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Novelty and impact:

Incidence of oesophageal and gastric cancer is higher among men than among women. In the first prospective study of a range of male hormonal and reproductive factors and upper gastrointestinal cancer risk, the authors found some evidence that male pattern baldness was associated with gastric cancer risk, particularly for frontal male pattern baldness. These findings provide support for future studies that directly test circulating sex steroid hormone levels in relation to upper gastrointestinal cancer risk.

Article category: Cancer epidemiology

Abbreviations: BMI, body mass index; CIs, confidence intervals; HR, hazard ratio; HRT, hormone replacement therapy; ICD, International Classification of Diseases; ONS, Office of National Statistics; UK, United Kingdom.

ABSTRACT

Incidence of upper gastrointestinal cancers of the oesophagus and stomach show a strong unexplained male predominance. Hormonal and reproductive factors have been associated with upper gastrointestinal cancers in women but there is little available data on men. To investigate this, we included 219,425 men enrolled in the UK Biobank in 2006–2010. Baseline assessments provided information on hormonal and reproductive factors (specifically hair baldness, number of children fathered, relative age at first facial hair and relative age voice broke) and incident oesophageal or gastric cancers were identified through linkage to UK cancer registries. Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. During 8 years of follow-up, 309 oesophageal 210 gastric cancers occurred. There was some evidence that male pattern baldness, was associated with gastric cancer risk (adjusted HR 1.35, 95% CI 0.97, 1.88), particularly for frontal male pattern baldness (adjusted HR 1.52, 95% CI 1.02, 2.28). There was little evidence of association between other hormonal and reproductive factors and risk of oesophageal or gastric cancer, overall or by histological subtype. In the first study of a range of male hormonal and reproductive factors and gastric cancer, there was a suggestion that male pattern baldness, often used as a proxy of sex hormone levels, may be associated with gastric cancer. Future prospective studies that directly test circulating sex steroid hormone levels in relation to upper gastrointestinal cancer risk are warranted.

Keywords: sex hormones, men, reproductive factors, upper gastrointestinal cancers, UK Biobank

INTRODUCTION

Upper gastrointestinal cancers of the oesophagus and stomach account for 455,800 and 951,600 new cancers diagnosed worldwide, respectively[1]. Significant morbidity and mortality is associated with these cancers; in the UK, only 15% of oesophageal and 19% of gastric cancer patients survive more than five years after diagnosis[2-4], underlining the need for better understanding of aetiological factors to aid prevention. The most striking epidemiological feature of these cancers is their strong male predominance[5,6], which is most obvious for adenocarcinomas[7,8] and is suggestive of sex steroid hormone involvement (including oestrogens and androgens).

Testosterone, an important anabolic hormone, increases tissue proliferation and has been shown to stimulate the growth of cancer cells *in vitro*[9,10]. Increased levels of testosterone in men and women has been associated with a 30-80% increase in early death after cancer diagnosis[11]. With regard to upper gastrointestinal cancers specifically, mounting preclinical evidence suggests that androgens and androgen receptor-signalling may be important in their pathogenesis; testosterone supresses wound healing and castration in male rats has been shown to inhibit gastric carcinogenesis[12]. Androgen receptor, a key mediator of inflammatory signals in oesophageal cancer progression[13], is expressed in both oesophageal and gastric cancer tissues[14-18] and has been correlated with poorer prognosis in gastric cancer patients[18]. Moreover, its overexpression has been shown to promote cell migration, invasion and proliferation in oesophageal and gastric cancer *in vivo*[13,19,20].

Rates of oesophageal cancer (and specifically oesophageal adenocarcinoma) among men with a previous prostate cancer diagnosis are lower than expected, indicating that the androgen-lowering effects of androgen deprivation therapy may be contributing to a reduced oesophageal cancer risk[21,22]. Only one study has evaluated the influence of reproductive

factors and risk of upper gastrointestinal cancer in men[23]. Lu et al. observed significant reductions in oesophageal adenocarcinoma and oesophageal squamous cell carcinoma risk in men who had fathered children and in men who were older at first fatherhood in a case-control study that utilised administrative record linkages in Sweden[23]. However, only oesophageal cancer was evaluated in this study and other important markers of male sex hormone exposure (such as male pattern baldness pattern) were not investigated. Further aetiological research to understand why upper gastrointestinal cancer rates are so much higher in men than women has been highlighted as a priority in the gastrointestinal cancer field[7].

We therefore prospectively investigated novel associations between hormonal and reproductive factors and risk of oesophageal and gastric cancer in a large UK population-based cohort of middle-aged men.

METHODS

Data sources

The UK Biobank is a large prospective cohort study which recruited over 500,000 men and women aged 40-69 years from one of 22 assessment centres located across England, Scotland and Wales between 2006 and 2010[24]. Touchscreen questionnaires were used at baseline to obtain information on a wide range of risk factors for chronic disease (e.g., demographics, diet, lifestyle, prior medical history and reproductive factors). Anthropometric measurements including height, weight, waist and hip circumference were also obtained at baseline. The UK Biobank is routinely linked to UK cancer registry data from the Health and Social Care Information Centre (in England and Wales) and the Scottish Cancer Registry (in Scotland) and death records from the UK Office of National Statistics (ONS). The UK Biobank was

approved by the North West Multi-Centre Research Ethics Committee, and all participants provided written informed consent.

Study population

We included men enrolled in the UK Biobank without a previous history of cancer (excluding non-melanoma skin cancer) at or before baseline. Incident cases of oesophageal (ICD 10 C15) and gastric cancer (ICD 10 C16) were identified through linkage to UK national cancer registries. Cases of oesophageal and gastric cancer were further classed by histology, as adenocarcinoma (ICD-O morphology codes 8140–8573) or squamous cell carcinoma (ICD-O 8050–8082). Gastric cancers were classed by location, where possible, as cancers of the gastric cardia (C16.0) and gastric non-cardia sites (C16.1–16.5). Participants were followed from baseline until cancer diagnosis, emigration, death or end of follow-up (October 2014).

Hormonal and reproductive factors

Hormonal exposures included male pattern baldness and male pattern baldness pattern, fathered children status, number of children fathered, relative age at first facial hair and relative age at first voice broke were obtained from participants at baseline (from touchscreen questions). Participants with missing data for an exposure of interest were excluded from the relevant analysis.

Covariates

Information on risk factors for upper gastrointestinal cancers was retrieved from electronic touchscreen records collected at baseline and included smoking history, alcohol consumption, and dietary factors (e.g. average weekly intakes of fruit and vegetables, red and processed

meat). Body mass index (BMI) and waist-to-hip ratio was measured at baseline. Socioeconomic deprivation was retrieved from Townsend score (based upon postcode of usual residence[25]).

Statistical analysis

Baseline cohort characteristics were compared between oesophageal or gastric cancer cases and non-cases using Chi-square tests for categorical variables. Cox proportional hazards regression models (with age as the underlying timescale variable) were used to estimate the unadjusted and adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI) for associations between hormonal and reproductive factors and risks of oesophageal and gastric cancer. All analyses were adjusted for age (as the underlying timescale), Townsend deprivation index (presented as quintiles), smoking status (by pack-years; never, former <20 pack-years, former 20+ pack-years, current <20 pack years and current ≥20 pack years), alcohol intake (never drinker, former drinker, current light-moderate/occasional drinker [<14 units per week], current heavy drinker [14+ units per week]), body mass index (BMI) (<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25-29.9 kg/m^2, ≥30 kg/m^2), waist-to-hip ratio according to whether it met the guideline of the International Diabetes Federation criteria (≤94cm in men)[26] and average weekly intakes of fruit and vegetables (<2, 2-5, >5). Additional adjustments were made for average weekly intakes of red meat (Never/ <1, 1-3, >3) and processed meat (Never/ <1, 1, >1). Sub-group analyses were conducted by histology (oesophageal adenocarcinoma and squamous cell carcinoma) and gastric cancer location (gastric cardia and non-cardia).

RESULTS

UK Biobank cohort

A total of 219,426 men were included in the final cohort, following exclusion of 9,748 participants with a previous history of cancer. Of these, 309 men were diagnosed with oesophageal cancer and 210 were diagnosed with gastric cancer during a mean follow-up of 5.5 years (maximum 8.5 years). Baseline characteristics of oesophageal and gastric cancer cases and non-cases are presented in Table 1. Oesophageal and gastric cancer cases were more likely to be older, be current and former heavy smokers, be former alcohol drinkers, be obese, and have a higher waist-to-hip ratio while oesophageal cancer cases were also more likely to report higher weekly intakes of red and processed meat.

Association between hormonal and reproductive factors and risk of oesophageal and gastric cancer

Results for associations between male hormonal and reproductive factors and risk of oesophageal and gastric cancer are listed in Table 2. Overall, no significant associations were observed for any of the hormonal exposures and risk of oesophageal cancer. For gastric cancer, there was a suggestion that men who reported having male pattern baldness had an increased risk of gastric cancer compared to those who reported no male pattern baldness, albeit the result failed to reach statistical significance (adjusted HR 1.35, 95% CI 0.97, 1.88; p=0.08). Frontal only male pattern baldness was significantly associated with an increased risk of gastric cancer compared to no male pattern baldness (adjusted HR 1.52, 95% CI 1.02, 2.28). Other markers of sex hormone exposure were not associated with gastric cancer including fathered children, increasing number of children fathered, relative age at first facial

hair or relative age voice broke. The findings were not materially altered following additional adjustments for red and processed meat intakes (data not shown).

Sub group analysis by histological subtype and tumour location

Results by histological subtype including oesophageal adenocarcinoma, oesophageal squamous cell carcinoma and gastric adenocarcinoma are presented in Table 3. Overall, no significant associations were observed for any of the examined hormonal or reproductive factors and risk of oesophageal adenocarcinoma. Fathering children was associated with a reduction in oesophageal squamous cell carcinoma in unadjusted analysis (HR 0.48, 95% CI 0.24, 0.97); however, after adjustment for potential confounders, results attenuated and became statistically non-significant (adjusted HR 0.56, 95% CI 0.27, 1.15). Results for gastric adenocarcinoma were broadly similar to that of gastric cancer with a weak positive association observed for male pattern baldness, although not statistically significant (adjusted HR 1.39, 95% CI 0.97, 1.98; p=0.07), Table 3.

Results by gastric cancer location are listed in Table 4. Male pattern baldness was associated with a non-significant increase in risk of gastric cardia cancer (adjusted HR 1.59, 95% CI 0.97, 2.61, p=0.07). Hazard ratios remained elevated with increasing extent of baldness (e.g., frontal and severe vertex baldness; adjusted HR 1.58, 95% CI 0.86, 2.93). An increase in gastric non-cardia cancer in men who reported male pattern baldness was not apparent (adjusted HR 1.13, 95% CI 0.72, 1.76). Similarly, no other significant associations were identified for other hormonal and reproductive factors and risk of gastric non-cardia cancer. Results were similar after additional adjustment for red and processed meat intakes (data not shown).

DISCUSSION

Our study, which utilised prospectively recorded information from the UK Biobank, found little evidence of associations between sex hormone and reproductive factors and risk of oesophageal or gastric cancer in men however frontal male pattern baldness specifically was associated with a significant increase in gastric cancer risk. As this is the first study to evaluate the association between male pattern baldness and risk of gastric cancer, further epidemiological studies are required to replicate our findings.

Because of the integral role of androgenic action in hair loss, previous studies on male pattern baldness and cancer risk have focused on prostate cancer risk[27,28]. However, in the Health Professionals Follow-Up Study, Keum et al.[29] recently reported that subtypes of male pattern baldness at age 45 (including frontal only baldness and frontal-plus-mild-vertex baldness) were significantly associated with an increased risk of colon cancer, a cancer which also demonstrates a sex disparity in incidence, albeit not as marked as oesophageal or gastric cancer[4].

We found no significant associations between markers of hormonal exposure and risk of oesophageal cancer or oesophageal histological subtypes. In contrast to our study, a large case-control study in Sweden found significant reductions in oesophageal adenocarcinoma (OR 0.76, 95% CI 0.65, 0.90) and oesophageal squamous cell carcinoma (OR 0.57, 95% CI 0.49, 0.67) in men who had fathered children but no significant dose-response was observed for increasing number of children fathered[23]. The authors found similar effects for reproductive factors in women and went on to suggest the possibility of confounding by non-hormonal exposures[23]. Nevertheless, fatherhood and number of children have been shown to independently influence testosterone levels in men[30]. Differences in methodologies may partly explain the discrepancies with our findings; for example, information on number of

children fathered was obtained from Swedish registries whereas we used self-report measures. Similar to our study though, Lu et al. found no significant relationship for increasing number of children fathered[23]. In women, although results from individual studies have been inconsistent, pooled analyses have found positive associations for menopause[31] and inverse associations for breastfeeding[31,32], longer years of fertility[33] and HRT use[31,33,34], providing some support that endogenous and exogenous oestrogen exposure may lower oesophageal and gastric cancer risk in women.

The weak evidence of an association between frontal baldness and gastric cancer risk is difficult to interpret and requires confirmation. If real, this could reflect that male pattern male pattern baldness, or androgenetic alopecia, is mediated by dihydrotestosterone, the potent metabolite of testosterone[35]. There is growing evidence suggesting that male pattern balding status could serve as a clinical marker for circulating sex hormone concentrations[36-38]. Moreover, preclinical experimental evidence supports a gastric cancer-promoting effect for testosterone[12] and androgen receptor overexpression *in vivo* has been shown to promote cell migration, invasion and proliferation in gastric cancer[20]. Taken together, it is possible that androgens might play a role in the development of these cancers, and could provide a logical explanation for the male dominance in their incidence. Better understanding of whether androgen receptors influence the development of oesophageal and gastric cancer is essential considering that intervention before malignancy presents an opportunity for prevention.

Few studies have investigated circulating testosterone levels in relation to risk of oesophageal or gastric cancer. An Irish population-based case-control study identified a higher ratio of androgens to oestrogens in oesophageal adenocarcinoma patients compared to controls, something which was particularly marked for testosterone:oestradiol ratio[39]. In a small case-

control study of 33 individuals, pre-operative serum testosterone levels were found to be significantly higher in oesophageal adenocarcinoma patients compared to age-matched controls[17]. However, testosterone levels were measured following oesophageal adenocarcinoma diagnosis and following surgery, testosterone levels in oesophageal adenocarcinoma cases decreased to levels of the controls[17]. Barrett's oesophagus, the precursor of oesophageal adenocarcinoma, has been positively associated with circulating free androgens in men[40,41] and was particularly marked in men with higher waist-to-hip ratios[41]. These results suggest that the balance of androgens to oestrogens could be important in the progression from Barrett's to oesophageal adenocarcinoma but cautious interpretation is required as sex hormone levels were measured post-diagnosis (in cases) meaning reverse causality cannot be ruled out[17,39-41,]. Population-based studies with prospective blood collection are therefore required to replicate these findings. No study has investigated the influence of circulating sex hormone levels on gastric cancer risk. Although we adjusted all analyses for both BMI and waist-hip ratio as measures of total and abdominal obesity, respectively, further study of the interaction between obesity, androgens, and male gender in the genesis of upper gastrointestinal cancers is required. Given that abdominal obesity is particularly associated with both oesophageal adenocarcinoma and gastric cancer risk[42] and obese individuals generally have lower circulating levels of androgens[43,44] (possibly due to the conversion of testosterone to oestrogens by aromatase[45], detailed investigation of steroid hormone metabolism in adipose tissue located in close proximity to the oesophagus and stomach is also warranted.

Strengths and weaknesses

We utilised a large, well-characterised, population-based cohort of middle-aged men with prospectively collected information on hormonal and reproductive factors, therefore minimising biases associated with retrospective study designs. Linkage to national cancer registries allowed for robust verification of oesophageal and gastric cancer cases, and allowed for analysis by histological subtype and tumour location. The availability of detailed information on a range of lifestyle factors including anthropometric measures and dietary intake (e.g. fruit and vegetable intake) was also of benefit to limit potential confounding. We were unable to account for dietary factors that have previously been implicated with sex hormones, for example isoflavones and phyto-oestrogens[46,47], however epidemiological studies have failed to show associations between intake of these compounds and circulating sex hormone concentrations[48,49]. There was missing data for a small proportion of participants meaning that we cannot rule out the potential for residual confounding. Data on hormonal and reproductive factors was self-reported and was therefore subject to misclassification. This may be particularly relevant for information recalled from decades prior to study recruitment such as relative age at first voice broke and relative age at first facial hair. Studies in women however have indicated that early hormonal factors such as age at menarche are recalled with reasonable accuracy[50] which may extend to men. Moreover, the validity of self-reported male pattern baldness in epidemiological studies has been shown to have sufficient accuracy to ensure reliability and validity of results[51]. The UK Biobank had a relatively low participation response rate of 5% which could suggest that it is not representative of the sampling population and there may be potential for "healthy volunteer" selection bias. However, considering its large size and population variability in exposures, valid assessment of exposure-disease relationships may be widely generalizable and does not require participants to be representative of the population at large[24,52]. Approximately 95% of the UK Biobank cohort is of white ethnicity; therefore, our results may not be generalisable

to other ethnicities. Despite the large size of our cohort, some sub-group analyses by tumour type were limited by small numbers, in particular oesophageal squamous cell carcinoma. Gastroesophageal reflux is a strong risk factor for oesophageal adenocarcinoma and, although we did not have reliable information on reflux in the UK Biobank, the prevalence of this exposure and the effect on oesophageal adenocarcinoma risk have been shown to be similar in both men and women[53] Indeed, associations between reflux with oesophageal adenocarcinoma in females have been reported to be similar if not stronger compared to males[54], suggesting that reflux is unlikely to be hormonally mediated. We did not have information on *Helicobacter pylori* (*H. pylori*) status of participants but *H. pylori* has shown a similar prevalence in men and women[55,56] and previous studies in females indicate that baseline *H. pylori* serostatus does not modify associations between hormonal and reproductive factors and risk of gastric cancer[57,58]. We did not have robust information on prior Barrett's oesophagus, the precursor condition to oesophageal adenocarcinoma; however, only a small proportion of subjects with known Barrett's oesophagus progress to oesophageal adenocarcinoma[59]. Finally, although we had information on a range of surrogate markers for lifetime sex hormone exposure, which enabled novel investigations of upper gastrointestinal cancer risk, prospective studies with direct assessments of circulating oestrogen and androgen concentrations (as well as their ratios) are needed to provide a more accurate assessment of the role of sex hormones in these malignancies.

Conclusion

In conclusion, in the first prospective study to investigate a range of male hormonal factors and risk of oesophageal and gastric cancer, there was suggestive evidence that male pattern baldness may be associated with an increased gastric cancer risk. Considering the complex patterns of expression of both oestrogen and androgen receptors in oesophageal and gastric

cancer, prospective studies of the association between sex steroid hormone levels (as well as their ratios) and risk of upper gastrointestinal cancers in both sexes are required.

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References:

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global Cancer Statistics. CA Cancer J Clin 2012; 65:87-108.

2. Cancer Research UK. Oesophageal Cancer Survival Statistics. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/survival.

3. Cancer Research UK. Stomach Cancer Survival Statistics. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer/survival.

4. Office for National Statistics. Cancer Incidence and Mortality in the United Kingdom, 2008-10. Stat Bull. 2012.

5. Lagergren J, Lagergren P. Recent developments in esophageal adenocarcinoma. CA Cancer J Clin. 2013; 63:232–248.

6. Chandanos E, Lagergren J. Oestrogen and the enigmatic male predominance of gastric cancer. Eur J Cancer. 2008; 44: 2397-2403.

7. Coupland VH, Allum W, Blazeby JM, Mendall MA, Hardwick RH, Linklater KM, et al. Incidence and survival of oesophageal and gastric cancer in England between 1998 and 2007, a population-based study. BMC Cancer. 2012; 12:11.

8. Colquhoun A, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut. 2015; 64:1881-8.

9. Tutton PJ BD. The influence of androgens, anti-androgens, and castration on cell proliferation in the jejunal and colonic crypt epithelia, and in dimethylhydrazine-induced adenocarcinoma of rat colon. Virchows Arch B Cell Pathol Incl Mol Pathol.

1982; 38:351–5.

10. Maasberg M, Rotsch M, Jaques G, Enderle-Schmidt U, Weehle R HK. Androgen receptors, androgen-dependent proliferation, and 5 alpha-reductase activity of small-cell lung cancer cell lines. Int J Cancer. 1989; 43:685–91.

11. Ørsted DD, Nordestgaard BG, Bojesen SE. Plasma testosterone in the general population, cancer prognosis and cancer risk: A prospective cohort study. Ann Oncol. 2014; 25:712–8.

12. Furukawa H, Iwanaga T, Koyama H, Taniguchi H. Effect of Sex Hormones on Carcinogenesis in the Stomachs of Rats. Cancer Res. 1982; 42:5181-5182.

13. Dong H, Xu J, Li W, Gan J, Lin W, Ke J, et al. Reciprocal androgen receptor/interleukin-6 crosstalk drives oesophageal carcinoma progression and contributes to patient prognosis. J Pathol. 2017; 241: 448–462.

14. Jukic Z, Radulovic P, Stojković R, Mijic A, Grah J KB et al. Gender Difference in Distribution of Estrogen and Androgen Receptors in Intestinal-type Gastric Cancer. Anticancer Res. 2017;37:197-202.

15. Rashid F, Khan RN, Iftikhar SY. Probing the link between oestrogen receptors and oesophageal cancer. World J Surg Oncol. 2010; 8:9.

16. Gan L, He J, Zhang X, Zhang Y-J, Yu G-Z, Chen Y, et al. Expression profile and prognostic role of sex hormone receptors in gastric cancer. BMC Cancer. 2012;12:1

17. Awan AK, Iftikhar SY, Morris TM, Clarke PA, Grabowska AM, Waraich N, et al. Androgen receptors may act in a paracrine manner to regulate oesophageal adenocarcinoma growth. Eur J Surg Oncol. 2007; 33 561-568.

18. Kominea A, Konstantinopoulos PA, Kapranos N, Vandoros G, Gkermpesi M AP et al.

Androgen receptor (AR) expression is an independent unfavorable prognostic factor in gastric cancer. J Cancer Res Clin Oncol. 2004;130:253-258.

19. Sukocheva OA, Li B, Due SL, Hussey DJ, Watson DI. Androgens and esophageal cancer: What do we know? World J Gastroenterol 2015; 21: 6146-6156

20. Zhang B, Du T, Zang M, Chang Q, Fan Z, Li J, et al. Androgen receptor promotes gastric cancer cell migration and invasion via AKT-phosphorylation dependent upregulation of matrix metalloproteinase 9. Oncotarget. 2014;5:10584–95.

21. Cooper SC, Croft S, Day R, Thomson CS, Trudgill NJ. Patients with prostate cancer are less likely to develop oesophageal adenocarcinoma: could androgens have a role in the aetiology of oesophageal adenocarcinoma? Cancer Causes Control. 2009; 20:1363–1368.

22. Cooper SC, Trudgill NJ. Subjects with prostate cancer are less likely to develop esophageal cancer: Analysis of SEER 9 registries database. Cancer Causes Control. 2012;23:819–25.

23. Lu Y, Lagergren J. Reproductive factors and risk of oesophageal cancer, a population-based nested case–control study in Sweden. Br J Cancer. 2012; 107:564-569.

24. Allen N, Sudlow C, Downey P, Peakman T, Danesh J, Elliott P, et al. UK Biobank: Current status and what it means for epidemiology. Heal Policy Technol. 2012; 1:123-126.

25. Townsend P. Deprivation. J Soc Policy. 1987;16:125–46.

26. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. International Diabetes Federation (IDF). 2006.

27. Zhou CK, Levine PH, Cleary SD, Hoffman HJ, Graubard BI, Cook MB. Male pattern

baldness in relation to prostate cancer – specific mortality : a prospective analysis in the NHANES I Epidemiologic Follow-up Study. Am J Epidemiol. 2016;183:210-217.

28. Zhou CK, Littman AJ, Levine PH, Hoffman HJ, Cleary SD, White E, Cook MB. Male pattern baldness in relation to prostate cancer risks: an analysis in the VITamins And Lifestyle (VITAL) cohort study. Prostate. 2015;75:415-423.

29. Keum N, Cao Y, Lee DH, Park SH, Rosner B, Fuchs CS et al. Male pattern baldness and risk of colorectal neoplasia. Br J Cancer. 2016; 114:110-117.

30. Jasienska G, Jasienski M, Ellison PT. Testosterone levels correlate with the number of children in human males, but the direction of the relationship depends on paternal education. Evol Hum Behav. 2012; 33; 665–671.

31. Wang BJ, Zhang B, Yan SS, Li ZC, Jiang T, Hua CJ, et al. Hormonal and reproductive factors and risk of esophageal cancer in women: a meta-analysis. Dis Esophagus 2016; 29:448-54.

32. Cronin-Fenton DP, Murray LJ, Whiteman DC, Cardwell C, Webb PM, Jordan SJ, et al. Reproductive and sex hormonal factors and oesophageal and gastric junction adenocarcinoma: A pooled analysis. Eur J Cancer. 2010; 46: 2067-2076.

33. Camargo MC, Goto Y, Zabaleta J, Morgan DR, Correa P, Rabkin CS. Sex Hormones, Hormonal Interventions, and Gastric Cancer Risk: a Meta-analysis. Cancer Epidemiol Biomarkers Prev. 2012; 21:20-38.

34. Lagergren K, Lagergren J, Brusselaers N. Hormone replacement therapy and oral contraceptives and risk of oesophageal adenocarcinoma: A systematic review and meta-analysis. Int J Cancer. 2014; 135: 2183–2190.

35. Ellis JA, Sinclair RD. Male pattern baldness: current treatments, future prospects. Drug Discov Today. 2008; 13(17-18):791-7.

36. Bang HJ, Yang YJ, Lho DS, Lee WY, Sim WY, Chung BC. Comparative studies on level of androgens in hair and plasma with premature male-pattern baldness. J Dermatol Sci 2004;34(1):11-16.

37. Sanke S, Chander R, Jain A, Garg T, Yadav P. A Comparison of the Hormonal Profile of Early Androgenetic Alopecia in Men With the Phenotypic Equivalent of Polycystic Ovarian Syndrome in Women. JAMA Dermatol 2016;152(9):986-991.

38. Cipriani R, Ruzza G, Foresta C, Veller Fornasa C, Peserico A. Sex hormone-binding globulin and saliva testosterone levels in men with androgenetic alopecia. Br J Dermatol 1983;109(3):249-252.

39. Petrick JL, Falk RT, Hyland PL, Carron P, Pfeiffer RM, Wood SN et al. Association between circulating levels of sex steroid hormones and esophageal adenocarcinoma in the FINBAR study. PLoS One 2018; 13(1) e0190325.

40. Cook MB, Wood SN, Cash BD, Young P, Acosta RD, Falk RT et al. Association between circulating levels of sex steroid hormones and Barrett's esophagu s in men: a case-control analysis. Clin Gastroenterol Hepatol 2015; 13: 673-82.

41. Cook MB, Wood S, Hyland PL, Caron P, Drahos J, Falk RT, PFeiffer RM et al. Sex steroid hormones in relation to Barrett's esophagus: an analysis of the FINBAR Study. Andrology 2017;5(2):240-247.

42. Steffen A, Huerta JM, Weiderpass E, Beuno-de-Mesquita HB, May AM, Siersema PD et al. General and abdominal obesity and risk of esophageal and gastric adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2015; 137:646–657.

43. Whiteman DC, Sadeghi S, Pandeya N, Smithers BM, Gotley DC, Bain CJ, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut. 2008; 57:173–80.

44. Eriksson J, Haring R, Garup N, Vandenput L, Wallasschfski H, Lorentzen E et al. Causal relationship between obesity and serum testosterone status in men: A bi-directional mendelian randomization analysis. PLoS One. 2017; 12(4):e0176277.

45. Simpson E, Rubin G, Clyne C Robertson K, O'Donnell L, Jones M, Davis S. The role of local estrogen biosynthesis in males and females. Trends Endocrinol Metab. 2000; 11:184–8.

46. Adlercreutz H, Mazur W. Phyto-oestrogens and Western diseases. Ann Med 1997; 29: 95-120.

47. Key TJ, Allen NE, Spencer EA, Travis RC. The effect of diet on risk of cancer. Lancet 2002; 360: 861-8.

48. Holmes MD, Spiegelman D, Willett WC, Manson JE, Hunter DJ, Barbieri RL et al. Dietary fat intake and endogenous sex steroid hormone levels in postmenopausal women. J Clin Oncol 2000; 18: 3668-3676.

49. Allen NE, Key TJ. The effects of diet on circulating sex hormone levels in men. Nutr Res Revs 2000; 13: 159-184.

50. Must A, Phillips SM, Naumova EN, Blum M, Harris S, Dawson-Hughes B, et al. Recall of early menstrual history and menarcheal body size: After 30 years, how well do women remember? Am J Epidemiol. 2002; 155:672-9.

51. Taylor R, Matassa J, Leavy JE, Fritschi L. Validity of self reported male baldness patterns in epidemiological studies. BMC Public Health. 2004; 4:60.

52. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with the general population. Am J Epidemiol 2017; 86: 1026-1034.

53. Cook MB, Wild CP, Forman D. A systematic review and meta-analysis of the sex ratio for Barrett's esophagus, erosive reflux disease, and nonerosive reflux disease. Am J

Epidemiol. 2005; 162: 1050-1061.

54. Cook MB, Corley DA, Murray LJ, Liao LM, Kamangar F, Ye W, et al. Gastroesophageal reflux in relation to adenocarcinomas of the esophagus: A pooled analysis from the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON). PLoS One. 2014; 9: e103508.

55. Chen J, Bu XL, Wang QY, Hu PJ, Chen MH. Decreasing seroprevalence of Helicobacter pylori infection during 1993-2003 in Guangzhou, southern China. Helicobacter. 2007; 12:164–9.

56. Malaty HM, El-Kasabany A, Graham DY, Miller CC, Reddy SG, Srinivasan SR, et al. Age at acquisition of Helicobacter pylori infection: A follow-up study from infancy to adulthood. Lancet. 2002; 359:931-35.

57. Duell EJ, Travier N, Leila LB, Boutron-Ruault MC, Clavel-Chapelon F, Palli D, et al. Menstrual and reproductive factors, exogenous hormone use, and gastric cancer risk in a cohort of women from the european prospective investigation into cancer and nutrition. Am J Epidemiol. 2010; 172:1384-93.

58. Freedman ND, Chow W-H, Gao Y-T, Shu X-O, Ji B-T, Yang G, et al. Menstrual and reproductive factors and gastric cancer risk in a large prospective study of women. Gut. 2007; 56:1671–7.

59. Spechler SJ. Barrett esophagus and risk of esophageal cancer. JAMA. 2013; 10:627–36.

Table 1. Characteristics of oesophageal and gastric cancer cases and non-cases in men within the UK Biobank

	Oesophageal cancer		Gastric cancer	
Characteristic	**Cases n (%)**	**Non-cases n (%)**	**Cases n (%)**	**Non-cases n (%)**
	(n=309)	*(n= 219,116)*	*(n=210)*	*(n= 219,215)*
Age at baseline (years)				
<50	11 (3.6)	52,398 (23.9)	14 (6.7)	52,395 (23.9)
50-<55	24 (7.8)	32,283 (14.7)	21 (10)	32,286 (14.7)
55-<60	63 (20.4)	38,630 (17.6)	25 (11.9)	38,668 (17.6)
60-<65	86 (27.8)	52,375 (23.9)	65 (31)	52,396 (23.9)
≥65	125 (40.5)	43,430 (19.8)	85 (40.5)	43,470 (19.8)
Socioeconomic status				
1 (least deprived)	57 (18.5)	44,053 (20.1)	36 (17.2)	44,074 (20.1)
2	51 (16.5)	43,456 (19.9)	33 (15.8)	43,474 (19.9)
3	52 (16.8)	43,007 (19.7)	45 (21.5)	43,014 (19.7)
4	70 (22.7)	43,159 (19.7)	43 (20.6)	43,186 (19.7)
5 (most deprived)	79 (25.6)	45,151 (20.6)	52 (24.9)	45,178 (20.6)
Missing	*0*	*290*	*1*	*289*
Smoking status[a]				
Never	80 (26)	107,148 (49.2)	65 (31.4)	107,163 (49.2)
Former light smoker	82 (26.6)	56,970 (26.2)	54 (26.1)	56,998 (26.2)
Former heavy smoker	81 (26.3)	26,060 (12)	51 (26.6)	26,090 (12)
Current light smoker	23 (7.5)	14,014 (6.4)	11 (5.3)	14,026 (6.4)
Current heavy smoker	42 (13.6)	13,562 (6.2)	26 (12.6)	13,578 (6.2)
Missing	*1*	*1,362*	*4*	*1,360*
Alcohol intake[b]				
Never drinker	4 (1.3)	6,202 (2.9)	7 (3.4)	6,199 (2.9)
Current light-moderate drinker	131 (42.7)	98,171 (45.1)	89 (42.6)	98,213 (45.1)
Current heavy drinker	151 (49.2)	105,734 (48.6)	97 (46.4)	105,788 (48.6)
Former drinker	21 (6.8)	7,659 (3.5)	16 (7.7)	7,664 (3.5)
Missing	*2*	*1,350*	*1*	*1,351*
BMI status (kg/m^2)				
Underweight (<18.5)	1 (0.3)	507 (0.2)	3 (1.4)	505 (0.2)
Normal (18.5-<25)	42 (13.7)	54,272 (25)	32 (15.2)	54,282 (24.9)
Overweight (25-<30)	151 (49.4)	107,414 (29.4)	113 (53.8)	107,452 (49.4)
Obese (30+)	112 (36.6)	55,335 (25.4)	62 (29.5)	55,385 (25.5)
Missing	*3*	*1,588*	*0*	*1,591*
Waist:hip ratio[c]				
Below IDF guideline	110 (35.7)	117,669 (54)	85 (40.5)	117,694 (54)
Above IDF guideline	198 (64.3)	100,366 (46)	125 (59.5)	100,439 (46)
Missing	*1*	*1,081*	*0*	*1,082*
Fruit & vegetable intake (servings per week)				
<2	88 (29.5)	54,906 (26)	54 (26.7)	54,940 (26)
2-5	126 (42.3)	88,756 (42)	76 (37.6)	88,806 (42)
>5	84 (28.2)	67,654 (32)	72 (35.6)	67,666 (32)
Missing	*11*	*7,800*	*8*	*7,803*
Processed meat intake (servings per week)				
Never/ <1	62 (20.1)	58,471 (26.8)	55 (26.3)	58,478 (26.8)
1	94 (30.5)	64,966 (29.8)	69 (33)	64,991 (29.8)
>1	152 (49.4)	94,600 (43.4)	85 (40.7)	94,667 (43.4)

Missing	*1*	*1,079*	*1*	*1,079*
Red meat intake (servings per week)				
Never/ <1	106 (34.9)	97,306 (45.1)	77 (37.6)	97,335 (45.1)
1-3	101 (33.2)	63,067 (29.2)	70 (34.2)	63,098 (29.2)
≥3	97 (31.9)	55,308 (25.6)	58 (28.3)	55,347 (25.6)
Missing	*5*	*3,435*	*5*	*3,435*

[a] By pack years (light=<20 pack-years; heavy=>20 pack-years)

[b] Light-moderate (special occasions, 1-3 times per month, <14 units/week), heavy (>14 units/week)

[c] Based on International Diabetes Federation criteria (>94cm in men; >80cm in women).

Table 2. Hormonal and reproductive factors and risk of oesophageal and gastric cancer in men within the UK Biobank

		Oesophageal cancer (n=309)			Gastric cancer (n=210)		
Characteristic	**Person-years**	**Cases n**	**HR (95%CI)**	**Adjusted[a] HR (95% CI)**	**Cases n**	**HR (95%CI)**	**Adjusted[a] HR (95% CI)**
Male pattern baldness							
No	383,248	87	Ref	Ref	48	Ref	Ref
Yes	799,540	215	1.02 (0.80, 1.31)	1.05 (0.81, 1.35)	157	1.36 (0.99, 1.88)	1.35 (0.97, 1.88)
Missing		*7*			*5*		
Male pattern baldness pattern							
No baldness	383,248	87	Ref	Ref	48	Ref	Ref
Frontal only	272,458	55	0.91 (0.65, 1.27)	0.94 (0.67, 1.33)	50	1.48 (1.00, 2.20)	1.52 (1.02, 2.28)
Frontal and mild vertex	313,218	91	1.02 (0.76, 1.37)	1.03 (0.76, 1.40)	65	1.33 (0.92, 2.20)	1.28 (0.87, 1.88)
Frontal and severe vertex	213,863	69	1.14 (0.83, 1.57)	1.18 (0.85, 1.64)	42	1.28 (0.84, 1.93)	1.28 (0.83, 1.95)
Missing		*7*		P_{trend}=0.31	*5*		P_{trend}=0.34
Fathered children							
No	248,723	51	Ref	Ref	35	Ref	Ref
Yes	934,168	250	1.01 (0.74, 1.36)	1.02 (0.75, 1.40)	171	1.02 (0.70, 1.46)	1.10 (0.75, 1.62)
Missing		*8*			*4*		
Number of children fathered							
0	248,723	51	Ref	Ref	35	Ref	Ref
1	151,412	41	1.16 (0.77, 1.76)	1.14 (0.74, 1.74)	27	1.12 (0.68, 1.86)	1.19 (0.70, 2.00)
2	495,538	126	0.94 (0.68, 13.1)	1.01 (0.72, 1.42)	82	0.91 (0.61, 1.36)	1.03 (0.67, 1.57)

3+	287,217	83	1.04 (0.73, 1.48)	0.99 (0.69, 1.42)	62	1.14 (0.75, 1.73)	1.17 (0.76, 1.81)
Missing		*8*		P_{trend}=0.79	*4*		P_{trend}=0.61
Relative age at first facial hair							
Younger than average	78,766	18	Ref	Ref	6	Ref	Ref
About average age	918,381	248	0.93 (0.58, 1.50)	0.93 (0.57, 1.50)	170	1.95 (0.86, 4.40)	1.91 (0.85, 4.33)
Older than average	149,263	25	0.71 (0.39, 1.29)	0.69 (0.37, 1.28)	20	1.71 (0.69, 4.26)	1.79 (0.72, 4.47)
Missing		*18*		P_{trend}=0.20	*14*		P_{trend}=0.42
Relative age voice broke							
Younger than average	48,226	14	Ref	Ref	4	Ref	Ref
About average age	980,197	247	0.68 (0.40, 1.16)	0.68 (0.39, 1.16)	174	1.72 (0.64, 4.65)	1.75 (0.65, 4.73)
Older than average	65,391	15	0.77 (0.37, 1.59)	0.90 (0.43, 1.86)	8	1.44 (0.43, 4.78)	1.64 (0.49, 5.45)
Missing		*33*		P_{trend}=0.85	*24*		P_{trend}=0.53

[a] Adjusted for socioeconomic status, alcohol status, smoking status, BMI, waist-hip ratio and fruit and vegetable intake.

Table 3. Hormonal and reproductive factors and risk of oesophageal and gastric cancer by histological subtype in men within the UK Biobank

		Oesophageal adenocarcinoma (n=253)			Oesophageal squamous cell carcinoma (n=39)			Gastric adenocarcinoma (n=180)		
Characteristic	**Person-years**	**Cases n**	**HR (95%CI)**	**Adjusted[a] HR (95% CI)**	**Cases n**	**HR (95%CI)**	**Adjusted[a] HR (95% CI)**	**Cases n**	**HR (95%CI)**	**Adjusted[a] HR (95% CI)**
Male pattern baldness										
No	383,248	73	Ref	Ref	9	Ref	Ref	41	Ref	Ref
Yes	799,540	175	1.00 (0.76, 1.31)	1.02 (0.77, 1.36)	30	1.35 (0.64, 2.85)	1.35 (0.63, 2.87)	135	1.36 (0.96, 1.94)	1.36 (0.95, 1.95)
Missing		*5*			*0*			*4*		
Male pattern baldness pattern										
No baldness	383,248	73	Ref	Ref	9	Ref	Ref	41	Ref	Ref
Frontal only	272,458	48	0.94 (0.66, 1.36)	0.98 (0.68, 1.43)	5	0.80 (0.27, 2.39)	0.79 (0.26, 2.36)	41	1.42 (0.92, 2.19)	1.47 (0.94, 2.28)
Frontal and mild vertex	313,218	72	0.97 (0.70, 1.34)	0.98 (0.70, 1.38)	17	1.79 (0.80, 4.03)	1.78 (0.78, 4.06)	56	1.34 (0.89, 2.01)	1.28 (0.84, 1.94)
Frontal and severe vertex	213,863	55	1.10 (0.77, 1.56)	1.13 (0.78, 1.62)	8	1.25 (0.48, 3.26)	1.32 (0.51, 3.45)	38	1.34 (0.86, 2.09)	1.35 (0.86, 2.14)
Missing		*5*		P_{trend}=0.60	*0*		P_{trend}=0.26	*4*		P_{trend}=0.25
Fathered children										
No	248,723	40	Ref	Ref	11	Ref	Ref	30	Ref	Ref
Yes	934,168	207	1.07 (0.76, 1.51)	1.07 (0.75, 1.53)	27	0.48 (0.24, 0.97)	0.56 (0.27, 1.15)	146	1.01 (0.68, 1.49)	1.10 (0.72, 1.68)
Missing		*6*			*1*			*4*		
Number of children fathered										
0	248,723	40	Ref	Ref	11	Ref	Ref		Ref	Ref
1	151,412	34	1.24 (0.78, 1.96)	1.19 (0.74, 1.91)	5	0.64 (0.22, 1.84)	0.70 (0.24, 2.03)	30	1.21 (0.71, 2.06)	1.29 (0.74, 2.25)
2	495,538	104	1.00 (0.69, 1.45)	1.04 (0.71, 1.53)	12	0.40 (0.17, 0.91)	0.52 (0.23, 1.22)	25	0.86 (0.56, 1.33)	0.98 (0.62, 1.56)
3+	287,217	69	1.12 (0.75, 1.65)	1.05 (0.70, 1.59)	10	0.55 (0.23, 1.30)	0.54 (0.22, 1.32)	121	1.14 (0.73, 1.80)	1.18 (0.74, 1.90)
Missing		*6*		P_{trend}=0.98	*1*		P_{trend}=0.14	4		P_{trend}=0.72
Relative age at first facial hair										
Younger than average	78,766	17	Ref	Ref	1	Ref	Ref	6	Ref	Ref
About average age	918,381	204	0.81 (0.50, 1.34)	0.82 (0.50, 1.35)	31	2.03 (0.28, 14.94)	1.94 (0.26, 14.26)	114	1.64 (0.72, 3.72)	1.60 (0.71, 3.64)
Older than average	149,263	19	0.57 (0.30, 1.09)	0.56 (0.29, 1.10)	5	2.53 (0.30, 21.67)	2.25 (0.26, 19.29)	17	1.45 (0.57, 3.69)	1.54 (0.61, 3.91)
Missing		*13*		P_{trend}=0.08	*2*		P_{trend}=0.50	*13*		P_{trend}=0.54
Relative age voice broke										
Younger than average	48,226	12	Ref	Ref	2	Ref	Ref	4	Ref	Ref
About average age	980,197	206	0.67 (0.37, 1.19)	0.66 (0.37, 1.19)	29	0.56 (0.13, 2.34)	0.56 (0.13, 2.35)	147	1.45 (0.53, 3.91)	1.47 (0.54, 3.99)
Older than average	65,391	14	0.84 (0.39, 1.81)	1.01 (0.46, 2.19)	0	-	-	6	1.08 (0.30, 3.82)	1.25 (0.35, 4.45)
Missing		*21*		P_{trend}=0.87	*8*			*23*		P_{trend}=0.81

[a] Adjusted for socioeconomic status, alcohol status, smoking status, BMI, waist-hip ratio and fruit and vegetable intake.

Table 4. Hormonal and reproductive factors and risk of gastric cancer by tumour location in men within the UK Biobank

Characteristic	Person-years	Gastric cardia (n=101)			Gastric non-cardia (n=52)		
		Cases n	HR (95%CI)	Adjusted[a] HR (95% CI)	Cases n	HR (95%CI)	Adjusted[a] HR (95% CI)
Male pattern baldness							
No	383,248	21	Ref	Ref	12	Ref	Ref
Yes	799,540	78	1.55 (0.96, 2.52)	1.59 (0.97, 2.61)	39	1.37 (0.71, 2.62)	1.13 (0.72, 1.76)
Missing		*2*			*1*		
Male pattern baldness pattern							
No baldness	383,248	21	Ref	Ref	12	Ref	Ref
Frontal only	272,458	22	1.50 (0.82, 2.72)	1.61 (0.88, 2.95)	16	1.89 (0.89, 3.99)	1.40 (0.82, 2.39)
Frontal and mild vertex	313,218	33	1.56 (0.90, 2.70)	1.59 (0.90, 2.79)	14	1.16 (0.54, 2.52)	1.01 (0.59, 1.72)
Frontal and severe vertex	213,863	23	1.61 (0.89, 2.91)	1.58 (0.86, 2.93)	9	1.10 (0.46, 2.63)	1.01 (0.56, 1.82)
Missing		*2*		P_{trend}=0.14	*1*		P_{trend}=0.81
Fathered children							
No	248,723	21	Ref	Ref	10	Ref	Ref
Yes	934,168	80	0.79 (0.49, 1.29)	0.83 (0.50, 1.39)	39	0.83 (0.41, 1.67)	1.41 (0.79, 2.51)
Missing		*0*			*3*		
Number of children fathered							
0	248,723	21	Ref	Ref	10	Ref	Ref

1	151,412	12	0.83 (0.41, 1.69)	0.87 (0.42, 1.81)	7	1.03 (0.39, 2.71)	1.55 (0.74, 3.27)
2	495,538	36	0.67 (0.39, 1.14)	0.73 (0.41, 1.30)	32	0.76 (0.35, 1.64)	1.38 (0.75, 2.56)
3+	287,217	32	0.99 (0.57, 1.72)	0.96 (0.54, 1.72)	*3*	0.85 (0.37, 1.95)	1.38 (0.72, 2.64)
Missing		*0*		P_{trend}=0.84			P_{trend}=0.44
Relative age at first facial hair							
Younger than average	78,766	3	Ref	Ref	3	Ref	Ref
About average age	918,381	84	1.92 (0.61, 6.08)	1.94 (0.61, 6.17)	40	0.93 (0.29, 3.03)	1.91 (0.60, 6.06)
Older than average	149,263	11	1.88 (0.52, 6.73)	2.04 (0.57, 7.34)	5	0.86 (0.20, 3.58)	1.56 (0.42, 5.77)
Missing		*3*		P_{trend}=0.38	*4*		P_{trend}=0.81
Relative age voice broke							
Younger than average	48,226	1	Ref	Ref	0	Ref	Ref
About average age	980,197	90	-	-	41	1.13 (0.36, 5.59)	1.11 (0.35, 3.52)
Older than average	65,391	4			2	0.96 (0.21, 4.29)	1.04 (0.23, 4.66)
Missing		*6*					

[a] Adjusted for socioeconomic status, alcohol status, smoking status, BMI, waist-hip ratio and fruit and vegetable intake