week).
[b]*P* values adjusted using the FDR method for multiple testing.

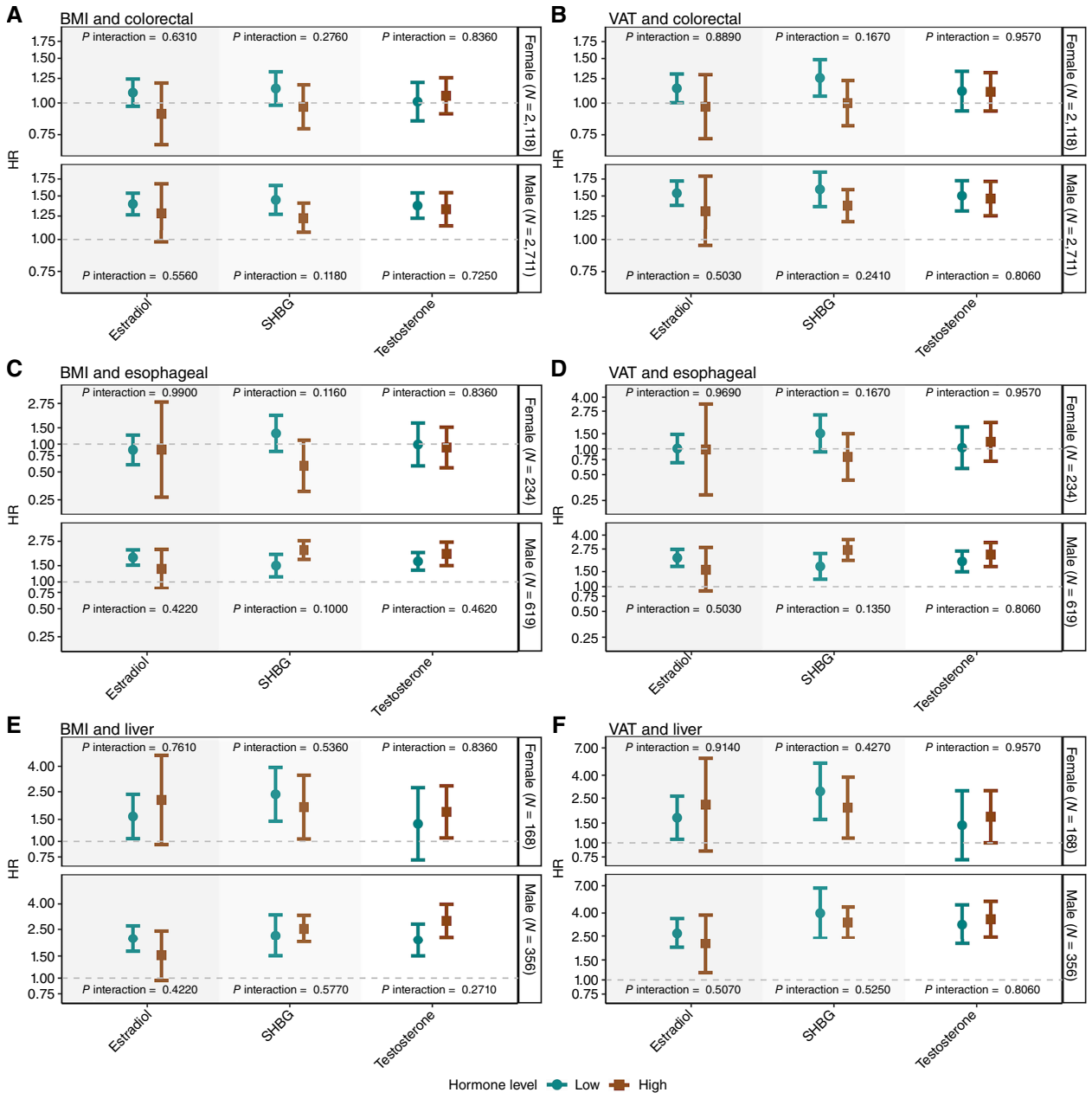

Figure 1.

HRs for the association between adiposity (BMI and estimated VAT) per one unit increase from the 10th to 90th percentile and colorectal, esophageal, and liver cancer incidences by hormone level and sex, UK Biobank. **A–F,** Associations between BMI (**A**) and VAT (**B**) and colorectal cancer; between BMI (**C**) and VAT (**D**) and esophageal cancer; and between BMI (**E**) and VAT (**F**) and liver cancer. Models were adjusted for age, education level, race, height, MET hours per week, smoking status, alcohol intake, aspirin usage, processed meat consumption, previous bowel cancer screening, family history of cancer, vegetable intake (pieces/day), fruit intake (pieces/day), vitamin D in blood, and cereal intake (servings/week) *P* values for interaction were adjusted using the FDR method for multiple testing. *N*, number of cancer cases.

When restricting to never smokers only, 145,299 females and 101,591 males were included. SHBG remained an important modifier for males in the relationship between adiposity and colorectal, esophageal, and liver cancers, in which the association with adiposity was stronger for esophageal and liver cancers among high versus low levels of SHBG but weaker for colorectal cancer (Supplementary Table S2). Among never-smoking females, high SHBG levels increased the HR for adiposity and esophageal cancer (BMI: HR = 1.23; 95% CI, 0.65–2.35; VAT: HR = 1.28; 95% CI, 0.65–2.52), in contrast to the full cohort analysis in which high SHBG levels were protective (BMI: HR = 0.64; 95%

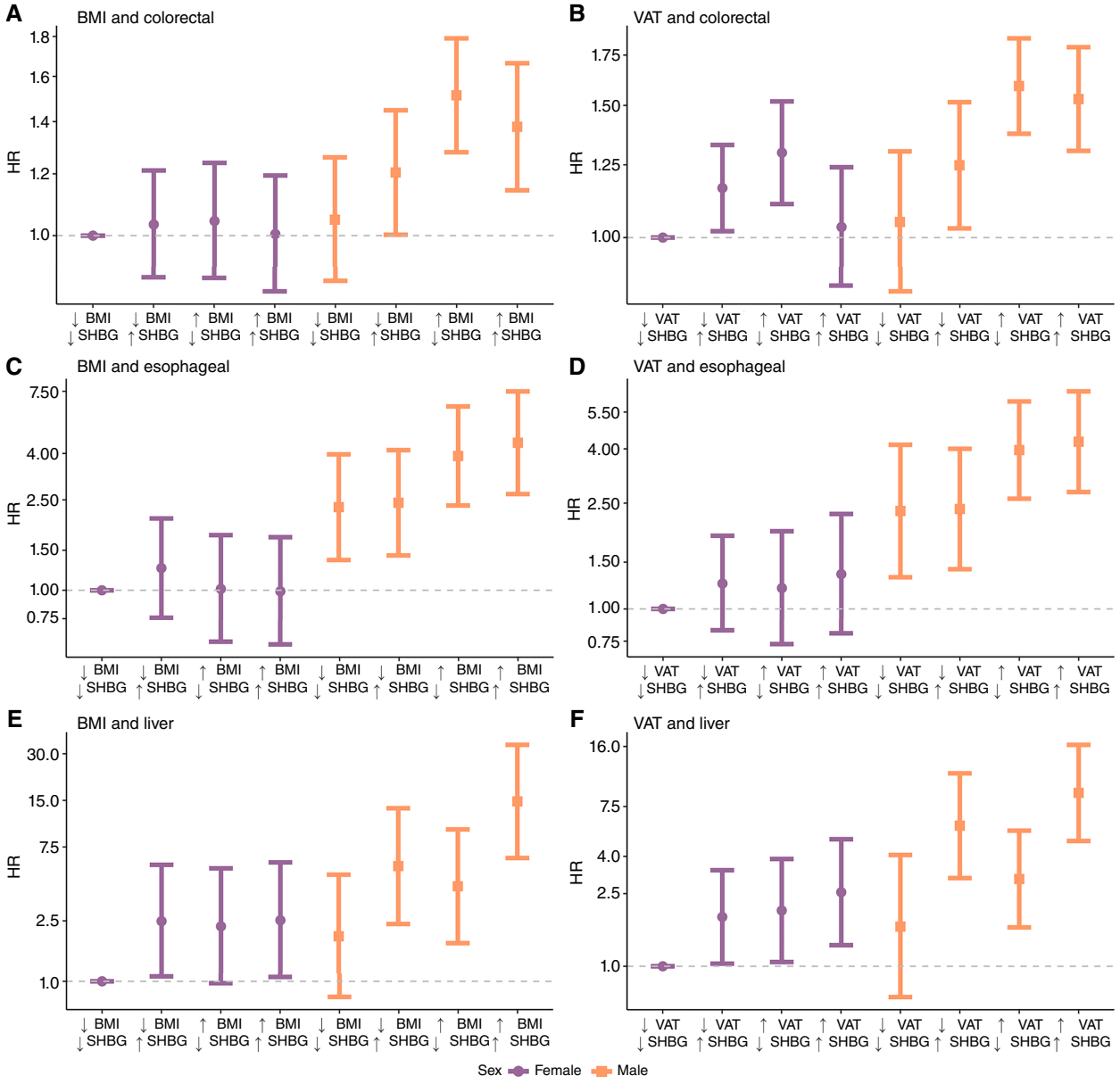

Figure 2.

Joint association analysis of sex, adiposity (BMI and estimated VAT), and SHBG on colorectal, esophageal, and liver cancer incidences, UK Biobank. The joint effect of sex, SHBG, and adiposity on cancer. Adiposity type and cancer as follows: BMI (**A**) and VAT (**B**) on colorectal cancer; BMI (**C**) and VAT (**D**) on esophageal cancer; and BMI (**E**) and VAT (**F**) on liver cancer. Adiposity and SHBG were categorized as high and low based on medium values. Models were adjusted for age, education level, race, height, MET hours per week, smoking status, alcohol intake, aspirin usage, processed meat consumption, previous bowel cancer screening, family history of cancer, vegetable intake (pieces/day), fruit intake (pieces/day), vitamin D in blood, and cereal intake (servings/week).

CI, 0.38–1.07; VAT: HR = 0.82; 95% CI, 0.49–1.37). Lastly, the association between estimated VAT and liver cancer was much stronger among never smokers in males with a high SHBG level (HR = 7.54; 95% CI, 4.06–14.00) than in the full cohort (HR = 4.18; 95% CI, 2.96–5.90), although directionality remained the same.

After excluding individuals with less than 1 year of follow-up (N = 3,951) and less than 5 years of follow-up (N = 23,223), the directionality and magnitude of the HRs remained unchanged, and interactions were consistent with the main analysis (Supplementary Table S3).

Discussion

In this prospective cohort study of 451,500 individuals followed for a median of 13 years, adiposity was more strongly associated with colorectal, esophageal, and liver cancers in males compared with females. The association

between adiposity and risk of these three cancers differed based on the level of SHBG. In males with high SHBG levels, adiposity was more strongly associated with esophageal and liver cancers but more weakly with colorectal cancer compared with those with low SHBG. In females, there was a stronger association between adiposity and esophageal cancer in those with low versus high SHBG levels.

Our study confirms the results of another analysis in the UK Biobank (2) that found statistically significant sex differences in the association of BMI and VAT with risk of colorectal, esophageal, and liver cancers, as well as other large cohort studies (15–19). We further examined the sex hormone level as a potential modifier in the relationship of adiposity with cancer, adding to the growing literature documenting the complex role of SHBG in cancer development. SHBG binds with estradiol and testosterone, regulating sex hormone bioavailability to tissues and cells (20). Recent research has shown that SHBG may reduce chronic inflammation independent of its regulation of estradiol and testosterone by inhibiting gene expression of cytokines and breaking down triacylglycerols of differentiated adipocytes (21). Levels of SHBG have been inversely associated with C-reactive protein, a biomarker of inflammation, even after controlling for other sex hormones (22) and have been inversely associated with conditions such as metabolic syndrome and type II diabetes (23, 24).

Despite the plausibility of a protective role of SHBG in inflammation and the hypothesized potential to lower risk of inflammation-related cancers, epidemiologic evidence with regard to the role of SHBG in relation to incidence of colorectal cancer is inconsistent. A prospective cohort study in the UK Biobank and a nested case–control study in four cohorts of health professionals found that SHBG was associated with a decreased risk of colorectal cancer in men after adjusting for BMI, supporting our finding that SHBG plays a protective role in colorectal cancer in males (25, 26). In contrast, a Mendelian randomization study (2021) found no association between genetically predicted SHBG and risk of colorectal cancer among males and reported no interaction between circulating SHBG at UK Biobank enrollment and BMI (<25, ≥25), although the differences in estimates were quite large (HR = 1.46 vs. 0.96 for low vs. high SHBG; $P_{\text{interaction}} = 0.05$; ref. 27). A prospective cohort study in the UK Biobank also reported no association (28). However, both studies adjusted for C-reactive protein and IGF1, with the Mendelian randomization study additionally adjusted for HbA1c, biomarkers that may be on the causal path between SHBG and colorectal cancer. In women, several epidemiologic studies have found no association between SHBG and colorectal cancer (25, 26, 29). In a study of postmenopausal women enrolled in the Women's Health Initiative clinical trial, no interaction was found between sex hormone level and adiposity, classified as BMI less than 30 compared with greater than 30 ($P_{\text{interaction}} = 0.58$), consistent with the results of our study ($P_{\text{interaction}} = 0.60$; ref. 29). That study also showed no effect modification by BMI on the association between estradiol and colorectal cancer, aligning with our findings.

Our study found that higher SHBG levels increased the HR between adiposity and both liver and esophageal cancers in males. Prior studies have documented an association between increased SHBG levels and liver cancer (30–32) but have not found the same increased risk for esophageal cancer (30, 32–34). The Liver Cancer Pooling Project in US men found that higher SHBG levels increased the odds of liver cancer [OR (95% CI) = 1.63 (1.27–2.11); ref. 30]. In patients with liver cirrhosis, increased SHBG was predictive of the development of liver cancer (35). A multicancer study in the UK Biobank found an association between SHBG and liver cancer among men but not among postmenopausal women; however, no relationship was found for esophageal cancer (31). These results were supported in a recent meta-analysis including 11 prospective cohort studies, 15 nested case–control studies, and 3 case–cohort studies (32). The mechanisms by which adiposity and SHBG interact to increase risk of liver cancer are unclear; however, liver cirrhosis and liver disease have been associated with increased SHBG levels. SHBG is synthesized and regulated by the liver, and SHBG may be desialylated from cirrhosis, which makes it more likely to be taken up in the liver (35).

Our study found consistently increased HRs for the associations between estimated VAT and cancer compared with models using BMI, providing evidence for the utility of VAT over BMI in cancer studies. Additionally, we observed less modification by sex hormone level in models with VAT compared with BMI, likely because VAT more effectively accounts for sex differences in the distribution of adiposity—another advantage of using VAT over BMI. Although few large-scale cohort studies have assessed body composition beyond BMI, measures of BMI fail to differentiate between fat mass and lean mass and have a reported sensitivity of only 50% in classifying excess adiposity (36). In contrast, VAT is a measure of body fat accumulating centrally in the body around vital organs. Excess VAT can lead to insulin resistance and inflammation creating a protumorigenic environment (5). Several studies have demonstrated the role of central adiposity as a better predictor of cancer compared with BMI (37).

Strengths and limitations

We examined effect modification by sex hormone levels in the association between adiposity and cancer in multiple nonreproductive cancers. We employed a novel and validated equation to estimate VAT, which has been previously lacking in large cohort studies. Including both the measurements of BMI and estimated VAT offers a particular insight into the mechanisms underlying the sex differences, given the variation in fat distributions based on sex. Additionally, owing to the UK Biobank's extensive size, substantial volume of sex hormone measurements, and over a

decade of follow-up, our study was adequately powered to detect effect modification by sex hormone level.

Our study has several limitations. First, the measurement of adiposity and sex hormone levels were available only at baseline. Studies examining adiposity throughout the life course are needed as the timing of exposure may change the association with cancer risk. Second, estradiol levels in most of our study participants fell below the detection limit of 73 pmol/L (82%) using the chemiluminescent immunoassay, forcing our study to classify estradiol as high and low based on detection, although variation in estradiol levels below the detection limit may be important for cancer risk. Future studies are needed in cohorts with greater analytic sensitivity in estradiol measurements. Third, hormone levels can vary throughout the day, during a menstrual cycle, and over the life course and by factors such as nutrient intake and pulsatile secretion (38). Although variations in estradiol throughout the menstrual cycle are large, our sensitivity analysis excluding premenopausal women showed similar results to our main analysis. Additionally, SHBG is highly correlated between the follicular and luteal phases of the menstrual cycle, and one measurement of SHBG in premenopausal women is a reliable estimate of the SHBG level over a 3-year period (39). Additionally, we anticipate the misclassification of hormone levels to be nondifferential, likely biasing our results toward the null. Lastly, participants in the UK Biobank cohort are mostly White, with greater access to care and tend to be healthier than the general population. Thus, these results may not be generalizable, and research on additional populations is warranted.

Conclusion

Our study demonstrates that adiposity may play a stronger role in promoting colorectal, esophageal, and liver cancers in males compared with females and provides evidence for effect modification by SHBG level. Although we considered SHBG, testosterone, and estradiol separately in our analyses, future studies are needed to understand how these hormones may work synergistically or in opposition to the development of cancer. Alternative pathways influencing sex differences in how adiposity causes cancer should be examined such as insulin resistance and inflammation. Overall, with an increase in the prevalence of obesity globally, the mechanism linking adiposity and cancer should be further explored. Our results suggest that the role of SHBG should be investigated as a potential target for prevention strategies.

Data Avaliability

The data analyzed in this study are available through the UK Biobank resources application 46466. Although we do not have permission to share the data directly, the data in the UK Biobank are available to researchers who meet the approval criteria and gain permission from the UK Biobank (https://www.ukbiobank.ac.uk/, RRID: SCR_012815).

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

L. Lucas: Formal analysis, investigation, visualization, methodology, writing–original draft. **Y. Lu:** Writing–review and editing. **E. Giovannucci:** Writing–review and editing. **M. Song:** Conceptualization, resources, data curation, supervision, project administration, writing–review and editing.

Acknowledgments

We thank all the participants and staff in the UK Biobank. This research has been conducted using the UK Biobank resource under application 46466. L.A. Lucas is supported by the Harvard Education and Research Center (T42 OH008416). E.L. Giovannucci is funded as an American Cancer Society Clinical Research Professor (CRP-23-1014041).

Note

Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

Received August 28, 2025; revised September 25, 2025; accepted September 29, 2025; posted first October 1, 2025.

References

1. Pati S, Irfan W, Jameel A, Ahmed S, Shahid RK. Obesity and cancer: a current overview of epidemiology, pathogenesis, outcomes, and management. Cancers 2023;15:485.
2. Rask-Andersen M, Ivansson E, Höglund J, Ek WE, Karlsson T, Johansson Å. Adiposity and sex-specific cancer risk. Cancer Cell 2023;41:1186–97.e4.
3. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism 2022;133:155217.
4. Heo J-W, Kim S-E, Sung M-K. Sex differences in the incidence of obesity-related gastrointestinal cancer. Int J Mol Sci 2021;22:1253.
5. Donohoe CL, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and cancer risk. Diabetol Metab Syndr 2011;3:12.
6. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. Nat Rev Cancer 2015;15:484–98.
7. Asarian L, Geary N. Modulation of appetite by gonadal steroid hormones. Philos Trans R Soc Lond B Biol Sci 2006;361:1251–63.
8. Lu Y, Zhao YC, Liu K, Bever A, Zhou Z, Wang K, et al. A validated estimate of visceral adipose tissue volume in relation to cancer risk. J Natl Cancer Inst 2024;116:1942–51.
9. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.
10. UK biobank anthropometry version 1.0 [cited 2024 Jul 14]. Available from: https://biobank.ctsu.ox.ac.uk/ukb/ukb/docs/Anthropometry.pdf.
11. UK Biobank Biomarker assay quality procedures: approaches used to minimise systematic and random errors (and the wider epidemiological implications) [cited 2024 Jul 14]. Available from: https://biobank.ndph.ox.ac.uk/crystal/crystal/docs/biomarker_issues.pdf.
12. Schmitz D, Ek WE, Berggren E, Höglund J, Karlsson T, Johansson Å. Genome-wide association study of estradiol levels and the causal

effect of estradiol on bone mineral density. J Clin Endocrinol Metab 2021;106:e4471–86.
13. Peters SAE, Woodward M.. Oestradiol and the risk of myocardial infarction in women: a cohort study of UK Biobank participants. Int J Epidemiol 2021;50:1241–9.
14. Møller H, Richards S, Hanchett N, Riaz SP, Lüchtenborg M, Holmberg L, et al. Completeness of case ascertainment and survival time error in English cancer registries: impact on 1-year survival estimates. Br J Cancer 2011;105:170–6.
15. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5 to 24 million UK adults. Lancet Lond Engl 2014;384:755–65.
16. Matsuo K, Mizoue T, Tanaka K, Tsuji I, Sugawara Y, Sasazuki S, et al. Association between body mass index and the colorectal cancer risk in Japan: pooled analysis of population-based cohort studies in Japan. Ann Oncol 2012;23:479–90.
17. Engeland A, Tretli S, Bjørge T. Height and body mass index in relation to esophageal cancer; 23-year follow-up of two million Norwegian men and women. Cancer Causes Control 2004;15: 837–43.
18. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. Am J Clin Nutr 2007;86: 556–65.
19. Yao K-F, Ma M, Ding G-Y, Li Z-M, Chen H-L, Han B, et al. Meta-analysis reveals gender difference in the association of liver cancer incidence and excess BMI. Oncotarget 2017;8:72959–71.
20. Hammond GL. Access of reproductive steroids to target tissues. Obstet Gynecol 2002;29:411–23.
21. Yamazaki H, Kushiyama A, Sakoda H, Fujishiro M, Yamamotoya T, Nakatsu Y, et al. Protective effect of sex hormone-binding globulin against metabolic syndrome: in vitro evidence showing anti-inflammatory and lipolytic effects on adipocytes and macrophages. Mediators Inflamm 2018;2018:3062319.
22. Liao C-H, Li H-Y, Yu H-J, Chiang H-S, Lin M-S, Hua C-H, et al. Low serum sex hormone-binding globulin: marker of inflammation?. Clin Chim Acta Int J Clin Chem 2012;413:803–7.
23. Goldštajn MŠ, Toljan K, Grgić F, Jurković I, Baldani DP. Sex hormone binding globulin (SHBG) as a marker of clinical disorders. Coll Antropol 2016;40:211–8.
24. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2006;295:1288–99.
25. McMenamin ÚC, Liu P, Kunzmann AT, Cook MB, Coleman HG, Johnston BT, et al. Circulating sex hormones are associated with gastric and colorectal cancers but not esophageal adenocarcinoma in the UK Biobank. Am J Gastroenterol 2021;116:522–9.
26. Lin JH, Zhang SM, Rexrode KM, Manson JE, Chan AT, Wu K, et al. Association between sex hormones and colorectal cancer risk in men and women. Clin Gastroenterol Hepatol 2013;11: 419–24.e1.
27. Dimou N, Mori N, Harlid S, Harbs J, Martin RM, Smith-Byrne K, et al. Circulating levels of testosterone, sex hormone binding globulin and colorectal cancer risk: observational and mendelian randomization analyses. Cancer Epidemiol Biomark Prev 2021;30:1336–48.
28. Peila R, Arthur RS, Rohan TE. Sex hormones, SHBG and risk of colon and rectal cancer among men and women in the UK Biobank. Cancer Epidemiol 2020;69:101831.
29. Murphy N, Strickler HD, Stanczyk FZ, Xue X, Wassertheil-Smoller S, Rohan TE, et al. A prospective evaluation of endogenous sex hormone levels and colorectal cancer risk in postmenopausal women. J Natl Cancer Inst 2015;107:djv210.
30. Wu Z, Petrick JL, Florio AA, Guillemette C, Beane Freeman LE, Buring JE, et al. Endogenous sex steroid hormones and risk of liver cancer among US men: results from the Liver Cancer Pooling Project. JHEP Rep Innov Hepatol 2023;5:100742.
31. Watts EL, Perez-Cornago A, Knuppel A, Tsilidis KK, Key TJ, Travis RC. Prospective analyses of testosterone and sex hormone-binding globulin with the risk of 19 types of cancer in men and postmenopausal women in UK Biobank. Int J Cancer 2021;149:573–84.
32. Liu Z, Zhang Y, Lagergren J, Li S, Li J, Zhou Z, et al. Circulating sex hormone levels and risk of gastrointestinal cancer: systematic review and meta-analysis of prospective studies. Cancer Epidemiol Biomark Prev 2023;32:936–46.
33. Xie S-H, Ness-Jensen E, Rabbani S, Langseth H, Gislefoss RE, Mattsson F, et al. Circulating sex hormone levels and risk of esophageal adenocarcinoma in a prospective study in men. Am J Gastroenterol 2020;115:216–23.
34. Xie S-H, Fang R, Huang M, Dai J, Thrift AP, Anderson LA, et al. Association between levels of sex hormones and risk of esophageal adenocarcinoma and barrett's esophagus. Clin Gastroenterol Hepatol 2020;18:2701–9.e3.
35. Ganne-Carrié N, Chastang C, Uzzan B, Pateron D, Trinchet JC, Perret G, et al. Predictive value of serum sex hormone binding globulin for the occurrence of hepatocellular carcinoma in male patients with cirrhosis. J Hepatol 1997;26:96–102.
36. Okorodudu DO, Jumean MF, Montori VM, Romero-Corral A, Somers VK, Erwin PJ, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. Int J Obes 2010;34:791–9.
37. Moore LL, Bradlee ML, Singer MR, Splansky GL, Proctor MH, Ellison RC, et al. BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham study adults. Int J Obes Relat Metab Disord 2004;28:559–67.
38. Abbara A, Adams S, Phylactou M, Izzi-Engbeaya C, Mills EG, Thurston L, et al. Quantifying the variability in the assessment of reproductive hormone levels. Fertil Steril 2024;121:334–45.
39. Missmer SA, Spiegelman D, Bertone-Johnson ER, Barbieri RL, Pollak MN, Hankinson SE. Reproducibility of plasma steroid hormones, prolactin, and insulin-like growth factor levels among premenopausal women over a 2- to 3-year period. Cancer Epidemiol Biomarkers Prev 2006;15:972–8.

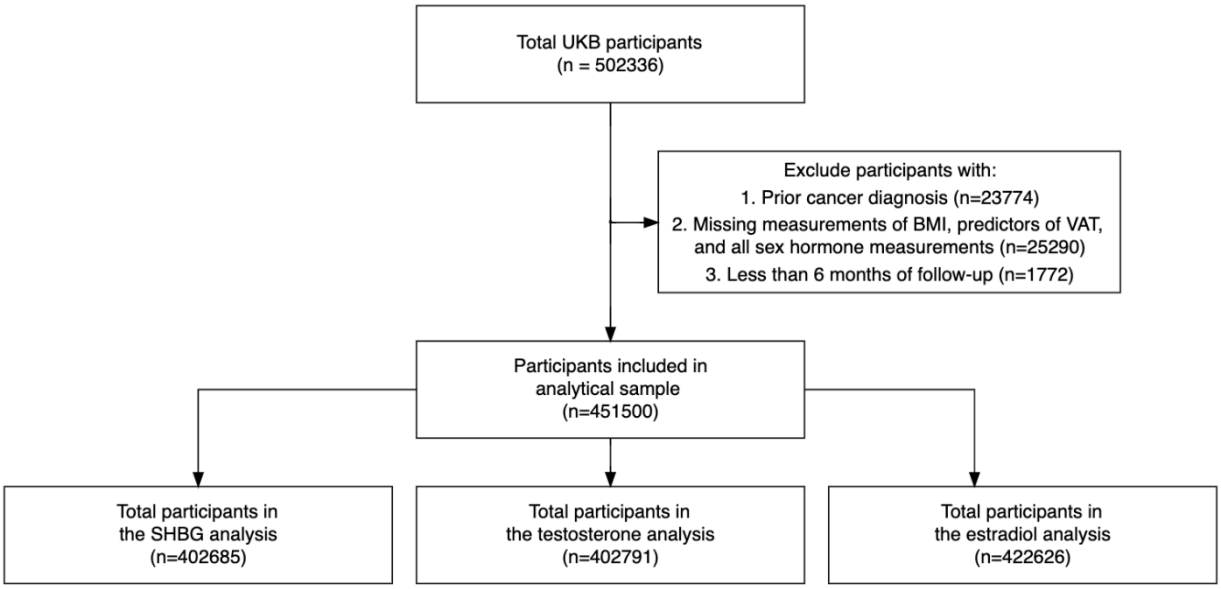

Figure S1. Inclusion criteria for study analytic sample from the UK Biobank
Participants in the UK Biobank were excluded from the analysis if they had a history of cancer, missing measurements of adiposity and sex hormones, and short follow-up (less than 6 months).
UKB: UK Biobank, BMI: body mass index, VAT: visceral adipose tissue
Predictors of VAT included height, weight, hip circumference, waist circumference, and age

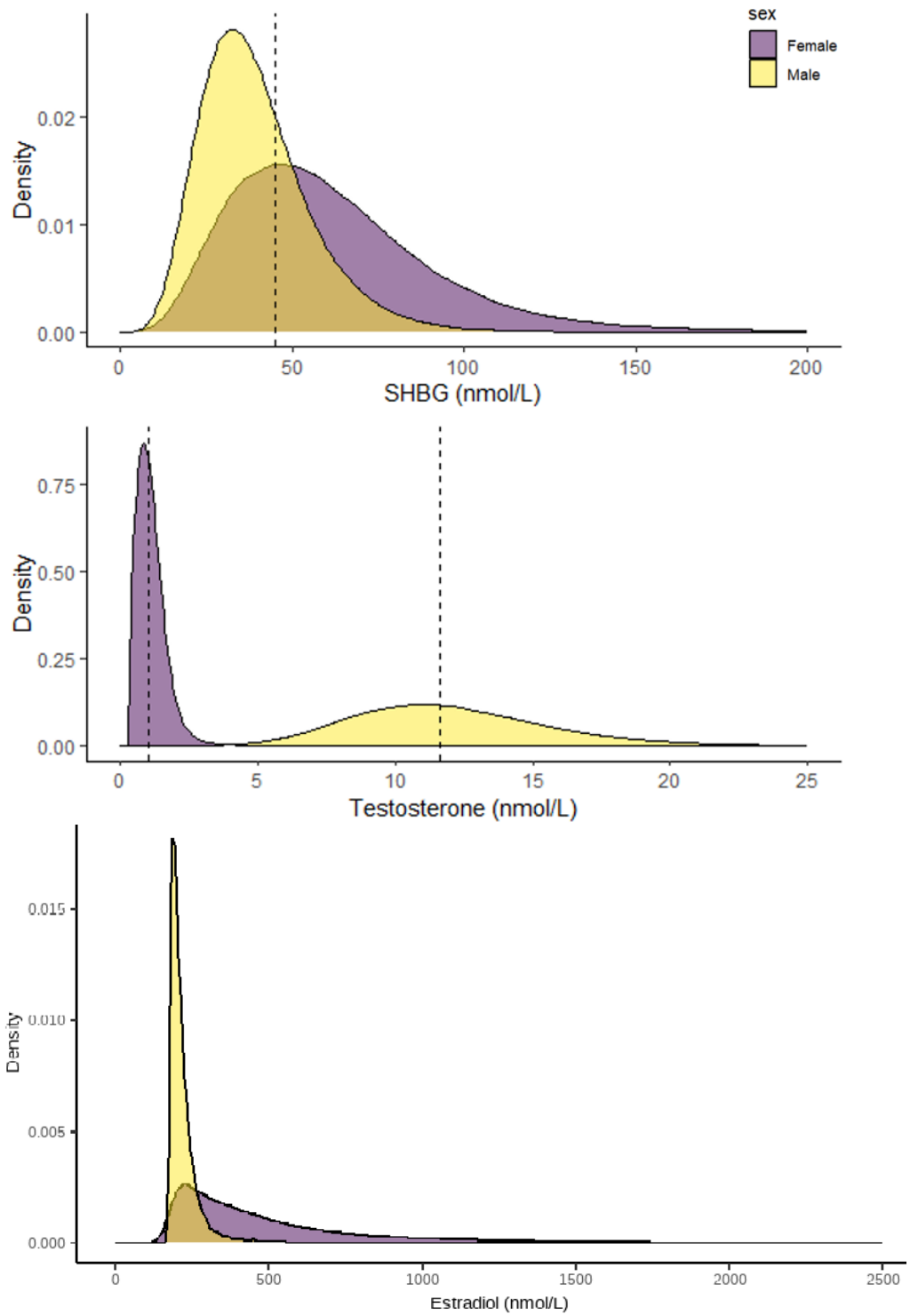

Figure S2. The distribution of SHBG and testosterone in the UK Biobank Cohort by sex. The dotted line represents classification as high and low as determined by the median values.

Table S1: The association between adiposity (BMI and estimated VAT) per unit increase from the 10th to the 90th percentile and colorectal, esophageal, and liver cancer incidence by hormone level among post-menopausal females, UK Biobank

			Low Hormone Level		High Hormone Level		
	Cancer Type	Hormone	HR[a] (95% CI)	P value	HR[a] (95% CI)	P value	$P_{interaction}$[b]
BMI	Colorectal	E2	1.11 (0.97,1.28)	0.126	0.76 (0.42,1.36)	0.353	0.620
		SHBG	1.06 (0.85,1.3)	0.614	1 (0.83,1.21)	0.978	0.715
		T	1.03 (0.84,1.26)	0.771	1.08 (0.88,1.32)	0.461	0.743
	Esophageal	E2	0.71 (0.47,1.08)	0.109	0.98 (0.11,8.57)	0.987	0.775
		SHBG	1.33 (0.72,2.45)	0.364	0.66 (0.38,1.16)	0.151	0.283
		T	0.64 (0.34,1.23)	0.180	0.96 (0.55,1.67)	0.878	0.743
	Liver	E2	1.54 (1,2.39)	0.051	1.92 (0.56,6.6)	0.300	0.775
		SHBG	1.84 (0.91,3.7)	0.090	1.37 (0.77,2.42)	0.286	0.715
		T	1.04 (0.49,2.22)	0.918	1.32 (0.76,2.32)	0.326	0.743
Estimated VAT	Colorectal	E2	1.16 (1.01,1.34)	0.041	0.9 (0.5,1.64)	0.732	1.000
		SHBG	1.27 (1.01,1.6)	0.041	0.99 (0.81,1.21)	0.931	0.197
		T	1.16 (0.94,1.43)	0.166	1.11 (0.89,1.38)	0.351	0.766
	Esophageal	E2	0.79 (0.52,1.21)	0.281	1.21 (0.13,11.55)	0.869	1.000
		SHBG	1.54 (0.77,3.06)	0.219	0.79 (0.45,1.39)	0.409	0.197
		T	0.62 (0.32,1.21)	0.159	1.23 (0.69,2.2)	0.484	0.353
	Liver	E2	1.66 (1.04,2.65)	0.034	1.66 (0.37,7.4)	0.508	1.000
		SHBG	2.39 (1.08,5.3)	0.032	1.51 (0.83,2.74)	0.178	0.353
		T	1.1 (0.5,2.41)	0.816	1.37 (0.75,2.52)	0.304	0.766

[a] Models were adjusted for age, education level, race, height, MET hours per week, smoking status, alcohol intake, aspirin usage, processed meat consumption, previous bowel cancer screening, family history of cancer, vegetable intake (pieces/day), fruit intake (pieces/day), vitamin D in blood, and cereal intake (servings/week)

[b] P values for interaction were adjusted using FDR method for multiple testing

BMI: body mass index; VAT: visceral adipose tissue; SHBG: sex hormone binding globulin; T: testosterone; E2: estradiol

Table S3. The association between adiposity (BMI and estimated VAT) per unit increase from the 10th to the 90th percentile and colorectal, esophageal, and liver cancer incidence by hormone level among participants with at least one year of follow-up (A.) and at least five years of follow-up (B.) in the UK Biobank

			Low Hormone Level		High Hormone Level		
	Cancer Type	Hormone	HR[a] (95% CI)	P value	HR[a] (95% CI)	P value	$P_{interaction}$[b]
A. Analysis with 1-year lag time (N=447,549)							
BMI	**Female**						
	Colorectal	E2	1.12 (0.98,1.27)	0.096	0.95 (0.72,1.27)	0.746	0.886
		SHBG	1.12 (0.93,1.35)	0.223	1.03 (0.87,1.22)	0.698	0.508
		T	1.02 (0.85,1.22)	0.818	1.13 (0.96,1.34)	0.143	0.912
	Esophageal	E2	0.96 (0.66,1.4)	0.832	0.88 (0.27,2.87)	0.828	0.886
		SHBG	1.82 (1.08,3.09)	0.025	0.75 (0.45,1.27)	0.289	0.050
		T	1.02 (0.59,1.76)	0.943	1.04 (0.62,1.73)	0.890	0.965
	Liver	E2	1.72 (1.13,2.6)	0.011	1.87 (0.73,4.81)	0.192	0.886
		SHBG	2.69 (1.49,4.85)	0.001	1.69 (1,2.87)	0.051	0.359
		T	1.45 (0.75,2.82)	0.273	1.79 (1.1,2.92)	0.020	0.912
	Male						
	Colorectal	E2	1.41 (1.27,1.56)	0.000	1.29 (0.97,1.7)	0.075	0.550
		SHBG	1.48 (1.32,1.66)	0.000	1.14 (0.95,1.38)	0.149	0.029
		T	1.37 (1.21,1.54)	0.000	1.34 (1.15,1.57)	0.000	0.854
	Esophageal	E2	1.85 (1.52,2.25)	0.000	1.41 (0.86,2.3)	0.172	0.462
		SHBG	1.65 (1.31,2.09)	0.000	2.31 (1.69,3.16)	0.000	0.084
		T	1.7 (1.35,2.13)	0.000	2 (1.48,2.71)	0.000	0.565
	Liver	E2	2.07 (1.61,2.66)	0.000	1.54 (0.96,2.45)	0.072	0.462
		SHBG	1.87 (1.33,2.64)	0.000	3.23 (2.46,4.24)	0.000	0.029
		T	2 (1.47,2.73)	0.000	2.88 (2.1,3.95)	0.000	0.287
VAT	**Female**						
	Colorectal	E2	1.16 (1.01,1.32)	0.036	1.02 (0.76,1.38)	0.893	0.934
		SHBG	1.36 (1.11,1.67)	0.004	1 (0.84,1.2)	0.984	0.043
		T	1.12 (0.93,1.35)	0.231	1.18 (0.98,1.41)	0.078	0.744
	Esophageal	E2	1.11 (0.75,1.64)	0.602	1 (0.29,3.37)	0.995	0.934
		SHBG	2.27 (1.24,4.17)	0.008	0.95 (0.56,1.6)	0.849	0.043
		T	1.08 (0.61,1.91)	0.790	1.32 (0.77,2.25)	0.316	0.744
	Liver	E2	1.83 (1.17,2.88)	0.009	1.92 (0.66,5.59)	0.230	0.934
		SHBG	3.29 (1.62,6.67)	0.001	1.91 (1.09,3.34)	0.024	0.226
		T	1.54 (0.76,3.12)	0.230	1.78 (1.03,3.07)	0.040	0.744
	Male						
	Colorectal	E2	1.56 (1.39,1.75)	0.000	1.32 (0.95,1.84)	0.097	0.514
		SHBG	1.62 (1.41,1.87)	0.000	1.34 (1.11,1.62)	0.002	0.145
		T	1.49 (1.29,1.72)	0.000	1.49 (1.26,1.75)	0.000	0.983

Table S3. The association between adiposity (BMI and estimated VAT) per unit increase from the 10th to the 90th percentile and colorectal, esophageal, and liver cancer incidence by hormone level among participants with at least one year of follow-up (A.) and at least five years of follow-up (B.) in the UK Biobank

			Low Hormone Level		High Hormone Level		
	Cancer Type	Hormone	HR[a] (95% CI)	P value	HR[a] (95% CI)	P value	$P_{interaction}$[b]
	Esophageal	E2	2.18 (1.72,2.76)	0.000	1.58 (0.86,2.91)	0.142	0.514
		SHBG	1.89 (1.42,2.54)	0.000	2.83 (1.98,4.06)	0.000	0.145
		T	2 (1.5,2.67)	0.000	2.36 (1.69,3.29)	0.000	0.977
	Liver	E2	2.59 (1.9,3.54)	0.000	2.08 (1.14,3.8)	0.018	0.514
		SHBG	3.03 (1.97,4.68)	0.000	4.13 (2.91,5.87)	0.000	0.260
		T	3.04 (2.01,4.59)	0.000	3.44 (2.36,5.01)	0.000	0.977
B. Analysis with 5-year lag time (N=428,277)							
BMI	**Female**						
	Colorectal	E2	1.05 (0.89,1.23)	0.590	1.19 (0.85,1.67)	0.307	0.651
		SHBG	1.16 (0.93,1.46)	0.195	0.99 (0.8,1.23)	0.942	0.307
		T	0.93 (0.74,1.17)	0.516	1.25 (1.02,1.52)	0.033	0.149
	Esophageal	E2	1.05 (0.66,1.66)	0.848	0.72 (0.15,3.43)	0.681	0.651
		SHBG	2.35 (1.23,4.47)	0.009	0.79 (0.42,1.47)	0.457	0.044
		T	0.96 (0.49,1.87)	0.909	1.09 (0.59,2)	0.792	0.787
	Liver	E2	1.59 (0.96,2.65)	0.072	2.26 (0.73,6.98)	0.158	0.651
		SHBG	2.66 (1.33,5.31)	0.006	1.31 (0.66,2.62)	0.441	0.219
		T	1.08 (0.44,2.62)	0.867	1.98 (1.11,3.51)	0.020	0.368
	Male						
	Colorectal	E2	1.4 (1.23,1.59)	0.000	1.38 (0.98,1.93)	0.064	0.926
		SHBG	1.53 (1.33,1.77)	0.000	1 (0.79,1.27)	0.998	0.007
		T	1.47 (1.27,1.7)	0.000	1.18 (0.96,1.44)	0.115	0.225
	Esophageal	E2	1.75 (1.36,2.25)	0.000	0.94 (0.47,1.9)	0.871	0.258
		SHBG	1.43 (1.06,1.94)	0.021	2.36 (1.61,3.47)	0.000	0.041
		T	1.57 (1.18,2.1)	0.002	1.82 (1.24,2.67)	0.002	0.759
	Liver	E2	2.38 (1.79,3.17)	0.000	1.57 (0.92,2.68)	0.095	0.258
		SHBG	2.13 (1.45,3.12)	0.000	3.55 (2.57,4.89)	0.000	0.041
		T	2.51 (1.8,3.49)	0.000	2.71 (1.85,3.97)	0.000	0.759
VAT	**Female**						
	Colorectal	E2	1.06 (0.89,1.25)	0.541	1.26 (0.88,1.8)	0.210	0.606
		SHBG	1.35 (1.05,1.74)	0.020	0.95 (0.76,1.19)	0.644	0.076
		T	0.99 (0.78,1.25)	0.935	1.3 (1.04,1.61)	0.020	0.263
	Esophageal	E2	1.22 (0.75,1.97)	0.426	0.79 (0.16,3.88)	0.769	0.606
		SHBG	2.81 (1.3,6.07)	0.009	1.08 (0.58,2)	0.817	0.076
		T	1.06 (0.53,2.12)	0.862	1.34 (0.7,2.55)	0.371	0.617
	Liver	E2	1.62 (0.93,2.81)	0.088	2.4 (0.65,8.84)	0.187	0.606
		SHBG	2.85 (1.22,6.62)	0.015	1.36 (0.66,2.81)	0.404	0.182

Table S3. The association between adiposity (BMI and estimated VAT) per unit increase from the 10th to the 90th percentile and colorectal, esophageal, and liver cancer incidence by hormone level among participants with at least one year of follow-up (A.) and at least five years of follow-up (B.) in the UK Biobank

			Low Hormone Level		High Hormone Level		
	Cancer Type	Hormone	HR[a] (95% CI)	P value	HR[a] (95% CI)	P value	$P_{interaction}$[b]
		T	1.17 (0.47,2.93)	0.733	1.9 (0.99,3.64)	0.053	0.575
	Male						
	Colorectal	E2	1.5 (1.3,1.74)	0.000	1.37 (0.91,2.06)	0.132	0.675
		SHBG	1.66 (1.4,1.98)	0.000	1.15 (0.91,1.46)	0.251	0.036
		T	1.59 (1.33,1.9)	0.000	1.27 (1.04,1.57)	0.022	0.300
	Esophageal	E2	2.07 (1.54,2.77)	0.000	0.99 (0.45,2.19)	0.982	0.253
		SHBG	1.64 (1.14,2.36)	0.008	2.86 (1.83,4.47)	0.000	0.077
		T	1.91 (1.34,2.73)	0.000	2.11 (1.39,3.2)	0.000	0.721
	Liver	E2	3 (2.08,4.34)	0.000	1.97 (0.98,3.96)	0.055	0.429
		SHBG	3.52 (2.14,5.8)	0.000	4.33 (2.84,6.6)	0.000	0.520
		T	4.2 (2.63,6.71)	0.000	3 (1.91,4.71)	0.000	0.444

[a] Models were adjusted for age, education level, race, height, MET hours per week, alcohol intake, aspirin usage, processed meat consumption, previous bowel cancer screening, family history of cancer, vegetable intake (pieces/day), fruit intake (pieces/day), vitamin D in blood, and cereal intake (servings/week)

[b] P values for interaction were adjusted using FDR method for multiple testing

BMI: body mass index; VAT: visceral adipose tissue; SHBG: sex hormone binding globulin; T: testosterone; E2: estradiol

Table S2: The association between adiposity (BMI and estimated VAT) per unit increase from the 10th to the 90th percentile and colorectal, esophageal, and liver cancer incidence by hormone level among never smokers, UK Biobank

			Low Hormone Level		High Hormone Level		
	Cancer Type	Hormone	HR[a] (95% CI)	P value	HR[a] (95% CI)	P value	$P_{interaction}$[b]
BMI	**Female**						
	Colorectal	E2	1.06 (0.89,1.26)	0.495	0.97 (0.68,1.39)	0.880	0.797
		SHBG	1.11 (0.86,1.44)	0.407	1.03 (0.83,1.28)	0.754	0.968
		T	1.02 (0.81,1.30)	0.853	1.09 (0.87,1.36)	0.445	0.767
	Esophageal	E2	1.15 (0.68,1.92)	0.604	0.87 (0.11,6.77)	0.894	0.797
		SHBG	1.70 (0.75,3.88)	0.206	1.23 (0.65,2.35)	0.526	0.968
		T	1.16 (0.54,2.52)	0.701	0.99 (0.47,2.10)	0.989	0.767
	Liver	E2	1.46 (0.80,2.66)	0.212	2.94 (0.97,8.93)	0.057	0.797
		SHBG	1.65 (0.64,4.22)	0.299	1.69 (0.81,3.52)	0.164	0.968
		T	0.89 (0.30,2.65)	0.834	1.31 (0.65,2.65)	0.453	0.767
	Male						
	Colorectal	E2	1.38 (1.19,1.61)	0.000	1.19 (0.79,1.80)	0.404	0.702
		SHBG	1.40 (1.18,1.66)	0.000	1.07 (0.81,1.42)	0.621	0.105
		T	1.42 (1.19,1.70)	0.000	1.23 (0.98,1.54)	0.080	0.445
	Esophageal	E2	1.96 (1.39,2.76)	0.000	1.66 (0.76,3.63)	0.208	0.702
		SHBG	1.73 (1.15,2.61)	0.009	3.01 (1.86,4.85)	0.000	0.105
		T	2.15 (1.49,3.11)	0.000	1.86 (1.10,3.13)	0.020	0.644
	Liver	E2	2.00 (1.30,3.08)	0.002	1.71 (0.83,3.50)	0.143	0.702
		SHBG	1.47 (0.79,2.77)	0.227	3.98 (2.60,6.11)	0.000	0.025
		T	1.60 (0.89,2.89)	0.118	3.85 (2.38,6.24)	0.000	0.059
VAT	**Female**						
	Colorectal	E2	1.10 (0.92,1.31)	0.315	1.08 (0.75,1.56)	0.675	0.946
		SHBG	1.33 (1.00,1.76)	0.050	1.05 (0.84,1.32)	0.644	0.599
		T	1.15 (0.90,1.47)	0.271	1.12 (0.89,1.42)	0.324	0.904
	Esophageal	E2	1.07 (0.61,1.86)	0.812	0.78 (0.09,7.04)	0.825	0.946
		SHBG	1.70 (0.64,4.49)	0.284	1.28 (0.65,2.52)	0.477	0.840
		T	0.99 (0.43,2.29)	0.984	1.14 (0.52,2.49)	0.751	0.904
	Liver	E2	1.50 (0.78,2.85)	0.221	3.05 (0.82,11.4)	0.098	0.946
		SHBG	2.09 (0.71,6.15)	0.180	1.83 (0.84,4.01)	0.131	0.840
		T	1.02 (0.34,3.11)	0.967	1.2 (0.55,2.61)	0.649	0.904
	Male						
	Colorectal	E2	1.55 (1.31,1.84)	0.000	1.31 (0.82,2.10)	0.264	0.926
		SHBG	1.67 (1.36,2.04)	0.000	1.2.0 (0.91,1.58)	0.205	0.080
		T	1.63 (1.32,2.02)	0.000	1.39 (1.10,1.76)	0.005	0.476
	Esophageal	E2	2.26 (1.48,3.45)	0.000	2.14 (0.78,5.92)	0.142	0.926
		SHBG	2.06 (1.23,3.45)	0.006	3.67 (1.98,6.80)	0.000	0.145
		T	2.70 (1.62,4.50)	0.000	2.26 (1.27,4.00)	0.005	0.637
	Liver	E2	3.13 (1.82,5.38)	0.000	2.72 (1.01,7.31)	0.047	0.926

Table S2: The association between adiposity (BMI and estimated VAT) per unit increase from the 10th to the 90th percentile and colorectal, esophageal, and liver cancer incidence by hormone level among never smokers, UK Biobank

			Low Hormone Level		High Hormone Level		
	Cancer Type	Hormone	HR[a] (95% CI)	P value	HR[a] (95% CI)	P value	$P_{interaction}$[b]
		SHBG	2.86 (1.33,6.12)	0.007	7.54 (4.06,14.00)	0.000	0.080
		T	3.00 (1.41,6.36)	0.004	5.82 (3.14,10.78)	0.000	0.476

[a] Models were adjusted for age, education level, race, height, MET hours per week, alcohol intake, aspirin usage, processed meat consumption, previous bowel cancer screening, family history of cancer, vegetable intake (pieces/day), fruit intake (pieces/day), vitamin D in blood, and cereal intake (servings/week)

[b] P values for interaction were adjusted using FDR method for multiple testing

BMI: body mass index; VAT: visceral adipose tissue; SHBG: sex hormone binding globulin; T: testosterone; E2: estradiol