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Circulating Sex Hormones are Associated with Gastric and Colorectal Cancer but not Esophageal Adenocarcinoma in the UK Biobank

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Abstract

Background: Gastrointestinal cancers show an unexplained male predominance, but few prospective studies have investigated sex hormones and gastrointestinal cancer risk.

Aims: To determine the impact of circulating sex hormones on risk of esophageal, gastric and colorectal cancer in men and women.

Methods: We included 219,425 men and 147,180 women from UK Biobank. Sex hormones were quantified using chemiluminescent immunoassay. Gastrointestinal cancers were identified from cancer registry linkages. Sex hormone concentrations and risk of gastrointestinal cancers were investigated using Cox proportional hazards regression.

Results: During 10 years of follow-up, 376 esophageal adenocarcinoma, 108 esophageal squamous cell carcinoma, 333 gastric and 2,868 colorectal cancer cases were identified. Increased hazard ratios (HRs) were found for sex hormone-binding globulin (SHBG) and risk of gastric cancer in men (Q4 v. Q1 HR 1.43, 95% CI 0.95, 2.17, P_{trend}=0.01). Free testosterone was inversely associated with esophageal squamous cell carcinoma in women (Q4 v. Q1 HR 0.32, 95% CI 0.11,

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Conflicts of interest:

The authors have no conflicts of interest to disclose.

0.98, P_{trend}=0.05). For colorectal cancer, SHBG was associated with a reduced risk among men (Q4 v. Q1 HR 0.89, 95% CI 0.77, 1.03, P_{trend}=0.04) and free testosterone concentrations a reduction in risk among women (Q4 v. Q1 HR 0.80, 95% CI 0.66, 0.97, P_{trend}=0.01). No associations were found for esophageal adenocarcinoma.

Conclusion: In this large prospective investigation of prediagnostic sex hormones and risk of gastrointestinal cancers, men with higher SHBG concentrations had higher gastric, yet lower colorectal, cancer risks while women with higher free testosterone levels had lower risk of esophageal squamous cell carcinoma and colorectal cancer.

Keywords

sex hormones; gastrointestinal cancer; cohort study; UK Biobank

Introduction:

Esophageal, gastric and colorectal cancer show an unexplained male predominance, which is most marked for esophageal adenocarcinoma, where incidence is up to eight times higher in men than women (1). Established risk factors such as smoking and obesity do not fully explain the observed disparity in incidence (2,3), which has led to the hypothesis that sex hormones, including estrogens and androgens, may be involved in the development of these cancers.

Epidemiological studies investigating the impact of exogenous sex hormone exposure report a 20 to 40% reduction in risk of esophageal adenocarcinoma (4,5), esophageal squamous cell carcinoma (6,7) gastric (8) and colorectal (5,9) cancer in women who use oral contraceptives or menopausal hormone therapy. In men, androgen deprivation therapy (ADT) use has been associated with a 30 to 40% increase in colorectal cancer risk, suggesting a potentially beneficial impact of androgens (10). In contrast, lower rates of esophageal adenocarcinoma (11) and squamous cell carcinoma (12) have been identified in men with prostate cancer, likely undergoing androgen deprivation therapy, suggesting androgens may be detrimental.

To date, there have been just two prospective studies of prediagnostic circulating sex hormones and risk of upper gastrointestinal cancers. Combined, these studies provide evidence for an inverse association between endogenous circulating testosterone and esophageal adenocarcinoma risk (13,14), but there was less evidence for inverse associations of estradiol, luteinizing hormone (LH), and dehydroepiandrosterone (DHEA) with esophageal adenocarcinoma (15). Meanwhile, no study has specifically investigated risk of esophageal squamous cell carcinoma or gastric cancer with respect to prediagnostic circulating sex hormones.

Colorectal cancer also shows a male predominance in incidence though not as marked as that seen for gastro-esophageal cancer. Some (16), but not all (17), studies of prediagnostic sex hormone concentrations in women have reported reductions in colorectal cancer risk with higher estradiol concentrations, while increases have been observed for higher testosterone (18) and sex hormone-binding globulin (SHBG) (16), a hepatically derived

glycoprotein and primary transport protein of sex hormones. Only one study has evaluated circulating sex hormones and colorectal cancer risk in men and showed inverse associations with circulating testosterone and SHBG (19).

Further prospective investigation of the role of sex hormones in the development of gastrointestinal cancers may identify novel targets for prevention and treatment. We therefore aimed to conduct the first study to evaluate prediagnostic circulating sex hormones, in both men and women, and risk of esophageal, gastric and colorectal cancer in a large prospective cohort.

Methods

Study Population

The UK Biobank is a cohort of over 500,000 men and women aged 40–69 years recruited across England, Scotland and Wales between 2006 and 2010 (20). Data collection at baseline included lifestyle, medical history and physical measures, along with biological samples. UK Biobank is linked to cancer registry data from the Health and Social Care Information Centre (England and Wales) and the Scottish Cancer Registry (Scotland) and death records from the UK Office of National Statistics. Completeness of UK cancer registries has been shown to be high (21). The UK Biobank was approved by the North West Multi-Centre Research Ethics Committee and participants provided written informed consent.

Study design

We conducted a prospective cohort study among males and postmenopausal females in the UK Biobank. Women who reported current use of menopausal hormone therapy were excluded. Gastrointestinal cancers included esophageal (International Classification of Diseases, ICD, 10 code C15), gastric (ICD 10 code C16) and colorectal (ICD 10 code 18–20). Esophageal and gastric cancers were further classified by histology, as adenocarcinoma (ICD-O morphology codes 8140–8573) or squamous cell carcinoma (ICD-O code 8050–8082). Gastric and colorectal cancers were classed by location, where possible, as cancers of the gastric cardia (ICD 10 code C16.0) and gastric non-cardia (ICD 10 code C16.1–16.5), colon (ICD 10 code C18, C19) and rectum (ICD 10 codes C20), respectively. Participants with a cancer diagnosis (except non-melanoma skin cancer) prior to baseline were excluded. The cohorts were followed from baseline to the date of first incident cancer or censoring on the earliest of death or March 30th 2016.

Sample Collection and laboratory assays

During the baseline visit, UK Biobank phlebotomists or nurses collected fasting blood samples from all participants at assessment centers. Blood samples were frozen at −80°C. SHBG, testosterone and estradiol, were analyzed by chemiluminescent immunoassay (Beckman Coulter, UK, Ltd) at the UK Biobank central laboratory in Stockport, UK. Internal quality control samples of known high, medium and low biomarker concentrations were run prior to each batch of participant samples and after each batch. In these quality

controls, coefficients of variation (CVs) were less than 16% (range=5.2% to 15.3%). The UK Biobank sampling and handling methods have been shown to be robust (22).

Sex hormone measurements

Free testosterone was calculated using previously validated methods (23). In all analyses, we replaced values below the lower limit of quantification (LOQ) with half the lower limit of quantification for SHBG (0.2% men, 0.2% women), testosterone (0.2% men, 18% women) and estradiol (91% men, 96% women), an approach similar to previous investigations (13,18). Expectedly, due to the inclusion of males and postmenopausal females, estradiol concentrations were below the LOQ for a large proportion of the cohort. We categorised sex hormones into fourths based upon quartiles for SHBG, testosterone and free testosterone while for estradiol, values below the LOQ were categorized into the low group and the remainder were grouped into the high group.

Covariates

Interview and touch screen questionnaires at baseline were used to obtain information on covariates including age and sex, while lifestyle factors included smoking status (never smoker, former smoker or current smoker) and alcohol consumption (never, <1 day per week, 1–2 days per week, 3–4 days per week or >4 days per week). Body mass index (BMI), categorized as under or normal weight [<25kg/m^2], overweight [25–30 kg/m^2], obese [>30 kg/m^2]), was calculated from height and weight measurements taken by research staff. Information on diabetes and medication use was retrieved from interview/touch screen. Socioeconomic deprivation was retrieved from Townsend score (24) based upon postcode of residence.

Statistical Analysis

Characteristics between cases and non-cases were compared using frequencies and percentages. Cox proportional hazards regression was used to calculate hazard ratios (HR) and 95% confidence intervals (CIs) for associations between circulating sex hormones and risk of esophageal (adenocarcinoma or squamous), gastric and colorectal cancer. Age was the underlying time scale and individuals were considered at risk from birth and under observation from age at baseline, left truncated. Models were stratified by sex and contained age, deprivation, BMI, alcohol (except esophageal adenocarcinoma), smoking, diabetes and aspirin and statin use (colorectal cancer only). Schoenfeld residuals were checked to determine the proportional hazards assumption. Sub-group analysis was conducted by cancer site (gastric cardia or non-cardia, colon or rectal) and sensitivity analysis excluded participants with a gastrointestinal cancer diagnosis in first year after baseline and additional adjustment was made for processed meat and fruit and vegetable intake (gastric and colorectal cancer). We also presented our findings for esophageal adenocarcinoma risk in men and colorectal cancer risk in men and women with respect to previous studies (Figure, Supplemental Digital Content 1).

Results:

We included 220,150 males and 147,180 females and during 10 years of follow-up, 376 esophageal adenocarcinoma (333 male, 43 female; M:F 5:1), 108 esophageal squamous cell carcinoma (57 male, 51 female; M:F 0.7:1), 333 gastric (256 male, 77 female; M:F 2.2:1) and 2,868 colorectal (1,892 male, 976 female; M:F 1.3:1) cancer cases were identified. Characteristics of participants are listed in Tables 1 (males) and 2 (females). In males, cases were more likely to be older, be smokers, and have a higher BMI compared to non-cases, with the exception of esophageal squamous cell carcinoma cases who were more likely to have a lower BMI. Aside from esophageal adenocarcinoma, male cases were more likely to be alcohol drinkers while esophageal squamous cell carcinoma cases were more likely to live in deprived areas compared to non-cases. Men with esophageal adenocarcinoma, gastric and colorectal cancer were more likely to have diabetes and use aspirin and statins, Table 1. In females, esophageal squamous cell carcinoma cases were more likely to be older, alcohol drinkers and have a lower BMI. Women with gastric cancer were more likely to be alcohol drinkers, have diabetes while both gastric cancer colorectal cancer cases were more likely older, and use aspirin and statins, Table 2.

The associations between circulating sex hormones and risk of gastrointestinal cancers are presented in Tables 3 and 4. We observed no associations between sex hormones and esophageal adenocarcinoma risk in either males or females comparing the highest to the lowest concentrations. Esophageal squamous cell carcinoma risk was reduced in females comparing the highest to the lowest free testosterone concentrations (HR 0.32, 95% CI 0.11, 0.98, P_{trend}=0.05) while no associations were observed in men. For gastric cancer, higher SHBG across fourths was associated with an increased risk in men (HR 1.43, 95% CI 0.95, 2.17, P_{trend}=0.01), Table 3. In contrast, higher SHBG was associated with reduced risk of colorectal cancer in men (Q4 v Q1 HR 0.89, 95% CI 0.77, 1.04, P_{trend}=0.04). There was a reduced risk of colorectal cancer in females, comparing the highest to the lowest testosterone and free testosterone concentrations (HR 0.83, 95% CI 0.69, 1.00, P_{trend}=0.05, HR 0.80, 95% CI 0.66, 0.97, P_{trend}=0.01, respectively), Table 4. No associations were noted for gastrointestinal cancers and estradiol in either sex comparing the highest to the lowest concentrations, although there was limited ability to study these associations in women due to small case numbers, Tables 3 and 4.

Results remained similar in analysis by cancer sub-site (Supplemental Digital Content 2 and 3). In men, there was weak evidence of a reduced colon cancer risk comparing the highest to the lowest testosterone concentrations (HR 0.82, 95% CI 0.68, 0.98, P_{trend}=0.05), Supplementary Digital Content 2. Results were largely similar following exclusion of the first year after baseline (Tables, Supplemental Digital Content 4 and 5) and were unchanged for gastric and colorectal cancer after additional adjustment for processed meat and fruit and vegetable intake (data not shown).

Discussion:

In our prospective analysis of prediagnostic sex hormones in both men and women, we found that SHBG was positively associated with gastric cancer risk in men and free

testosterone was inversely associated with esophageal squamous cell carcinoma in women. For colorectal cancer, higher SHBG in men and testosterone concentrations in women were associated with a reduction in risk.

Although esophageal adenocarcinoma is the most male predominant cancer, we did not find any significant association between prediagnostic sex hormone concentrations and risk in men or women. Our results contrasts two prior cohort studies which in combination indicated an inverse association between testosterone and esophageal adenocarcinoma risk (13,14) (Figure, Supplemental Digital Content 1). The US-based study (13) used mass spectrometry to quantitate estradiol, finding evidence for an inverse association with esophageal/gastric cardia adenocarcinoma, but the Norwegian study (14), which used an immunoassay with 36% of samples below the lower limit of detection, was not able to replicate this result. Individual results from these prior studies also support inverse associations of DHEA and LH with esophageal/gastric cardia adenocarcinoma, and these observations merit follow-up in other cohorts, as well as expansion to women, despite the greater rarity of these cancers in this sex.

We found a reduced risk of esophageal squamous cell carcinoma in women with higher levels of free testosterone, and a similar reduction for testosterone, but not statistically significant, suggesting that sex hormone modulation may be beneficial in high-risk females. However, the underlying biological mechanisms linking sex hormones and esophageal squamous cell carcinoma are not well understood. Expression of both estrogen receptor β and androgen receptors have been shown in esophageal squamous cell carcinoma tissues (25,26) and *in vitro* evidence has demonstrated growth promoting effects for testosterone in esophageal squamous cell carcinoma cell lines (27). Despite this, no previous study has investigated risk of esophageal squamous cell carcinoma with respect to circulating prediagnostic circulating sex hormones.

Similarly, no study has specifically investigated gastric cancer risk with respect to sex hormone levels, despite a two-fold higher incidence in men compared to women (28). We found an increased risk of gastric cancer in men with higher circulating concentrations of SHBG. Polymorphisms in SHBG, and well as *COMT* (involved in estrogen inactivation) have been associated with gastric cancer risk (29) and epidemiological studies in women have shown some protective associations for longer years of fertility and use of hormone replacement therapy, suggesting that estrogen may be protective (8). Higher SHBG levels have been hypothesised to reduce concentrations of free estrogen, which in turn may promote gastric cancer development (30) but we found no association with estradiol concentrations and gastric cancer risk in men, and we were unable to conduct analysis of estradiol in women due to small numbers. Although SHBG plays an integral role in the regulation of free estradiol and testosterone in circulation, it may have biological functions independent of sex hormone binding (31). Given the limited evidence, our novel findings for both gastric cancer and esophageal squamous cell carcinoma require verification in other prospective cohorts to determine potential applications of sex hormones or analogs in the prevention of these cancers. Future studies will require collaborative pooling of cohorts to ensure sufficient sample sizes, particularly for women.

We found weak evidence of a reduction in colorectal cancer risk in men with increasing levels of SHBG which is similar to the findings from the only prior investigation within the Health Professional Follow-Up Study (19), indicating that SHBG may have potential as a target in future colorectal cancer prevention studies in men. In women, our finding of a reduced colorectal cancer risk with higher concentrations of testosterone and free testosterone contrasts a Japanese nested case-control study that reported a doubling of risk with the highest testosterone levels and no significant association for free testosterone concentrations (Figure, Supplemental Digital Content 1) but more than 60% of participants had testosterone levels lower than LOQ (18). Differences in ethnicity may also explain discrepancies and we also included considerably more colorectal cancer cases (1,131 cases versus 185 cases (18)). In men, we found suggestive evidence that testosterone concentrations were inversely associated with colorectal cancer, similar to the only previously conducted study (19); however, our estimate was weaker and did not reach statistical significance. Preclinical evidence suggests that androgens exert protective effects against colorectal carcinogenesis; expression of androgen receptors in colorectal cancer tissue has been shown to be lower than that found in normal mucosa (32,33) and administration of androgens protects against colorectal cancer in *in vivo* studies (34,35). Use of ADT in men with prostate cancer has been associated with a 30–40% higher risk of colorectal cancer (10). Further large prospective investigations are needed to extend our findings, given the accumulating evidence of a potentially beneficial effect of androgens in colorectal cancer carcinogenesis.

Our lack of association between estradiol concentrations and risk of colorectal cancer in women is similar to four previous population-based studies (17–19,36) but contrasts two US studies (16,37) (Figure, Supplemental Digital Content 1). A case-control study nested in the Women's Health Initiative (WHI) Clinical Trial reported a 42–57% reduced risk in women with the highest concentrations of estradiol, free estradiol and estrone concentrations (16), while a case-cohort study in the WHI-Observational Study observed a 53% increased risk in women with the highest estradiol levels (37). Although these studies included considerably fewer colorectal cancer cases, divergent results may be due to differences in study design and hormone assays utilised. Circulating estrone levels were positively associated with risk of colorectal cancer in a nested case-control study in the New York University Women's Health Study, but no association was apparent for estradiol (36). Estrone is biologically weaker than estradiol but is found in higher quantities in postmenopausal women, therefore future studies should aim to also incorporate measurements of this hormone, especially in postmenopausal women.

Our study is the largest to date and for the first time in a cohort, we were able to include both men and women but some analysis in women, particularly estradiol, were limited by reduced numbers. A strength was that serum samples were collected up to 10 years prior to cancer, reducing potential reverse causation. Selection bias was limited as sex hormones were measured in the whole study population and we were able to investigate a number of gastrointestinal cancers, minimizing potential measurement error. For the first time, we were able to investigate risk of gastric and esophageal squamous cell carcinoma, and esophageal adenocarcinoma cancer in women.

As described, a large proportion of participants had estradiol levels below the LOQ, which is expected in males and postmenopausal females using chemiluminescent immunoassay and although we replaced these values with half of the LOQ value, the resultant dichotomized exposure may have attenuated associations preventing us from replicating results of some studies. Testosterone and SHBG values were available for most participants (testosterone: 93% males, 78% females; SHBG: 86% males, 84% females). The UK Biobank participants are generally healthier compared to the UK population, but risk factor–disease estimations are generalizable (38). Sex hormone concentrations were measured at one time-point but serum samples have shown good correlation with concentrations up to three years after baseline (39). We cannot rule out potential residual confounding, for example, pack-years of smoking, duration of diabetes, colonoscopy (colorectal cancer), or H. pylori (gastric cancer). We used an area-based deprivation measure, which is relatively crude however; it is likely be a proxy for other confounders associated with deprivation. Finally, a number of associations were investigated therefore increasing the chance of Type 1 error.

Conclusion

In a large prospective cohort study of prediagnostic sex hormones and risk of gastrointestinal cancers in men and women, we found evidence that higher levels of SHBG were associated with a higher risk of gastric cancer, but lower risk of colorectal cancer, in men. Free testosterone was associated with a reduction in colorectal cancer and esophageal squamous cell carcinoma in women. Additional prospective studies, particularly among women, are required to verify our novel findings in order to determine the utility of sex hormone modulation in the prevention of gastrointestinal cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

WHAT IS KNOWN

- Gastrointestinal cancers show an unexplained male predominance in incidence
- Few prospective studies have investigated sex hormones and gastrointestinal cancer risk

WHAT IS NEW HERE

- Men with higher SHBG concentrations had higher gastric yet lower colorectal, cancer risks
- Women with higher free testosterone levels had lower risk of esophageal squamous cell carcinoma and colorectal cancer
- Additional prospective studies, particularly among women, are required to verify our novel findings

Table 1.

Characteristics of gastrointestinal cancer cases and non-cases among men in the UK Biobank

	Esophageal adenocarcinoma		Esophageal squamous cell carcinoma		Gastric cancer		Colorectal cancer	
	Cases n (%)	Non-cases n (%)	Cases n (%)	Non-cases n (%)	Cases n (%)	Non-cases n (%)	Cases n (%)	Non-cases n (%)
Age at baseline								
<50	11 (3.3%)	52,493 (23.9%)	3 (5.3%)	52,501 (23.9%)	18 (7.0%)	52,486 (23.9%)	104 (5.5%)	52,400 (24.0%)
50–59	91 (27.3%)	71,093 (32.3%)	17 (29.8%)	71,167 (32.3%)	54 (21.1%)	71,130 (32.3%)	507 (26.8%)	70,677 (32.4%)
60–69	225 (67.6%)	95,115 (43.3%)	34 (59.6%)	95,306 (43.3%)	177 (69.1%)	95,163 (43.3%)	1,260 (66.6%)	94,080 (43.1%)
70+	6 (1.8%)	1,116 (0.5%)	3 (5.3%)	1,119 (0.5%)	7 (2.7%)	1,115 (0.5%)	21 (1.1%)	1,101 (0.5%)
Deprivation								
1 (least deprived)	63 (18.9%)	44,297 (20.2%)	5 (8.6%)	44,355 (20.2%)	42 (16.4%)	44,318 (20.2%)	409 (21.6%)	43,951 (20.1%)
2	67 (20.1%)	43,727 (19.9%)	4 (7.0%)	43,790 (19.9%)	38 (14.8%)	43,756 (19.9%)	407 (21.5%)	43,387 (19.9%)
3	58 (17.4%)	43,058 (19.6%)	14 (24.6%)	43,102 (19.6%)	52 (20.3%)	43,064 (19.6%)	358 (18.9%)	42,758 (19.6%)
4	67 (20.1%)	43,319 (19.7%)	8 (14.0%)	43,378 (19.7%)	60 (23.4%)	43,326 (19.7%)	339 (17.9%)	43,047 (19.7%)
5 (most deprived)	78 (23.4%)	45,123 (20.5%)	26 (45.6%)	45,175 (20.5%)	63 (24.6%)	45,138 (20.5%)	378 (20.0%)	44,823 (20.5%)
Missing	0 (0.0%)	293 (0.1%)	0 (0.0%)	293 (0.1%)	1 (0.4%)	292 (0.1%)	1 (0.1%)	292 (0.1%)
Smoking status								
Never	79 (23.7%)	107,501 (48.9%)	17 (29.8%)	107,563 (48.9%)	78 (30.5%)	107,502 (48.9%)	725 (38.3%)	106,855 (49.0%)
Former	188 (56.5%)	83,294 (37.9%)	24 (42.1%)	83,458 (37.9%)	128 (50.0%)	83,354 (37.9%)	929 (49.1%)	82,553 (37.8%)
Current	63 (18.9%)	27,658 (12.6%)	15 (26.3%)	27,706 (12.6%)	48 (18.8%)	27,673 (12.6%)	226 (12.0%)	27,495 (12.6%)
Missing	3 (0.9%)	1,364 (0.6%)	1 (1.8%)	1,366 (0.6%)	2 (0.8%)	1,365 (0.6%)	12 (0.6%)	1,355 (0.6%)
Body mass index								
Normal/underweight	46 (13.8%)	54,984 (25.0%)	15 (26.3%)	55,015 (25.0%)	45 (17.6%)	54,985 (25.0%)	381 (20.1%)	54,649 (25.0%)
Overweight	154 (46.3%)	107,739 (49.0%)	32 (56.1%)	107,861 (49.0%)	131 (51.2%)	107,762 (49.0%)	924 (48.8%)	106,969 (49.0%)
Obese	130 (39.0%)	55,501 (25.3%)	8 (14.0%)	55,623 (25.3%)	79 (30.9%)	55,552 (25.3%)	573 (30.3%)	55,058 (25.2%)
Missing	3 (0.9%)	1,593 (0.7%)	2 (3.5%)	1,594 (0.7%)	1 (0.4%)	1,595 (0.7%)	14 (0.7%)	1,582 (0.7%)
Alcohol consumption								
Never (5)	22 (6.6%)	13,902 (6.3%)	8 (14.0%)	13,916 (6.3%)	27 (10.5%)	13,897 (6.3%)	84 (4.4%)	13,840 (6.3%)
<1 day per wk (4)	65 (19.5%)	35,648 (16.2%)	5 (8.8%)	35,708 (16.2%)	55 (21.5%)	35,658 (16.2%)	245 (12.9%)	35,468 (16.3%)
1–2 days per wk (3)	91 (27.3%)	56,722 (25.8%)	6 (10.5%)	56,807 (25.8%)	65 (25.4%)	56,748 (25.8%)	463 (24.5%)	56,350 (25.8%)
3–4 days per wk (2)	71 (21.3%)	57,351 (26.1%)	18 (31.6%)	57,404 (26.1%)	45 (17.6%)	57,377 (26.1%)	511 (27.0%)	56,911 (26.1%)

	Esophageal adenocarcinoma		Esophageal squamous cell carcinoma		Gastric cancer		Colorectal cancer	
	Cases n (%)	**Non-cases n (%)**	**Cases n (%)**	**Non-cases n (%)**	**Cases n (%)**	**Non-cases n (%)**	**Cases n (%)**	**Non-cases n (%)**
>4 days per wk (1)	82 (24.6%)	55,456 (25.2%)	19 (33.3%)	55,519 (25.2%)	63 (24.6%)	55,475 (25.2%)	584 (30.9%)	54,954 (25.2%)
Missing	2 (0.6%)	738 (0.3%)	1 (1.8%)	739 (0.3%)	1 (0.4%)	739 (0.3%)	5 (0.3%)	735 (0.3%)
Diabetes	48 (14.4%)	15,170 (6.9%)	3 (5.3%)	15,215 (6.9%)	29 (11.3%)	15,189 (6.9%)	201 (10.6%)	15,017 (6.9%)
Aspirin use	85 (25.5%)	40,814 (18.6%)	14 (24.6%)	40,885 (18.6%)	80 (31.3%)	40,819 (18.6%)	441 (23.3%)	40,458 (18.5%)
Statin use	115 (34.5%)	47,601 (21.7%)	18 (31.6%)	47,698 (21.7)	79 (30.9)	47,637 (21.7)	582 (30.8)	47,134 (21.6)

Table 2.

Characteristics of gastrointestinal cancer cases and non-cases among postmenopausal women in the UK Biobank

	Esophageal adenocarcinoma		Esophageal squamous cell carcinoma		Gastric cancer		Colorectal cancer	
	Cases n (%)	Non-cases n (%)	Cases n (%)	Non-cases n (%)	Cases n (%)	Non-cases n (%)	Cases n (%)	Non-cases n (%)
Age at baseline								
<50	0 (0.0%)	3,976 (2.7%)	0 (0%)	3,976 (2.7%)	0 (0.0%)	3,976 (2.7%)	12 (1.2%)	3,964 (2.7%)
50–59	15 (34.9%)	56,368 (38.3%)	10 (19.6%)	56,373 (38.3%)	15 (19.5%)	56,368 (38.3%)	274 (28.1%)	56,109 (38.4%)
60–69	28 (65.1%)	85,903 (58.4%)	41 (80.4%)	85,890 (58.4%)	60 (77.9%)	85,871 (58.4%)	672 (68.9%)	85,259 (58.3%)
70+	0 (0.0%)	890 (0.6%)	0 (0.0%)	890 (0.6%)	2 (2.6%)	888 (0.6%)	18 (1.8%)	872 (0.6%)
Deprivation								
1 (least deprived)	5 (11.6%)	30,415 (20.7%)	7 (13.7%)	30,413 (20.7%)	8 (10.4%)	30,412 (20.7%)	215 (22.0%)	30,205 (20.7%)
2	8 (18.6%)	30,702 (20.9%)	14 (27.5%)	30,696 (20.9%)	17 (22.1%)	30,693 (20.9%)	218 (22.3%)	30,492 (20.9%)
3	12 (27.1%)	30,246 (20.6%)	11 (21.6%)	30,247 (20.6%)	13 (16.9%)	30,245 (20.6%)	188 (19.3%)	30,070 (20.5%)
4	6 (13.9%)	29,028 (19.7%)	7 (13.7%)	29,027 (19.7%)	19 (24.7%)	29,015 (19.7%)	181 (18.6%)	28,853 (19.7%)
5 (most deprived)	12 (27.9%)	26,596 (18.1%)	12 (23.5%)	26,596 (18.1%)	20 (26.0%)	26,588 (18.1%)	173 (17.7%)	26,435 (18.1%)
Missing	0 (0.0%)	150 (0.1%)	0 (0.0%)	150 (0.1%)	0 (0.0%)	150 (0.1%)	1 (0.1%)	149 (0.1%)
Smoking status								
Never	18 (41.9%)	85,647 (58.2%)	26 (51.0%)	85,639 (58.2%)	47 (61.0%)	85,618 (58.2%)	545 (55.8%)	85,120 (58.2%)
Former	19 (44.2%)	49,092 (33.4%)	18 (35.3%)	49,093 (33.4%)	23 (29.9%)	49,088 (33.4%)	354 (36.3%)	48,757 (33.4%)
Current	6 (13.9%)	11,826 (8.0%)	7 (13.7%)	11,825 (8.0%)	6 (7.8%)	11,826 (8.0%)	75 (7.7%)	11,757 (8.0%)
Missing	0 (0.0%)	872 (0.4%)	0 (0.0%)	572 (0.4%)	1 (1.3%)	571 (0.4%)	2 (0.2%)	570 (0.4%)
Body mass index								
Normal/underweight	13 (30.2%)	55,905 (38.0%)	25 (49.0%)	55,893 (38.0%)	31 (40.3%)	55,887 (38.0%)	351 (36.0%)	55,567 (38.0%)
Overweight	16 (37.2%)	56,065 (38.1%)	20 (39.2%)	56,061 (38.1%)	28 (36.4%)	56,053 (38.1%)	386 (39.5%)	55,695 (38.1%)
Obese	14 (32.6%)	34,461 (23.4%)	5 (9.8%)	34,470 (23.4%)	18 (23.4%)	34,457 (23.4%)	233 (23.9%)	34,242 (23.4%)
Missing	0 (0.0%)	706 (0.5%)	1 (2.0%)	705 (0.5%)	0 (0.0%)	706 (0.5%)	6 (0.6%)	700 (0.5%)
Alcohol consumption								
Never	5 (11.6%)	14,687 (10.0%)	13 (25.5%)	14,679 (10.0%)	6 (7.8%)	14,686 (10.0%)	109 (11.2%)	14,583 (10.0%)
<1 day per wk	15 (34.9%)	40,608 (27.6%)	12 (23.5%)	40,611 (27.6%)	24 (31.2%)	40,599 (27.6%)	281 (28.8%)	40,342 (27.6%)
1–2 days per wk	11 (25.6%)	36,508 (24.8%)	6 (11.8%)	36,513 (24.8%)	21 (27.3%)	36,498 (24.8%)	236 (24.2%)	36,283 (24.8%)
3–4 days per wk	7 (16.3%)	29,790 (20.2%)	6 (11.8%)	29,791 (20.3%)	16 (20.8%)	29,781 (20.2%)	171 (17.5%)	29,626 (20.3%)

	Esophageal adenocarcinoma		Esophageal squamous cell carcinoma		Gastric cancer		Colorectal cancer	
	Cases n (%)	Non-cases n (%)	Cases n (%)	Non-cases n (%)	Cases n (%)	Non-cases n (%)	Cases n (%)	Non-cases n (%)
>4 days per wk	5 (11.6%)	25,426 (17.3%)	14 (27.4%)	25,417 (17.3%)	9 (11.7%)	25,422 (17.3%)	178 (18.2%)	25,253 (17.3%)
Missing	0 (0.0%)	118 (0.1%)	0 (0.0%)	118 (0.1%)	1 (1.3%)	117 (0.1%)	1 (0.1%)	117 (0.1%)
Diabetes	3 (7.0%)	5,836 (4.0%)	2 (3.9%)	5,837 (4.0%)	9 (11.7%)	5,830 (4.0%)	50 (5.1%)	5,789 (4.0%)
Aspirin use	3 (7.0%)	17,392 (11.8%)	6 (11.8%)	17,389 (11.8%)	17 (22.1%)	17,378 (11.1%)	136 (13.9%)	17,259 (11.8%)
Statin use	7 (16.3%)	22,076 (15.0%)	9 (17.7%)	22,074 (15.0%)	19 (24.7%)	22,064 (15.0%)	180 (18.4%)	21,903 (15.0%)

Table 3.

Prediagnostic sex hormone concentrations and risk of gastrointestinal cancers in men in the UK Biobank

		Esophageal adenocarcinoma		Esophageal squamous cell carcinoma		Gastric cancer		Colorectal cancer	
	Person-years	Cases	Adjusted HR (95% CI)†	Cases	Adjusted HR (95% CI)†	Cases	Adjusted HR (95% CI)†	Cases	Adjusted HR (95% CI)†
SHBG (nmol/L)									
<27.84	331,099	56	1.00	8	1.00	39	1.00	356	1.00
27.84 to <36.86	327,675	62	0.92 (0.64, 1.33)	10	1.03 (0.39, 2.74)	40	0.83 (0.53, 1.31)	419	0.99 (0.85, 1.14)
36.86 to <48.06	325,641	77	1.10 (0.78, 1.57)	13	1.09 (0.43, 2.81)	67	1.37 (0.91, 2.07)	394	0.84 (0.72, 0.97)
≥48.06	321,946	84	1.15 (0.80, 1.64)	19	1.24 (0.49, 3.13)	78	1.43 (0.95, 2.17)	452	0.89 (0.77, 1.04)
Missing		54	P_{trend}=0.29	7	P_{trend}=0.60	32	P_{trend}=0.01	271	P_{trend}=0.04
Testosterone (nmol/L)									
<9.44	352,334	102	1.00	9	1.00	64	1.00	505	1.00
9.44 to <11.63	353,707	73	0.87 (0.64, 1.17)	18	2.19 (0.95, 5.07)	52	0.88 (0.60, 1.28)	442	0.96 (0.84, 1.09)
11.63 to <14.14	354,207	72	0.93 (0.68, 1.27)	9	1.05 (0.40, 2.76)	62	1.16 (0.81, 1.66)	437	0.99 (0.87, 1.13)
≥14.14	353,475	63	0.90 (0.65, 1.26)	19	2.14 (0.91, 5.01)	60	1.24 (0.85, 1.79)	362	0.88 (0.77, 1.02)
Missing		23	P_{trend}=0.62	2	P_{trend}=0.27	18	P_{trend}=0.14	146	P_{trend}=0.16
Free testosterone (nmol/L)									
<0.18	320,069	101	1.00	15	1.00	87	1.00	541	1.00
0.18 to <0.21	323,835	78	0.97 (0.72, 1.31)	9	0.67 (0.29, 1.54)	42	0.56 (0.38, 0.81)	411	0.89 (0.78, 1.01)
0.21 to <0.25	326,815	60	0.90 (0.65, 1.25)	14	1.12 (0.53, 2.37)	51	0.88 (0.62, 1.26)	360	0.91 (0.79, 1.04)
≥0.25	329,622	38	0.79 (0.54, 1.17)	12	1.32 (0.60, 2.92)	40	0.90 (0.60, 1.34)	302	0.99 (0.86, 1.15)
Missing		56	P_{trend}=0.23	7	P_{trend}=0.37	36	P_{trend}=0.72	278	P_{trend}=0.72
Estradiol (pmol/L)									
<175.0	1,205,119	259	1.00	46	1.00	202	1.00	1506	1.00
≥175.0	122,367	31	1.17 (0.81, 1.70)	6	1.29 (0.55, 3.03)	22	1.07 (0.69, 1.66)	137	0.91 (0.76, 1.08)
Missing		43		5		32		249	

†Adjusted for age at baseline, deprivation, smoking status, BMI, alcohol consumption (except esophageal adenocarcinoma), diabetes, aspirin use and statin use (colorectal cancer only).

Table 4.

Prediagnostic sex hormone concentrations and risk of gastrointestinal cancers in women in the UK Biobank

		Esophageal adenocarcinoma		Esophageal squamous cell carcinoma		Gastric cancer		Colorectal cancer	
	Person-years	Cases	Adjusted HR (95% CI)†	Cases	Adjusted HR (95% CI)†	Cases	Adjusted HR (95% CI)†	Cases	Adjusted HR (95% CI)†
SHBG (nmol/L)									
<39.94	233,639	11	1.00	6	1.00	20	1.00	239	1.00
39.94 to <56.34	230,792	9	0.89 (0.36, 2.19)	13	1.88 (0.70, 5.04)	21	1.04 (0.55, 1.96)	210	0.91 (0.75, 1.10)
56.34 to <77.13	218,795	8	1.91 (0.35, 2.39)	9	1.28 (0.44, 3.74)	8	0.36 (0.15, 0.88)	219	1.01 (0.83, 1.23)
≥77.13	178,196	8	1.21 (0.44, 3.31)	14	2.03 (0.72, 5.75)	16	0.97 (0.46, 2.01)	171	0.97 (0.78, 1.21)
Missing		7	P_{trend}=0.76	9	P_{trend}=0.33	12	P_{trend}=0.40	137	P_{trend}=0.94
Testosterone (nmol/L)									
<0.54	256,948	12	1.00	19	1.00	19	1.00	295	1.00
0.54 to <0.91	245,946	5	0.44 (0.15, 1.23)	16	0.89 (0.45, 1.75)	19	1.17 (0.61, 2.23)	211	0.78 (0.65, 0.93)
0.91 to <1.29	230,301	7	0.66 (0.26, 1.67)	5	0.33 (0.12, 0.88)	18	1.22 (0.63, 2.36)	206	0.83 (0.69, 0.99)
≥1.29	212,509	15	1.50 (0.70, 3.24)	9	0.66 (0.30, 1.47)	15	1.14 (0.57, 2.27)	191	0.83 (0.69, 1.00)
Missing		4	P_{trend}=0.23	2	P_{trend}=0.09	6	P_{trend}=0.67	73	P_{trend}=0.05
Free testosterone (nmol/L)									
<0.006	219,576	9	1.00	18	1.00	17	1.00	260	1.00
0.006 to <0.01	215,286	5	0.57 (0.19, 1.69)	10	0.65 (0.29, 1.41)	16	1.08 (0.54, 2.17)	201	0.81 (0.68, 0.98)
0.01 to <0.02	213,233	10	1.12 (0.45, 2.77)	10	0.70 (0.32, 1.53)	16	1.11 (0.55, 2.24)	183	0.76 (0.63, 0.92)
≥0.02	209,615	12	1.30 (0.53, 3.20)	4	0.32 (0.11, 0.98)	15	1.12 (0.54, 2.31)	191	0.80 (0.66, 0.97)
Missing		7	P_{trend}=0.35	9	P_{trend}=0.05	13	P_{trend}=0.75	141	P_{trend}=0.01
Estradiol (pmol/L)									
<175.0	853,825	34	1.00	45	1.00	67	1.00	838	1.00
≥175.0	33,918	1	0.94 (0.13, 6.94)	0	-	0	-	20	0.85 (0.54, 1.33)
Missing		8		6		10		118	

†Adjusted for age at baseline, deprivation, smoking status, BMI, alcohol consumption (except esophageal adenocarcinoma), diabetes, aspirin use and statin use (colorectal cancer only).