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Obesity and incident gastrointestinal cancers: overall body size or central obesity measures, which factor matters?

Nahid Hashemi Madani[a], **Arash Etemadi**[b,c], **Mahdi Nalini**[d], **Hossein Poustchi**[e,f], **Alireza Khajavi**[g], **Elahe Mirzazade**[h], **Hosna Mirfakhraei**[h], **Akram Pourshams**[b,e], **Masoud Khoshnia**[b,i], **Abdolsamad Gharavi**[b,i], **Shahin Merat**[e,f], **Moahammad E. Khamseh**[a,*], **Reza Malekzadeh**[b,e,f]

[a]Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Science, Tehran, Iran

[b]Digestive Oncology Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran

[c]Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, Maryland, USA

[d]Cardiovascular Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

[e]Digestive Disease Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran

[f]Liver and Pancreatobiliary Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran

[g]Student Research Committee, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[h]Firoozabadi Clinical Research Development Unit, Iran University of Medical Science, Tehran, Iran

[i]Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran

[*]Corresponding Author: Mohammad E. Khamseh. Institute of Endocrinology and Metabolism, No. 10, Firoozeh St., Vali-asr Ave., Vali-asr Sq., Tehran, Iran. m.e.khamseh@gmail.com.

Authors' contributions

M.E.Kh, N.H.M, A.E, R.M, and M.N contributed to study concept and design. N.H.M, E.M, and H.M drafted the manuscript. H.P, A.E, M.Kh, A.P, Sh.M, and A.Gh acquired the data. M.E.Kh, N.H.M, and A.Kh, contributed to the analysis and interpretation of the data. M.E.Kh, N.H.M, A.E, and M.N critically revised the manuscript. A.Kh contributed to statistical analysis. M.E.Kh is the guarantor of this work, as such, has full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have participated in editing the manuscript and reviewed and approved the final version of the manuscript

Conflict of interest

The authors report no conflicts of interest relevant to this article.

Ethics approval and consent to participate

The ethical review committees of the Digestive Disease Research Institute of Tehran University of Medical Sciences, the US National Cancer Institute, and the International Agency for Research on Cancer approved the study protocol. Before the interviews, a written informed consent was obtained from each participant. The principal investigators of GCS (A.E and H.P) shared the data with us. Data were anonymized before use in this study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abstract

Body mass index (BMI) does not reflect the location or amount of body fat. We aimed to investigate the role of general and central obesity measures in the prediction of incident gastrointestinal (GI) cancers. In this analysis of Golestan Cohort Study, we included 47586 cancer-free individuals followed for 12.3 years (IQR: 10.5–13.2). We investigated the association of obesity measures including BMI, waist circumference (WC), and waist-to-hip ratio (WHR) at enrollment and the incidence of esophageal, gastric, colorectal, and pancreatic cancers. Cox proportional hazard models were used to estimate the association between covariates and GI cancer risk. We observed no significant associations between obesity measures and incidence of the above-mentioned GI cancers in men. In women, BMI, WC, and WHR were associated with significant reductions in the risk of esophageal squamous cell carcinoma (ESCC): HR: 0.67 (95% CI: 0.56–0.81), HR: 0.71 (95% CI: 0.60–0.84), and HR: 0.80 (95% CI: 0.68– 0.94), respectively. In addition, WHR was associated with significantly increased risks for colorectal cancer (HR: 1.39, 95% CI: 1.08–1.78) and gastric cancer (HR: 1.24, 95% CI: 1.01–1.51) in women. In this study, statistically significant associations between obesity measures and incident esophageal, gastric, and colorectal cancers were seen in women.

Keywords

central obesity; body mass index; esophagus squamous cell carcinoma; gastrointestinal cancer

Introduction

Obesity is a major contributor to the development of many chronic diseases, including type 2 diabetes (T2DM), cardiovascular disease (CVD), and cancer ([Garvey et al., 2016,Stone et al., 2018]). A recently published report by International Agency for Research on Cancer (IARC) concludes that obesity increases the risk of several site-specific cancers including the esophagus (adenocarcinoma), colon and rectum, gastric cardia, and pancreas ([Lauby-Secretan et al., 2016]). The majority of studies evaluating obesity and cancer risk have applied body mass index (BMI) as the main measure of obesity. However, an important limitation of BMI is its inability to consistently estimate the percentage and distribution of fat mass among individuals of different ages, genders, and ethnicities ([Garvey et al., 2016]). Waist circumference (WC) is recommended for the screening of obesity and obesity-related comorbidities, especially when BMI is less than 35 kg/m^2 ([Garvey et al., 2016]).

A prospective study of the U.S. population, aged 50 to 70 years, concluded that increased abdominal fat, but not general fat mass, is associated with an increase in the risk of death from specific cancers ([Leitzmann et al., 2011]). A more recent study of a Canadian population demonstrated that central adiposity is a stronger predictor of all- cancer risk than is body size ([Barberio et al., 2019]). However, there is some inconsistency regarding the association between WC and common gastrointestinal (GI) cancers. WC was previously introduced as a strong predictor of colon cancer ([Moore et al., 2004]) while a more recent study did not support this finding ([Karahalios et al., 2016]).

Epidemiological studies have consistently reported gender differences in the incidence of various cancers across different populations and regions (Dorak and Karpuzoglu, 2012). Previous studies have also indicated gender and ethnicity, as important factors, affecting the association between obesity and cancer incidence for certain cancer types (Renehan et al., 2008,Wang et al., 2016a). Meanwhile, there is substantial evidence of sex, age, and ethnic variations in WC and WHR (Organization, 2011). Considering the increasing prevalence of obesity in Iran, it seems essential to determine the appropriate obesity measure to specify cancer risk among both sexes in this population.

Materials and Methods

Study design and participants

Golestan Cohort Study (GCS) is a longitudinal, ongoing follow-up study of the individuals aged 40–75 years at baseline from Golestan province in northeastern Iran. This study primarily aimed to identify the risk factors for esophageal cancer previously established to have a high incidence rate in this area (Pourshams et al., 2010). During a 4-year period, 50045 individuals from both rural and urban areas were recruited to the GCS (Pourshams et al., 2010). The participants were excluded if they had any current or previous history of upper gastrointestinal (GI) cancers, were unwilling to participate at any stage of the study for any reason, and were temporary residents (Pourshams et al., 2010). The study was approved by the institutional review boards of the Digestive Disease Research Institute of the Tehran University of Medical Sciences (Ref: FWA00001331), the IARC (Ref: CN/23/ 3), and the US National Cancer Institute (NCI). Written informed consent was obtained from all participants (Pourshams et al., 2010).

We aimed to determine the anthropometric factors that influence the risk of the main GI cancers including cancers of the esophagus, stomach, colon and rectum, and pancreas. For the purpose of this study, we included all participants who were free of any of these specific cancers at the time of enrollment. Moreover, individuals with BMI< 18.5 kg/m^2 were excluded from this study.

Anthropometric data and covariates

The selected participants were contacted by the trained health workers and invited to visit the GCS center, a research center specifically established for this project in Gonbad, the second largest city of Golestan (Pourshams et al., 2010). Anthropometric measurements were performed at GCS center by trained personnel. Weight and height were measured in light clothes, without shoes, and in the upright position. WC was measured at the level of the minimal waist at the end of normal expiration and hip circumference (HC) was measured at the widest portion of the buttocks in a standing relaxed posture with feet close together. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Waist-to-hip ratio (WHR) was calculated as the ratio of WC divided by HC. In the same session, the structured questionnaires validated in the pilot phase of the study (Pourshams et al., 2005,Pourshams et al., 2010) were completed for each participant to provide information on sex, age, diabetes diagnosis (yes/no), smoking status (never/past/current), alcohol use (yes/no), opium use (yes/no), marital status (married/ single including divorced

or widowed), and educational attainment (illiterate/ less than 5 years/ 6–8 years/ 9–12 years/ >12 years). Data on home size and asset ownership were used to calculate a composite wealth score representing socioeconomic status as described before and categorized into quartiles (Islami et al., 2009).

Follow-up and outcome ascertainment

The participants are being followed up actively every 12 months. Moreover, they were instructed at the time of enrollment to contact the team in case of certain conditions such as hospitalization or the development of a new major disease. The participants are first contacted by telephone, if they are not accessible after seven attempts (on different days during two consecutive weeks), they will be visited at home by the team members. The GCS team completes a questionnaire during each phone call or home visit and records the occurrence of death, or development of any major disease, or hospitalization that has taken place since the previous follow-up visit. These contacts are registered and subsequently followed by a staff member. In the case of occurrence of cancers and deaths, the trained personnel gather all available medical documents including all clinical and pathologic reports, as well as hospital records from the medical centers in which any major diagnostic or therapeutic procedures were done. To verify the diagnosis of cancer or cause of death, two internists independently review all available documents and allocate the disease code for the outcome based on the10th revision of the International Statistical Classification of Diseases and Related Health Problems (Organization, 1992). In the case of disagreement, a third expert internist reviews the data and makes the final decision on the code. The data for cancer incidence is also completed and verified by linkage to the local cancer registry. The participants were followed-up until the incidence of a GI cancer (i.e. esophagus, stomach, colon, rectum, and pancreas), the incidence of any other cancer, death due to any cause or 31 December 2019, whichever came first.

Statistical analysis

The variables are described using means and standard deviations (SDs), medians and inter-quartile ranges (IQRs), and percentages. Since the time to occurrence of cancers was the response variable, Cox proportional hazards regression was utilized to estimate the impact of covariates. The proportional hazards assumption was tested, and no serious violation was detected. The analyses were stratified by sex. Main exposures namely BMI, WC, and WHR were included in the regression models as continuous variables. Additionally, the potential risk factors including age, marital status (married/single), educational level (illiterate/ less than 5 years/ 6–8 years/ 9–12 years/ >12 years), socioeconomic status (divided to four quartiles), history of diabetes (yes/no), smoking status (never/past/current), alcohol use (yes/no), and opium use (yes/no), area of residence (urban/rural), consumption of vegetables and hot tea (only for esophageal cancer) were included in the models. The HRs were also calculated on the basis of the categories of BMI and WC, applying the cut-off value of 90 cm for WC in both genders as recommended for Iranian population (Hadaegh et al., 2009,AZIZI et al., 2010).

Results

Overview of the study population

A total of 50045 individuals were enrolled in this prospective cohort study. We excluded 55 individuals diagnosed as having any type of cancer at the time of enrollment, and 2404 (4.80 %) subjects with a BMI <18.5 kg/m^2. Eventually, 47586 participants were included in the final analysis. The median follow-up period was 12.3 years (IQR: 10.5–13.2). A total of 933 participants (557 men and 376 women) developed one of the GI cancers during the follow-up: 352 cases of esophageal squamous cell carcinoma (ESCC), 352 cases of gastric cancer, 136 cases of colorectal cancer, and 93 cases of pancreatic cancer. Over the follow-up time, 1189 participants presented with other cancers (Figure 1).

Baseline characteristics of the cohort are presented in Table 1. BMI, WC, WHR, and other characteristics of the participants at the time of enrollment are presented by each of the above - mentioned GI cancer types, other cancers, and no cancers.

Overall body size and cancer risk

The associations between BMI and site-specific incidence of GI cancers are presented in Table 2. The risk of occurrence of GI cancers was calculated for each 1SD increase in BMI in the unadjusted and fully-adjusted models. After adjusting for all the potential risk factors, a significant inverse association was observed between BMI and incident ESCC in women (HR: 0.67, 95% CI: 0.56–0.81), but this association was not statistically significant in men (HR: 0.84, 95% CI: 0.70–1.00).

Moreover, no significant association was observed between BMI and incident gastric, colorectal, and pancreatic cancers among men and women. We further examined the impact of BMI on gastric cancer stratifying by the site. There was no significant association between BMI and the incident gastric cardia cancer neither in the women (HR: 1.20, 95% CI: 0.93–1.56) nor in the men (HR: 1.18, 95% CI: 0.10–1.40) (Supplementary Table 1).

Central obesity and cancer risk

Sex-stratified results of WC association with site-specific incidence of GI cancers are presented in Table 2. The risk was calculated for each 1SD increase in WC in the unadjusted and fully-adjusted models. In women, WC was associated with a significant reduction in ESCC risk after adjustment for other risk factors (HR: 0.71, 95% CI: 0.60–0.84). In men, the inverse association between WC and incident ESCC attenuated after adjusting for other potential risk factors (HR: 0.87, 95% CI: 0.74–1.02). Moreover, there was no significant association between WC and incident gastric, colorectal, and pancreatic cancers among men and women. We further examined the impact of WC on gastric cancer stratified by the cancer site. There was no significant association between WC and incident gastric cardia cancer either in women (HR: 1.15, 95% CI: 0.88–1.51) or in men (HR: 1.13, 95% CI: 0.95–1.34) (Supplementary Table 1).

We also evaluated the relationship between WHR and site-specific incidence of GI cancers in men and women. The results are presented in Table 2. The risk for the occurrence of GI

cancers was calculated for each 1SD increase in WHR in the unadjusted and fully-adjusted models. In women, WHR was associated with a significant reduction in the risk of ESCC after adjustment for other potential risk factors (HR: 0.80, 95% CI: 0.68– 0.94). In men, the inverse association between WHR and ESCC incidence attenuated after adjusting for other potential risk factors (HR: 0.90, 95% CI: 0.77–1.04). Upon adjusting for the risk factors, WHR significantly increased the risk of gastric cancer (HR: 1.24, 95% CI: 1.01–1.51) and colorectal cancer (HR: 1.39, 95% CI: 1.08–1.78) in women. However, no significant association was observed between WHR and the incident gastric, colorectal, and pancreatic cancers in the men. When we assessed the impact of WHR on gastric cancer stratified by the cancer site, we found no significant association between WHR and gastric cardia cancer either in women (HR: 1.27, 95% CI: 0.99–1.65) or in men (HR: 1.07, 95% CI: 0.90–1.26) (Supplementary Table 1).

Combination of BMI and WC in predicting common GI cancers

Since BMI and WC have a strong correlation as indicators of obesity, we categorized the participants into four groups based on BMI and WC (low WC/non-obese, low WC/obese, high WC/non-obese, and high WC/obese) and calculated the hazard ratios of GI cancers, using the low WC/non-obese group as the reference category. The risk for each incident cancer in obese participants did not show a significant difference between high and low WC groups (Figure 2).

Discussion

In this large cohort of Iranian people, each 1 SD increase in all obesity measures (BMI, WC, and WHR) was associated with a significant reduction in the risk for incident ESCC in women, adjusted for other potential risk factors. Moreover, each 1 SD increase in WHR was significantly associated with increases in the risk of incident colorectal and gastric cancers in women. However, we found no significant association between general or central obesity measures and the main GI cancers in the men. In this population, obesity is more common in women than in men, and a previous report from GCS study indicated that women in this region had a higher mean WHR compared with women in many other populations (Bahrami et al., 2006).

Esophageal squamous cell carcinoma

Although esophageal adenocarcinoma (EADC) is considered to be an obesity-related disease (Enzinger and Mayer, 2003), low BMI has been demonstrated to be associated with the ESCC risk (Smith et al., 2008). The current study indicated in addition to BMI, increased WC and WHR are also associated with significant reductions in the risk for ESCC in women. Several studies have showed inverse associations between BMI and ESCC risk (Steffen et al., 2009,Lahmann et al., 2012,Song et al., 2017,Cho et al., 2019),but only a few have investigated the relationship between central obesity and incident ESCC. A large number of studies demonstrated that obesity is associated with a significant reduction in the risk of ESCC (Smith et al., 2008,Clinton et al., 2020), and a few others indicated female sex hormones may protect against the development of ESCC (Gallus et al., 2001,Freedman et al., 2010,Bodelon et al., 2011). On the other hand, obesity is associated

with excessive production of estrogens due to the elevation of aromatase enzyme expression in adipose tissue (Siiteri, 1987), and the enhanced aromatase activity stimulated by pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF- α) (Siiteri, 1987). Moreover, obesity-associated reduction in sex hormone-binding globulin (SHBG) capacity can further increase the levels of free biologically active estrogens (Siiteri, 1987,Wallace et al., 2013). Thus, the protective role of obesity on incident ESCC in women might be mediated by estrogen. Studies investigating the mechanisms by which sex hormones affect ESCC have demonstrated that the estrogen receptor (ER) and androgen receptor (AR) are expressed in the ESCC tissues (Kalayarasan et al., 2008,Zhang et al., 2015). Moreover, some in-vitro study have showed that estrogens may inhibit cell growth in ESCC while testosterone could enhance it (Matsuoka et al., 1987). Furthermore, estrogens are thought to exert anti-inflammatory effects on the adipose tissue, which may protect women from obesity-associated diseases (Brown et al., 2010).

In our study, BMI, WC, and WHR were associated with a significant reduction in ESCC risk in men in unadjusted models. This effect disappeared after adjustment for other potential risk factors of ESCC including hot tea, opium addiction, vegetable consumption, educational level, and socioeconomic status (Sheikh et al., 2019). Risk factors such as hot tea and opium are more frequently used by men in this region, and they may overcome the protective effect of obesity on ESCC risk in men.

Gastric cancer

Data regarding the association between obesity and gastric cancer risk are heterogeneous. One previous study showed that overweight and obesity are associated with an increase in the risk for gastric cancer only in men (Yang et al., 2009) while another found positive associations in both men and women (Turati et al., 2013). Similar to our findings, the results from a more recent meta-analysis showed that increasing BMI is not a clear risk factor for gastric cancer (Chen et al., 2013). Although limited, the evidence from a few meta-analyses suggest the potential role of central obesity in the etiology of gastric cancer (Du et al., 2017,Lee et al., 2018). Likewise, our study showed that WHR is associated with a marginally significant increase in the risk of gastric cancer in women. Gastric cardia cancer has been listed as an obesity-related cancer by IARC (Lauby-Secretan et al., 2016), but there is not sufficient evidence for an association between obesity and gastric non-cardia cancer (Lauby-Secretan et al., 2016). When we restricted our analysis to the participants who developed gastric cardia cancer (n= 217), we still found no significant association with obesity measures either in women or in men. This finding could be explained by the regional and racial variations in the etiology of gastric cancer (Balakrishnan et al., 2017). Moreover, gastric cancer is highly dependent on diet (Rawla and Barsouk, 2019), and the substantial regional variation in the incidence of gastric cancer has been partly attributed to dietary factors (Tsugane and Sasazuki, 2007,Rawla and Barsouk, 2019). In Iran, the highest incidence of gastric cancer has been reported in Ardabil Province where the consumption of specific foods or snacks (e.g. black Halva, roasted/salted seeds) is common (Babaei et al., 2009). On the other hand, results from more recent studies have indicated that metabolically abnormal obesity (MAO), but not metabolically healthy obesity (MHO), increased the risk for incident gastric

cancer ([Hamaguchi et al., 2019,Hashimoto et al., 2020]). This distinction may be an important consideration when assessing the association between obesity and gastric cancer risk.

Colorectal cancer

Although obesity is a well-established risk factor for incident colon cancer, data on the differential effects of central obesity or general body size are inconsistent ([Moore et al., 2004,Keimling et al., 2013,Karahalios et al., 2016]). Results from the Framingham study indicated that the association between BMI and colon cancer diminished after adjusting for WC while the same thing did not happen when WC effects were adjusted for BMI ([Moore et al., 2004]). A recent meta-analysis has showed that the role of WC and WHR on colon cancer incidence is considerable ([Dong et al., 2017]). However, another recently published study found no significant association between BMI and colon cancer risk in both sexes while WC was shown to be a better predictor of colon cancer risk in men ([Andreasson et al., 2019]). In our study, WHR was significantly associated with colorectal cancer risk in women. The lack of a significant association among men in our study may be explained by the lower prevalence of obesity compared to women in our population. It has also been proposed that weight change may be a better predictor of colorectal cancer (CRC) in men ([Kim and Giovannucci, 2017]). However, since in our cohort anthropometric measures were assessed only at baseline, changes in obesity measures over time could not be examined.

Pancreatic cancer

A meta-analysis has showed that both general and central obesity increase pancreatic cancer risk ([Aune et al., 2012]). However, another prospective cohort study, found no convincing evidence that BMI is associated with pancreatic cancer risk ([Kuzmickiene et al., 2013]). The association between BMI and pancreatic cancer has been inconsistent in Asian populations. Pooled data from cohort studies with a considerable number of Japanese participants revealed a significant positive association between obesity and pancreatic cancer risk among men ([Koyanagi et al., 2018]). However, a meta-analysis aimed to reveal population-specific associations between BMI and cancer incidence did not find any association between increased BMI and pancreatic cancer incidence in the Asia–Pacific population ([Wang et al., 2016b]). Although moderate, the magnitude of the association between obesity and pancreatic cancer was enough to be listed as an obesity-related cancer by IARC. The reason why we could not find any significant association between obesity and pancreatic cancer might be due to the small number of pancreatic cancers in this study.

Strengths and limitations

The strengths of this study include its prospective design and a large number of participants with a low rate of loss to follow- up (1%). Misclassification of exposures has been minimized as anthropometric indices were measured at baseline by trained personnel at the referral center, in contrast to the self-reported data used in several previous studies. A comprehensive assessment of all obesity measures is another strength of this study. Moreover, we had relatively comprehensive information on the main risk factors for common GI cancers. However, we did not have longitudinal data to account for changes in the anthropometric variables over time.

Conclusions

This study confirmed an inverse association between general and central obesity and ESCC risk in women. Moreover, central obesity measures were significantly associated with the incidence of colorectal and gastric cancers among women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Andreasson A, Hagström H, Sköldberg F, Önnerhag K, Carlsson AC, Schmidt PT et al. (2019). The prediction of colorectal cancer using anthropometric measures: A Swedish population-based cohort study with 22 years of follow-up. United European gastroenterology journal 7(9):1250–1260. [PubMed: 31700638]

Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA et al. (2012). Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Annals of oncology : official journal of the European Society for Medical Oncology 23(4):843–852. doi: 10.1093/annonc/mdr398. [PubMed: 21890910]

AZIZI F, Khalili D, Aghajani H, ESTEGHAMATI A, Hosseinpanah F, DELAVARI A et al. (2010). Appropriate waist circumference cut-off points among Iranian adults: the first report of the Iranian National Committee of Obesity.

Babaei M, Jaafarzadeh H, Sadjadi A, Samadi F, Yazdanbod A, Fallah M et al. (2009). Cancer incidence and mortality in Ardabil: Report of an ongoing population-based cancer registry in Iran, 2004–2006. Iranian Journal of Public Health:35–45.

Balakrishnan M, George R, Sharma A, Graham DY (2017). Changing trends in stomach cancer throughout the world. Current gastroenterology reports 19(8):36. [PubMed: 28730504]

Barberio AM, Alareeki A, Viner B, Pader J, Vena JE, Arora P et al. (2019). Central body fatness is a stronger predictor of cancer risk than overall body size. Nature communications 10(1):1–12.

Bodelon C, Anderson GL, Rossing MA, Chlebowski RT, Ochs-Balcom HM, Vaughan TL (2011). Hormonal factors and risks of esophageal squamous cell carcinoma and adenocarcinoma in postmenopausal women. Cancer prevention research 4(6):840–850. [PubMed: 21505180]

Brown LM, Gent L, Davis K, Clegg DJ (2010). Metabolic impact of sex hormones on obesity. Brain research 1350:77–85. [PubMed: 20441773]

Chen Y, Liu L, Wang X, Wang J, Yan Z, Cheng J et al. (2013). Body mass index and risk of gastric cancer: a meta-analysis of a population with more than ten million from 24 prospective studies. Cancer Epidemiology and Prevention Biomarkers 22(8):1395–1408.

Cho JH, Shin CM, Han K-D, Yoon H, Park YS, Kim N et al. (2019). Abdominal obesity increases risk for esophageal cancer: a nationwide population-based cohort study of South Korea. Journal of Gastroenterology:1–10. [PubMed: 29961130]

Clinton SK, Giovannucci EL, Hursting SD (2020). The World Cancer Research Fund/American Institute for Cancer Research Third Expert Report on Diet, Nutrition, Physical Activity, and Cancer: Impact and Future Directions. The Journal of Nutrition 150(4):663–671. [PubMed: 31758189]

Dong Y, Zhou J, Zhu Y, Luo L, He T, Hu H et al. (2017). Abdominal obesity and colorectal cancer risk: systematic review and meta-analysis of prospective studies. Bioscience reports 37(6).

Dorak MT, Karpuzoglu E (2012). Gender differences in cancer susceptibility: an inadequately addressed issue. Frontiers in genetics 3:268. [PubMed: 23226157]

Du X, Hidayat K, Shi B-M (2017). Abdominal obesity and gastroesophageal cancer risk: systematic review and meta-analysis of prospective studies. Bioscience reports 37(3):BSR20160474. [PubMed: 28336766]

Enzinger PC, Mayer RJ (2003). Esophageal cancer. New England Journal of Medicine 349(23):2241–2252.

Freedman ND, Lacey JV Jr, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC (2010). The association of menstrual and reproductive factors with upper gastrointestinal tract cancers in the NIH-AARP cohort. Cancer: Interdisciplinary International Journal of the American Cancer Society 116(6):1572–1581.

Gallus S, Bosetti C, Franceschi S, Levi F, Simonato L, Negri E et al. (2001). Oesophageal cancer in women: tobacco, alcohol, nutritional and hormonal factors. British journal of cancer 85(3):341–345. [PubMed: 11487262]

Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM et al. (2016). American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocrine Practice 22(s3):1–203.

Hadaegh F, Zabetian A, Sarbakhsh P, Khalili D, James W, Azizi F (2009). Appropriate cutoff values of anthropometric variables to predict cardiovascular outcomes: 7.6 years follow-up in an Iranian population. International journal of obesity 33(12):1437–1445. [PubMed: 19752876]

Hamaguchi M, Hashimoto Y, Obora A, Kojima T, Fukui M (2019). Non-alcoholic fatty liver disease with obesity as an independent predictor for incident gastric and colorectal cancer: a population-based longitudinal study. BMJ open gastroenterology 6(1):e000295.

Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M (2020). Impact of metabolically healthy obesity on the risk of incident gastric cancer: a population-based cohort study. BMC endocrine disorders 20(1):11. [PubMed: 31959179]

Islami F, Kamangar F, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, Abedi-Ardekani B et al. (2009). Socio-economic status and oesophageal cancer: results from a population-based case-control study in a high-risk area. Int J Epidemiol 38(4):978–988. doi: 10.1093/ije/dyp195. [PubMed: 19416955]

Kalayarasan R, Ananthakrishnan N, Kate V, Basu D (2008). Estrogen and progesterone receptors in esophageal carcinoma. Diseases of the Esophagus 21(4):298–303. [PubMed: 18477250]

Karahalios A, Simpson JA, Baglietto L, MacInnis RJ, Hodge AM, Giles GG et al. (2016). Change in weight and waist circumference and risk of colorectal cancer: results from the Melbourne Collaborative Cohort Study. BMC cancer 16(1):157. [PubMed: 26917541]

Keimling M, Renehan AG, Behrens G, Fischer B, Hollenbeck AR, Cross AJ et al. (2013). Comparison of associations of body mass index, abdominal adiposity, and risk of colorectal cancer in a large prospective cohort study. Cancer Epidemiology and Prevention Biomarkers 22(8):1383–1394.

Kim H, Giovannucci EL (2017). Sex differences in the association of obesity and colorectal cancer risk. Cancer Causes & Control 28(1):1–4. [PubMed: 27878394]

Koyanagi YN, Matsuo K, Ito H, Tamakoshi A, Sugawara Y, Hidaka A et al. (2018). Body-Mass Index and Pancreatic Cancer Incidence: A Pooled Analysis of Nine Population-Based Cohort Studies With More Than 340,000 Japanese Subjects. Journal of epidemiology 28(5):245–252. doi: 10.2188/jea.JE20160193. [PubMed: 29225297]

Kuzmickiene I, Everatt R, Virviciute D, Tamosiunas A, Radisauskas R, Reklaitiene R et al. (2013). Smoking and other risk factors for pancreatic cancer: a cohort study in men in Lithuania. Cancer Epidemiol 37(2):133–139. doi: 10.1016/j.canep.2012.10.001. [PubMed: 23107757]

Lahmann PH, Pandeya N, Webb PM, Green AC, Whiteman DC, Study AC (2012). Body mass index, long-term weight change, and esophageal squamous cell carcinoma: Is the inverse association modified by smoking status? Cancer 118(7):1901–1909. [PubMed: 21960146]

Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K (2016). Body fatness and cancer—viewpoint of the IARC Working Group. New England Journal of Medicine 375(8):794–798.

Lee KR, Seo MH, Do Han K, Jung J, Hwang IC (2018). Waist circumference and risk of 23 site-specific cancers: a population-based cohort study of Korean adults. British journal of cancer 119(8):1018–1027. [PubMed: 30327562]

Leitzmann MF, Moore SC, Koster A, Harris TB, Park Y, Hollenbeck A et al. (2011). Waist circumference as compared with body-mass index in predicting mortality from specific causes. PloS one 6(4).

Matsuoka H, Sugimachi K, Ueo H, Kuwano H, Nakano S, Nakayama M (1987). Sex hormone response of a newly established squamous cell line derived from clinical esophageal carcinoma. Cancer research 47(15):4134–4140. [PubMed: 3607755]

Moore L, Bradlee M, Singer M, Splansky G, Proctor M, Ellison R et al. (2004). BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. International journal of obesity 28(4):559–567. [PubMed: 14770200]

Organization WH (1992). International statistical classification of diseases and related health problems: 10th revision (ICD-10). http://wwwwhoint/classifications/apps/icd/icd.

Organization WH (2011). Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8–11 December 2008.

Padmanabhan S, Waly MI, Taranikanti V, Guizani N, Rahman MS, Ali A et al. (2018). Modifiable and non-modifiable risk factors for colon and rectal cancer. In: Bioactive Components, Diet and Medical Treatment in Cancer Prevention. Springer; pp. 121–130.

Pourfarzi F, Whelan A, Kaldor J, Malekzadeh R (2009). The role of diet and other environmental factors in the causation of gastric cancer in Iran—a population based study. International journal of cancer 125(8):1953–1960. [PubMed: 19569234]

Pourshams A, Saadatian-Elahi M, Nouraie M, Malekshah A, Rakhshani N, Salahi R et al. (2005). Golestan cohort study of oesophageal cancer: feasibility and first results. British journal of cancer 92(1):176–181. [PubMed: 15597107]

Pourshams A, Khademi H, Malekshah AF, Islami F, Nouraei M, Sadjadi AR et al. (2010). Cohort profile: the Golestan Cohort Study—a prospective study of oesophageal cancer in northern Iran. International journal of epidemiology 39(1):52–59. [PubMed: 19332502]

Rawla P, Barsouk A (2019). Epidemiology of gastric cancer: global trends, risk factors and prevention. Przeglad gastroenterologiczny 14(1):26. [PubMed: 30944675]

Rawla P, Sunkara T, Barsouk A (2019). Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors. Przegląd Gastroenterologiczny 14(2):89. [PubMed: 31616522]

Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. The Lancet 371(9612):569–578.

Sheikh M, Poustchi H, Pourshams A, Etemadi A, Islami F, Khoshnia M et al. (2019). Individual and combined effects of environmental risk factors for esophageal cancer based on results from the Golestan Cohort Study. Gastroenterology 156(5):1416–1427. [PubMed: 30611753]

Siiteri PK (1987). Adipose tissue as a source of hormones. The American journal of clinical nutrition 45(1):277–282. [PubMed: 3541569]

Smith M, Zhou M, Whitlock G, Yang G, Offer A, Hui G et al. (2008). Esophageal cancer and body mass index: results from a prospective study of 220,000 men in China and a meta-analysis of published studies. International journal of cancer 122(7):1604–1610. [PubMed: 18059032]

Song H, Saito E, Sawada N, Abe SK, Hidaka A, Shimazu T et al. (2017). Body mass index change during adulthood and risk of oesophageal squamous-cell carcinoma in a Japanese population: the Japan Public Health (JPHC)-based prospective study. British journal of cancer 117(11):1715–1722. [PubMed: 28949955]

Steffen A, Schulze MB, Pischon T, Dietrich T, Molina E, Chirlaque M-D et al. (2009). Anthropometry and esophageal cancer risk in the European prospective investigation into cancer and nutrition. Cancer Epidemiology and Prevention Biomarkers 18(7):2079–2089.

Stone TW, McPherson M, Darlington LG (2018). Obesity and cancer: existing and new hypotheses for a causal connection. EBioMedicine 30:14–28. [PubMed: 29526577]

Thomas D (2010). Gene–environment-wide association studies: emerging approaches. Nature Reviews Genetics 11(4):259–272.

Tsugane S, Sasazuki S (2007). Diet and the risk of gastric cancer: review of epidemiological evidence. Gastric cancer 10(2):75–83. [PubMed: 17577615]

Turati F, Tramacere I, La Vecchia C, Negri E (2013). A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. Annals of oncology 24(3):609–617. [PubMed: 22898040]

Untawale S, Odegaard AO, Koh WP, Jin AZ, Yuan JM, Anderson KE (2014). Body mass index and risk of pancreatic cancer in a Chinese population. PLoS One 9(1):e85149. doi: 10.1371/journal.pone.0085149. [PubMed: 24454807]

Wallace IR, McKinley MC, Bell PM, Hunter SJ (2013). Sex hormone binding globulin and insulin resistance. Clinical endocrinology 78(3):321–329. [PubMed: 23121642]

Wang J, Yang D-L, Chen Z-Z, Gou B-F (2016a). Associations of body mass index with cancer incidence among populations, genders, and menopausal status: a systematic review and meta-analysis. Cancer Epidemiology 42:1–8. [PubMed: 26946037]

Wang J, Yang DL, Chen ZZ, Gou BF (2016b). Associations of body mass index with cancer incidence among populations, genders, and menopausal status: A systematic review and meta-analysis. Cancer Epidemiol 42:1–8. doi: 10.1016/j.canep.2016.02.010. [PubMed: 26946037]

Yang P, Zhou Y, Chen B, Wan H-W, Jia G-Q, Bai H-L et al. (2009). Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. European journal of cancer 45(16):2867–2873. [PubMed: 19427197]

Zhang Y, Pan T, Zhong X, Cheng C (2015). Androgen receptor promotes esophageal cancer cell migration and proliferation via matrix metalloproteinase 2. Tumor Biology 36(8):5859–5864. [PubMed: 25724186]

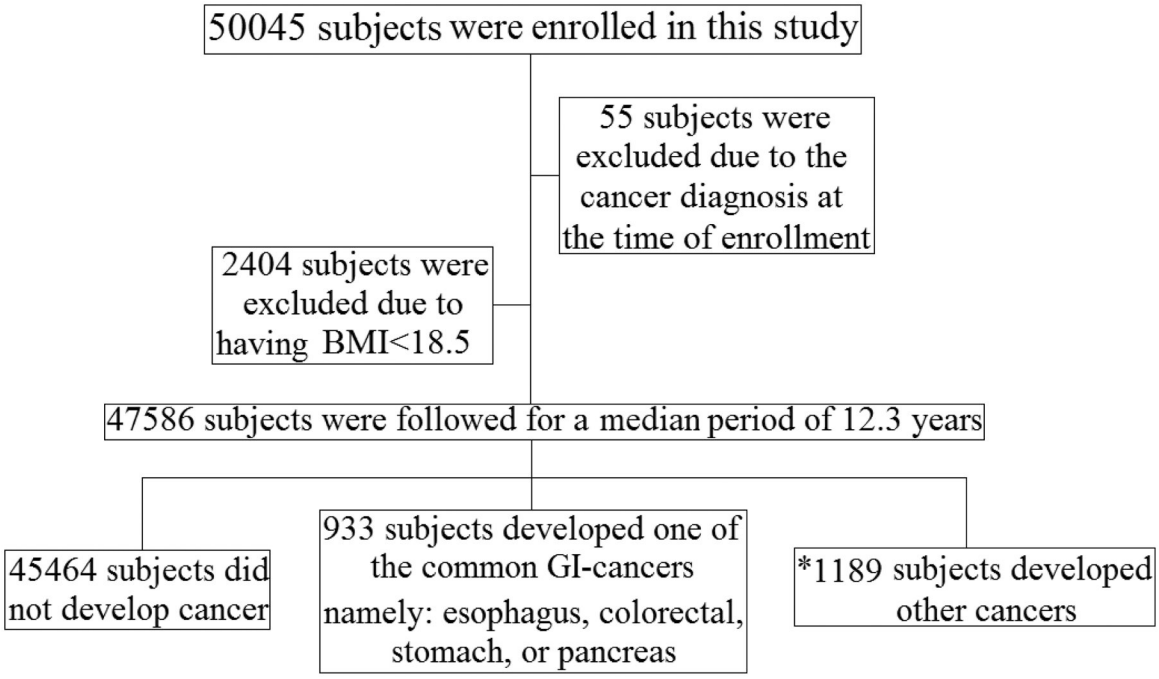

Figure 1.

Flow diagram of the study population.

*These participants have been censored after the diagnosis of cancer. GI-cancers; gastrointestinal cancers.

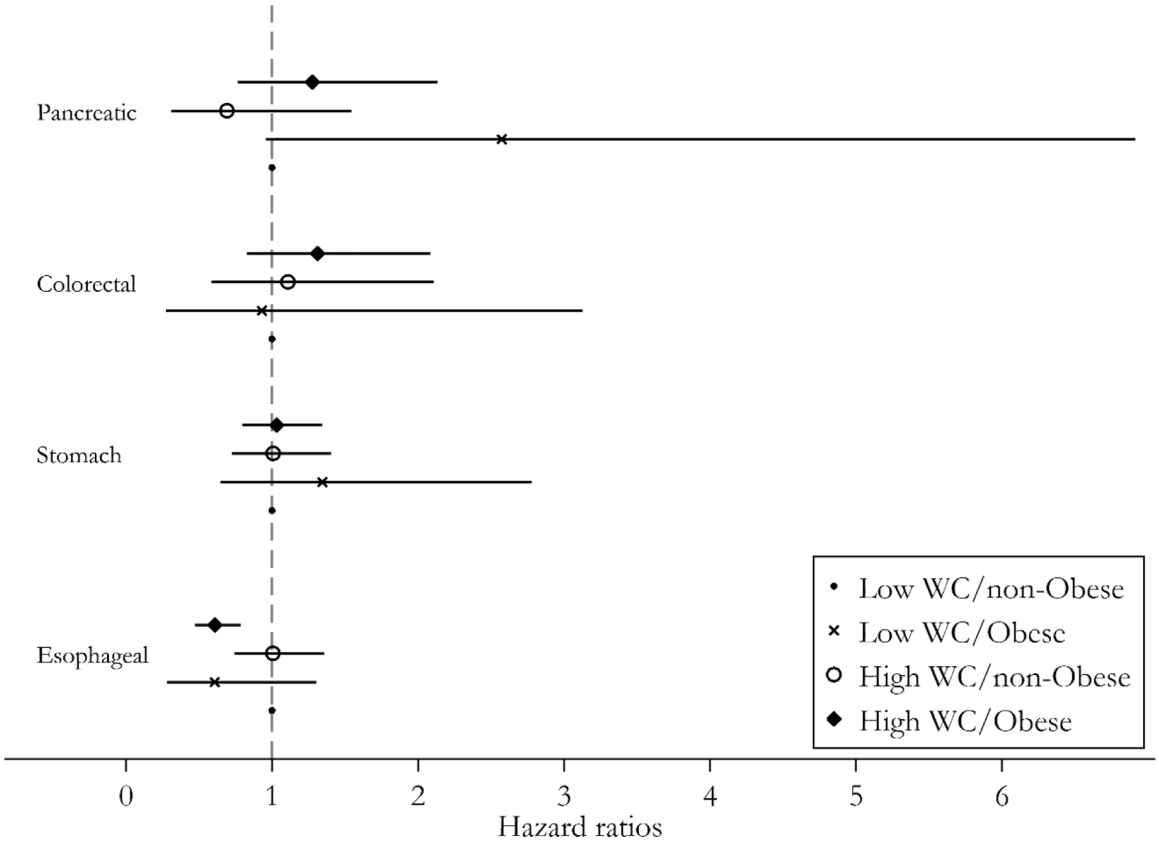

Figure 2.

Hazard ratio for common GI cancers by WC and BMI groups. Models are adjusted for age, sex, marital status, education level, socioeconomic status, smoking, opium use, alcohol use, area of residence (rural/urban), history of DM, consumption of vegetables, hot tea (only for esophagus cancer). Low WC (WC <90 cm), High WC (WC ≥ 90 cm). Obese (BMI: 25–35 kg/m^2), Non-obese (BMI < 25 kg/m^2). GI; gastrointestinal, BMI; body mass index, WC; waist circumference.

Table 1.

Baseline characteristics of the participants.

variables	*Esophageal cancer (n=352)	Gastric cancer (n=352)	Colon cancer (n=136)	Pancreatic cancer (n=93)	other cancers (n=1189)	No cancer (n=45464)
Age (yr)	58.98 (8.83)	58.95 (9.03)	54.83 (9.27)	58.79 (9.32)	55.56 (9.54)	51.73 (8.77)
BMI(kg/m^2)	24.92 (4.53)	26.26 (5.35)	27.69 (4.78)	26.67 (5.09)	26.58 (5.34)	27.18 (5.14)
WC (cm)	92.17 (12.45)	96.54 (13.45)	99.62 (12.12)	96.40 (12.75)	95.71 (13.48)	96.55 (12.95)
WHR	0.95 (0.08)	0.97 (0.08)	0.98 (0.08)	0.98 (0.07)	0.96 (0.08)	0.96 (0.08)
Marital status (% married)	79.6	86.9	90.4	81.7	86.2	88.3
Education level (%)						
Illiterate	84.1	80.7	57.4	74.2	71.0	69.6
≤ 5 yr	11.9	11.4	17.6	17.2	17.8	17.1
6–8 yr	4.0	2.0	5.9	1.1	3.2	4.6
9–12 yr	0.0	4.2	11.8	6.4	6.1	6.5
>12 yr	0.0	1.7	7.3	1.1	1.9	2.2
Socioeconomic status (%)†						
Quartile 1	40.3	38.4	21.3	30.1	27.4	26.6
Quartile 2	25.9	21.6	14.0	18.3	21.4	22.2
Quartile 3	22.4	24.1	21.3	30.1	26.7	25.5
Quartile 4	11.4	15.9	43.4	21.5	24.5	25.7
Smoking status (%)						
Never	81.5	73.9	80.2	75.3	76.3	83.9
Past	6.6	12.8	8.8	9.7	8.2	6.1
Current	11.9	13.3	11.0	15.0	15.5	10.0
Opium use (%)	21.9	24.7	11.0	20.4	22.8	15.3
Alcohol use (%)	0.6	4.8	8.1	5.4	6.1	3.3
Diabetes mellitus (%)	5.4	8.8	10.3	4.3	9.0	7.1
Area of residence (%urban)	9.1	13.6	39.0	24.7	25.2	20.5

Data are presented as mean (SD), or percentage.

†Socioeconomic status was categorized based on a composite wealth score resulted from multiple correspondence analysis on the ownership of house, vehicle, and some home appliances (Islami et al, 2009).

*Esophageal Squamous Cell Carcinoma. BMI; body mass index, WC; waist circumference, WHR; waist-hip-ratio.

Table 2.

Adjusted Cox proportional hazard ratios for incident individual GI cancers per SD of BMI, WC, and WHR.

variable	Total		Male		Female	
	Crude	adjusted	Crude	adjusted	Crude	adjusted
Esophagus						
BMI	0.584 (0.515,0.663)	0.732 (0.639,0.839)	0.640 (0.540,0.759)	0.836 (0.699,1.001)	0.587 (0.493,0.699)	0.672 (0.557,0.809)
WC	0.701 (0.628,0.782)	0.780 (0.693,0.878)	0.721 (0.617,0.842)	0.868 (0.737,1.022)	0.698 (0.598,0.815)	0.708 (0.599,0.837)
WHR	0.912 (0.821,1.014)	0.842 (0.752,0.942)	0.839 (0.723,0.974)	0.896 (0.769,1.044)	0.988 (0.851,1.147)	0.795 (0.676,0.936)
Stomach						
BMI	0.816 (0.730,0.913)	1.150 (1.017,1.299)	0.958 (0.846,1.086)	1.116 (0.977,1.274)	0.996 (0.817,1.215)	1.172 (0.959,1.434)
WC	0.999 (0.899,1.109)	1.122 (1.003,1.255)	1.013 (0.896,1.146)	1.094 (0.960,1.246)	1.132 (0.931,1.377)	1.170 (0.954,1.436)
WHR	1.200 (1.083,1.329)	1.145 (1.025,1.279)	1.123 (0.993,1.271)	1.094 (0.964,1.241)	1.445 (1.226,1.703)	1.235 (1.010,1.51)
Colorectal						
BMI	1.089 (0.925,1.282)	1.104 (0.914,1.333)	1.173 (0.948,1.451)	1.040 (0.815,1.327)	1.215 (0.954,1.547)	1.139 (0.878,1.478)
WC	1.260 (1.069,1.484)	1.174 (0.981,1.406)	1.297 (1.043,1.614)	1.131 (0.887,1.441)	1.287 (1.004,1.65)	1.211 (0.929,1.578)
WHR	1.332 (1.138,1.559)	1.255 (1.051,1.498)	1.314 (1.052,1.642)	1.155 (0.907,1.471)	1.385 (1.107,1.734)	1.389 (1.082,1.782)
Pancreas						
BMI	0.892 (0.722,1.103)	1.083 (0.863,1.358)	0.948 (0.712,1.262)	1.126 (0.831,1.524)	0.950 (0.703,1.284)	1.032 (0.759,1.403)
WC	0.988 (0.806,1.211)	1.056 (0.852,1.310)	0.925 (0.696,1.228)	1.005 (0.743,1.36)	1.096 (0.817,1.469)	1.089 (0.805,1.475)
WHR	1.220 (1.000,1.487)	1.161 (0.941,1.433)	1.134 (0.857,1.501)	1.138 (0.851,1.52)	1.324 (1.007,1.740)	1.175 (0.863,1.600)

Models are adjusted for age, marital status, education level, socioeconomic status, smoking, opium use, alcohol use, area of residence (rural/urban), history of DM, consumption of vegetables, hot tea (only for esophagus cancer). **SDs for total population:**BMI: 5.14 kg/m^2, WC: 12.97cm, WHR: 0.08. **SD for males:**BMI: 4.30 kg/m^2, WC: 12.48 cm, WHR: 0.07. **SD for females:**BMI: 5.40 kg/m^2, WC: 13.26 cm, WHR: 0.08. GI; gastrointestinal, BMI; body mass index, WC; waist circumference, WHR; waist-hip-ratio.