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# A prospective cohort study of obesity and risk of esophageal and gastric adenocarcinoma in the NIH-AARP Diet and Health study

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## Abstract

**Objective—**Incidence of esophageal adenocarcinoma (EAC) has increased rapidly over the past forty years and accumulating evidence suggests that obesity, as measured by body mass index (BMI), is a major risk factor. However, it remains unclear whether abdominal obesity is associated with esophageal and gastric adenocarcinoma.

**Design—**Cox proportional hazards regression was used to examine associations between overall and abdominal obesity with EAC and gastric adenocarcinoma among 218,854 participants in the prospective NIH-AARP cohort.

**Results—**253 incident EAC, 191 gastric cardia adenocarcinomas, and 125 gastric non-cardia adenocarcinomas accrued to the cohort. Overall obesity (BMI) was positively associated with EAC and gastric cardia adenocarcinoma risk (highest [≥35 kg/m$^2$] versus referent [18.5–<25 kg/m$^2$]; hazard ratio (HR) 95% confidence interval (95% CI); 2.11 (1.09–4.09) and 3.67 (2.00–6.71), respectively). Waist circumference was also positively associated with EAC and gastric cardia adenocarcinoma risk, (highest versus referent; HR (95% CI) 2.01 (1.35–3.00) and 2.22 (1.43–3.47), respectively), whereas waist-to-hip ratio (WHR) was positively associated with EAC risk only (highest versus referent; HR (95% CI) 1.81 (1.24–2.64)); persisted in patients with normal BMI (18.5–<25 kg/m$^2$). Mutual adjustment of WHR and BMI attenuated both, but did not eliminate the positive associations for either with risk of EAC. In contrast, the majority of the anthropometric variables were not associated with adenocarcinomas of the gastric non-cardia.

**Conclusion—**Overall obesity was associated with a higher risk of EAC and gastric cardia adenocarcinoma, whereas abdominal obesity was found to be associated with increased EAC risk; even in people with normal BMI.

### Keywords

adenocarcinoma; epidemiology; esophageal cancer; gastric adenocarcinoma; obesity

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**Conflict of Interest:** None.

## INTRODUCTION

Incidence of esophageal adenocarcinoma (EAC) has dramatically increased in recent decades, and this cancer is the most rapidly increasing cancer in the Western World.[1–3] Despite improvements in surgery and chemotherapy, the outlook for patients diagnosed with EAC remains poor, with a 5 year survival rate of less than 20%.[4] Several risk factors for EAC have been identified, including the presence of Barrett's esophagus (BE), gastroesophageal reflux disease (GERD), smoking, white race, male sex, and obesity.[5]

Explanations for increasing rates of EAC remain unclear, though the concurrent increase in the prevalence of obesity may be a partial explanation. The most recent World Cancer Research Fund and American Institute for Cancer Research report rated the evidence for a higher risk of EAC due to greater body fatness as 'convincing'.[5] A study from 2008, using results from published meta-analyses and large cohort studies, reported a steadily increasing impact of obesity on trends in EAC incidence rates (from an attributable risk percent of approximately 21% in 1976–1980 to approximately 36% in 2001–2004 to approximately 40% in 2007).[6] Although overall obesity has emerged as a leading candidate risk factor for EAC,[7–16] few studies have specifically examined body fat distribution, in particular measures of abdominal obesity.[17, 18].

Therefore, we examined the relation between height, overall (weight and body mass index (BMI)) and abdominal (waist circumference, waist-to-hip ratio (WHR)) obesity with EAC using a large prospective cohort. We also assessed these associations with adjacent adenocarcinomas of the gastric cardia and gastric non-cardia.

## MATERIALS AND METHODS

### Study population

The establishment and recruitment procedures of the NIH-AARP Diet and Health study have been described.[19] Between 1995 and 1996, a baseline questionnaire was mailed to 3.5 million AARP (formerly known as the American Association of Retired Persons) members aged 50–71 years eliciting information on demographic characteristics, dietary intake and health-related behaviors. Members resided in six US states (California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania) and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan). Of 617,119 questionnaires returned (17.6% of the 3.5 million mailed), a total of 566,401 respondents completed the survey in satisfactory detail and consented to participate in the study. A follow-up risk factor questionnaire was sent six months afterwards, which included information on waist and hip measurements. A total of 334,907 respondents completed and returned this survey. Of these respondents, we excluded subjects with a cancer diagnosis before returning the risk factor questionnaire (4552), proxy respondents (10,383), and those missing data for body mass index (6608), or coded as missing/error for waist or hip measurements (88,255). Subjects who reported extreme (>2 times the interquartile ranges of sex-specific Box-Cox log-transformed values) total energy intake (1672), BMI (2191), waist (578) and hip (1813) measurements were also excluded. Those subjects who died or were diagnosed with cancer on the first day of follow-up were excluded (1). The resulting cohort included 218,854 participants: 132,288 men and 86,566 women.

### Cohort follow-up

Within the NIH–AARP study, addresses for members of the cohort were updated annually through the US Postal Service national change of address database and also linkage to commercial address databases, such as those used by banks and credit card companies, and take into account response to mailings; all told these resources provide nearly complete

coverage. This method proved to be very robust as during 9 years of follow-up in a pilot study, only 2.5% (288/11,404) of surviving pilot study participants moved out of the cohort regions [20]. Overall, our study has had limited loss to follow-up, with less than 5% of participants moving out of the cancer catchment area. Vital status was ascertained by linkage to the Social Security Administration Death Master File in the United States (all legal US citizens are allocated a Social Security number), follow-up searches of the National Death Index (central computerized index of death record information), cancer registries (NIH-AARP cohort was designed to include only individuals living in cancer registry states/ metropolitan areas), questionnaire responses, and responses to other mailings. Follow-up time extended from study baseline (between 1995 and 1996) through December 31, 2006.

### Identification of cancer cases

Incident cancer cases were identified by linkage between the NIH-AARP cohort membership and ten state cancer registry databases, including the eight original states/ metropolitan areas plus those of Texas and Arizona to capture subjects who moved to these states. A validation study showed that approximately 90% of all incident cancer cases in the NIH–AARP cohort were identified by using this approach.[20] Cancer sites were identified by anatomic site and histologic code of the International Classification of Disease for Oncology (ICD-O, third edition).[21] Tumors with ICD-O codes 15.0–15.9 were classified as esophageal cancers; only esophageal tumors that could be classified histologically as EAC were included in this analysis. Tumors histologically confirmed as adenocarcinomas and with an ICD-O site code of 16.0 were classified as gastric cardia adenocarcinomas; those with codes 16.1–16.7 were classified as gastric non-cardia adenocarcinomas; C16.8 (overlapping tumors) and C16.9 (not otherwise specified) were excluded in this analysis. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute (NCI).

### Exposure assessment

The anthropometric variables height, weight and BMI were derived from information provided in the baseline questionnaire. WHR was calculated from the risk factor questionnaire; participants recorded waist and hip measurements, to the nearest 0.25 inch, in response to detailed instructions. Due to differing fat distribution between men and women, sex-specific quartiles were used for height, weight, waist circumference, hip circumference, and WHR. For BMI, we used predefined World Health Organization's (WHO) standard categories: underweight; <18.5 kg/m2, normal; 18.5–<25, overweight; 25–<30, obese; 30–<35 and morbidly obese; ≥35.

### Statistical analysis

All analyses were carried out using SAS 9.1 (SAS Institute, Cary, NC). We interpreted $P < 0.05$ and/or 95% confidence intervals that excluded 1 as statistically significant. We used two-sided tests exclusively. Follow-up time extended from the day of study entry to date of death, date of diagnosis of first upper gastrointestinal cancer or head and neck cancer, participant relocation out of the registry ascertainment area, or December 31, 2006, whichever date was earliest. We used multivariate Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (95% CI).

We fitted age and sex adjusted models (data not shown) for comparison to fully adjusted models that included total energy intake (daily kilocalories), antacid, aspirin and non-steroidal anti-inflammatory drug use (yes/no during the past 12 months), marital status (yes/ no), diabetes (yes/no), ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and Asian/Pacific Islander/Native American), cigarette smoking (never smokers, former smokers who smoked ≤20 cigarettes/day, former smokers who smoked >20 cigarettes/day, current

smokers who smoke ≤20 cigarettes/day and current smokers who smoke >20 cigarettes/day), education (high school graduate or less, post high school training or some college training, college graduate, and postgraduate education), vigorous physical activity (never, rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5 or more times per week), usual activity throughout the day (sit all day, sit much of the day/walk some times, stand/walk often/no lifting, lift/carry light loads and carry heavy loads), alcohol consumption (none, >0–0.5, >0.5–1, >1–2, >2–4, >4 drinks per day), red and white meat intake (grams per day), and fruit and vegetable intakes (both pyramid servings per day). For the less than 4% of the cohort who had missing data for a particular covariate, a separate indicator variable for missing was included in the models. As a sensitivity analysis, we also created parsimonious regression models by adding potential confounding variables and retaining those that changed the beta coefficients for the anthropometric variables by ≥10%. Risk estimates were similar for both fully adjusted and parsimonious models, and therefore only results from the fully adjusted models are referenced.

We evaluated interactions with smoking (ever/never) and between WHR and BMI (normal 18.5 -<25 kg/$m^2$ or overweight ≥25 kg/$m^2$) by performing stratified analysis and evaluating interaction terms.

In secondary analysis, we estimated whether abdominal obesity was associated with cancer risk statistically independently of the association with general obesity by mutually adjusting BMI and WHR for each other. In separate analyses, waist circumference and hip circumference were also mutually adjusted for each other.

Tests for trend across the categories of anthropometric variables were evaluated by assigning each participant the median category value and modeling this value as a continuous variable.

## RESULTS

Table 1 presents the cohort characteristics by sex-specific quartiles of WHR. A similar table by BMI was published previously.[16] During follow-up, we documented 253 cases of EAC (239 men and 14 women); 191 cases of gastric cardia adenocarcinoma (161 men and 30 women); and 125 cases of gastric non-cardia adenocarcinoma (89 men and 36 women). Men and women with higher WHR had fewer years of education, smoked more, reported less vigorous physical activity, consumed more calories and red meat per day, and were more likely to report diabetes.

Correlations between anthropometric variables are shown in Table 2. Briefly, the correlations of BMI with waist circumference, hip circumference, and WHR were 0.72, 0.72, and 0.35, respectively, and the correlation of waist circumference to hip circumference was 0.65. The correlations of WHR with waist circumference and hip circumference were 0.76 and 0.01, respectively.

Table 3 presents full multivariate-adjusted HR (95% CI) for associations between anthropometric variables and risk of EAC, gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma.

For EAC, weight, BMI, waist circumference, hip circumference, and WHR were positively associated with EAC risk (highest versus referent category; HR (95% CI) 2.66 (1.76–4.02), *P* for trend <0.01; 2.11 (1.09–4.09), *P* for trend <0.01; 2.01 (1.35–3.00), *P* for trend <0.01; 1.65 (1.15–2.36), *P* for trend = 0.01; and 1.81 (1.24–2.64), *P* for trend <0.01, respectively). Multivariate adjustment had only minor influence on the observed risk estimates from the age and sex adjusted models (data not shown). For height, no association for those in the

fourth quartile versus the referent was seen in the age and sex adjusted model (HR (95% CI) 1.06 (0.75–1.50), *P* for trend = 0.92), but a borderline significant inverse association was observed in the multivariate adjusted model (HR (95% CI) 0.69 (0.47–1.01), *P* for trend = 0.09).

Weight, BMI, waist circumference and hip circumference all displayed increasing risk of gastric cardia adenocarcinoma across their quartiles/categories (highest versus referent category; HR (95% CI) 2.52 (1.55–4.11), *P* for trend <0.01; 3.67 (2.00–6.71), *P* for trend <0.01; 2.22 (1.43–3.47), *P* for trend <0.01; 1.71 (1.14–2.58), *P* for trend = 0.01, respectively). WHR was associated with gastric cardia adenocarcinoma in the age and sex adjusted model (fourth quartile versus the referent; HR (95% CI) 1.57 (1.08–2.28), *P* for trend = 0.01), but was attenuated after multivariate adjustment (HR (95% CI) 1.37 (0.92–2.05), *P* for trend = 0.08). For height, no association for those in the fourth quartile versus the referent was seen in the age and sex adjusted model (HR (95% CI) 1.10 (0.76–1.61), *P* for trend = 0.97), but a suggested inverse association was found in the multivariate adjusted model (HR (95% CI) 0.70 (0.46–1.07), *P* for trend = 0.09).

No consistent associations were seen for gastric non-cardia adenocarcinoma with the majority of the anthropometric variables in the multivariate adjusted models. However, weight appeared to be positively associated with gastric non-cardia adenocarcinoma risk; fourth quartile versus the referent; HR (95% CI) 1.93 (1.05–3.54), and the *P* for trend approached significance = 0.07. WHR was also associated with gastric non-cardia adenocarcinoma in the age and sex adjusted model (fourth quartile versus the referent; HR (95% CI) 1.58 (1.05–2.37), *P* for trend = 0.02), and was marginally attenuated after multivariate adjustment (HR (95% CI) 1.56 (0.94–2.59), *P* for trend = 0.05).

We further evaluated whether smoking modified the relation of BMI and WHR with cancer risk using stratified models based on smoking status (smokers/nonsmokers). This was evaluated because smoking can potentially be a strong confounder or effect-modifier of the obesity-cancer association. In general the pattern of risks was similar to that for the overall population, nonsmokers, and smokers. Formal tests for interaction failed to reach statistical significance in any of the investigations (all *P* for interaction >0.05) (see supplemental table).

The association of WHR with cancer risk was also assessed using dichotomous stratification of BMI as normal 18.5–<25 kg/m$^2$ or overweight ≥25 kg/m$^2$ (data not shown). When looking at WHR continuously, per 0.1 unit increment, the positive association seen between WHR and risk of EAC in unstratified analysis (HR (95% CI) 1.27 (1.05–1.53)) remained evident in patients with normal BMI (HR (95% CI) 1.33 (0.85–2.07)), and overweight patients (HR (95% CI) 1.23 (0.99–1.53)). A positive association for WHR was also seen for risk of gastric cardia adenocarcinoma in patients with normal BMI (HR (95% CI) 1.64 (1.06–2.53)), yet it was not present in overweight patients (HR (95% CI) 1.04 (0.80–1.34)), or in unstratified analysis (HR (95% CI) 1.16 (0.93–1.44)). However, formal tests for interaction failed to reach statistical significance in any of these investigations (all *P* for interaction >0.05).

In secondary analyses that further mutually adjusted BMI and WHR (Table 4), the positive associations reported for risk of EAC were both attenuated but not eliminated (BMI: highest versus referent category; HR (95% CI) 1.77 (0.90–3.49), *P* for trend <0.01; WHR: highest versus referent category; HR (95% CI) 1.47 (0.99–2.18), *P* for trend = 0.02). For gastric cardia adenocarcinoma, adjustment of BMI for WHR had only minor influence on the BMI risk estimate (highest versus referent category; HR (95% CI) 3.28 (1.76–6.11), *P* for trend <0.01). WHR risk estimates remained nonsignificant, and were attenuated further after

mutual adjustment for BMI. Adjustment of waist circumference for hip circumference had minor effect on the risk estimates for either EAC or gastric cardia adenocarcinoma, whereas mutual adjustment of hip circumference for waist circumference resulted in null risk estimates for both EAC and gastric cardia adenocarcinoma. No consistent changes in associations were seen for gastric non-cardia adenocarcinoma after mutual adjustments.

## DISCUSSION

In the prospective NIH-AARP cohort, we found that overall obesity, as measured by BMI, was related to higher risk of EAC and gastric cardia adenocarcinoma. We also observed an increased risk of EAC with increasing abdominal obesity, as measured by waist circumference and WHR. Though waist circumference was also related to an increased risk of gastric cardia adenocarcinoma, no association with WHR was observed. The positive association between WHR and EAC risk persisted in patients with normal BMI, and mutual adjustment of WHR and BMI attenuated both, but did not eliminate the positive associations for either with risk of EAC. No consistent associations were seen for gastric non-cardia adenocarcinoma with the majority of the anthropometric variables.

The use of BMI as a marker of obesity has been widely used, with the observation of this current study that BMI is positively associated with risk of EAC being supported by case-control and cohort studies.[8–14, 16–18, 22–24] Because EAC and gastric cardia adenocarcinoma are adjacent tumors which are difficult to separate clinically, they potentially share many of the same risk factors. Therefore, it was unsurprising to find a strong positive association between BMI and gastric cardia adenocarcinoma. Although the pooled results from a meta-analysis of case-control studies found only a weak association between increased BMI and gastric cardia adenocarcinoma in studies from the United States and Europe and no clear association in studies from China,[8] results reported in previous cohort studies, which tend to be more robust, have shown similar results to our study.[11, 12, 16, 17, 22, 24] The lack of an association between BMI and gastric non-cardia adenocarcinoma observed in this current study is also in agreement with several previous studies;[11, 15, 22, 24] although a reduced risk with increasing BMI was demonstrated in a cohort study from Linxian, China [25] in a population considerably leaner than that of the current study.

Even though similar results were found for risk of EAC and gastric cardia adenocarcinoma with BMI, our models suggested that abdominal obesity (as measured by WHR) is associated only with EAC risk and not gastric cardia adenocarcinoma risk. This finding was somewhat surprising and unexpected, particularly due to their adjacent anatomic location, and similar risk factors as demonstrated within this current study. Nonetheless, we cannot rule out chance as the causal factor for this difference. Further studies are needed to address this potential discrepancy.

Our findings that abdominal obesity was also directly associated with risk of EAC helps further extend those observations reported for BMI. To our knowledge, only three other studies have prospectively examined abdominal obesity in relation to EAC.[15, 17, 18] Consistent with our study, a significant positive association was reported with waist circumference in all three, [15, 17, 18] although only two of these studies further adjusted abdominal obesity for BMI [17, 18]. In our study, associations of WHR with EAC risk were attenuated, but not eliminated by adjustment for BMI.

Higher WHR can be the result of a larger waist as well as a smaller hip, either of which could affect disease risk.[26] For example, studies of cardiovascular disease have noted that both large waist circumference and small hip circumference were related to disease risk in a

mutually adjusted model.[26–29] In the current study, the positive associations between waist circumference and EAC and gastric cardia adenocarcinoma risk remained after mutual adjustment for hip circumference; whereas associations between hip circumference and EAC and gastric cardia adenocarcinoma became nonsignificant after mutual adjustment for waist circumference. These results suggest that the positive association between WHR and EAC risk may be due to increasing waist circumference and perhaps visceral fat,[17, 18] rather than hip circumference which may be a marker of lean muscle mass. As waist circumference and WHR are crude measures of intra-abdominal fat, we cannot draw definite conclusions. Future studies with more accurate measures of visceral fat and fat distribution are needed to confirm and extend these findings. Nevertheless, it would appear from our results that both overall and abdominal obesity may be positively associated with EAC risk.

One potential mechanism linking obesity to EAC is mechanical. Obese individuals are thought to have higher prevalence of GERD due to increased intra-abdominal pressure on the lower esophageal sphincter.[30–32] Patients with GERD are commonly treated with medications to suppress the production of or neutralize gastric acid, e.g. antacids. If repeated exposure of esophageal epithelium to gastric acid is the underlying cause of EAC, then it might be predicted that among patients with GERD, those taking acid suppressant medications would have lower risks of EAC than those not taking such medications. However, previous studies do not appear to support these hypotheses, instead suggesting that obesity and GERD are independent risk factors,[10, 33] and reporting a lack of association between acid suppressant medications and EAC associated with GERD.[34, 35] Also, in a recent study and editorial,[36, 37] it was suggested that intra-abdominal fat is associated with an increased risk of erosive esophagitis in both males and females, independent of GERD. Unfortunately, our study lacked information on GERD and thus we could not explore this potential mechanism. However, we did carefully adjust our risk estimates for antacid use, although such adjustment had little effect.

An alternative hypothesis links obesity and cancer risk via the action of three hormonal systems; the insulin and insulin-like growth factor (IGF) axis, sex steroids, and adipokines.[9] These metabolic products are all associated with increasing obesity, and help modulate cellular proliferation and apoptosis.[38] Additionally, the sex-steroid hypothesis may help explain higher incidence rates of these cancers in men, through the presence of estrogen receptors in EAC.[39, 40] Limited evidence suggests that estrogen receptors might mediate a protective effect on estrogen in the development of esophageal cancer.[40] However, adipose tissue is one of the few in vivo tissue depots that express estrogen aromatase and is therefore a primary source of estrogen in both men and postmenopausal women.[41] Therefore, obesity seems unlikely to increase EAC risk through higher estrogen levels in obese people, as women have substantially lower rates of EAC than men.

Another finding from our study is an apparent protective effect of increased height on EAC and gastric cardia adenocarcinoma risk; borderline significance comparing highest versus referent category for EAC; HR (95% CI) 0.69 (0.47–1.01), *P* for trend = 0.09); and a potential protective effect for gastric cardia adenocarcinoma (highest versus referent category; HR (95% CI) 0.70 (0.46–1.07), *P* for trend = 0.09). This result is somewhat consistent with the limited number of previous studies for EAC, but not gastric cardia adenocarcinoma.[10, 42] As attained adult height reflects the integration of many genetic, environmental, hormonal, and also nutritional factors,[5] it is not clear which aspect of height may contribute to the suggested association observed in our study. Future studies are needed to confirm these findings.

We noted an intriguing positive association between WHR and cigarette smoking (Table 1), which is in contrast to the association of BMI in the same cohort.[16] Similar findings have

been reported in previous studies.[43, 44] It is possible that smoking habits may have an effect on fat distribution. Smoking could also affect the uptake and storage of triglyceride fatty acids, increasing fat mass. Differing associations between BMI and WHR with smoking requires further study to help underpin a possible causal relationship.

As smoking is a risk factor for increased risk of both EAC and gastric cardia adenocarcinoma,[45–47] we carefully adjusted our risk estimates for cigarette smoking. Adjustment for smoking had a modest effect on risk estimates. Risk estimates for the anthropometric variables generally appeared similar across stratum of cigarette smoking and tests for interaction were not significant. However, case numbers were limited in some joint-categories of cigarette smoking and adiposity.

Our study had several strengths, including its prospective nature, large size, and available data on a large number of adiposity measures and possible confounders. However, our study also had several limitations. As made evident from Table 2, BMI was highly correlated with waist circumference and hip circumference, but not WHR. Therefore, interpretation of risk estimates from models containing multiple adiposity measures must be treated with caution. We lacked information on possibly important confounders, such as *Helicobacter pylori* infection, a cause of gastric non-cardia adenocarcinoma, which may protect against EAC, [48] and may be associated with reduced obesity.[49] Anthropometric variables in our study relied on self-reported data and therefore misclassification of exposure is a potential source of bias. Finally, we had limited ability to evaluate gender differences due to few case numbers in women. As men and women tend to have different fat distributions, future pooled studies are needed to assess possible differences by sex.

In summary, anthropometric indices of overall obesity were associated with a higher risk of EAC and gastric cardia adenocarcinoma. We also found an increased risk of EAC with increasing abdominal obesity, as measured by WHR, which persisted in patients with normal BMI. Finally, mutual adjustment of WHR and BMI attenuated both, but did not eliminate the positive associations for either with risk of EAC. Associations between obesity and both cancer types suggest that interventions to reduce the prevalence of obesity may help to prevent adenocarcinomas of the esophagus and gastric cardia.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Biographies

Mark G. O'Doherty performed and interpreted the statistical analyses and drafted the manuscript. Neal D. Freedman and Christian C. Abnet participated in interpreting the results, editing the manuscript, and providing study supervision. Albert R. Hollenbeck and Arthur Schatzkin participated in study design, data collection, results interpretation, and manuscript editing. In addition, Neal D. Freedman, Albert R. Hollenbeck, Arthur Schatzkin, and Christian C. Abnet provided study supervision.

## SIGNIFICANCE OF THIS STUDY

**What is already known about this subject**

- Incidence of esophageal adenocarcinoma (EAC) has increased rapidly over the past forty years, and is the most rapidly increasing cancer in the Western World.
- Epidemiological evidence suggests that obesity, as measured by body mass index (BMI), may be a major risk factor. However, associations between body fat distribution, particularly abdominal obesity, have not been widely studied.

**What are the new findings**

- Overall obesity (BMI) was associated with a higher risk of EAC and gastric cardia adenocarcinoma, whereas abdominal obesity, as measured by waist circumference and waist-to-hip ratio (WHR) was associated with increased EAC risk.
- Waist circumference was also related to increased risk of gastric cardia adenocarcinoma, but no association with WHR was observed.
- The positive association between WHR and EAC risk persisted in patients with normal BMI (18.5–<25 kg/m$^2$), and mutual adjustment of WHR and BMI attenuated both, but did not eliminate the positive associations for either with risk of EAC.

**How might it impact on clinical practice in the foreseeable future?**

- Associations between obesity and both EAC and gastric cardia adenocarcinoma suggests that interventions to reduce the prevalence of obesity may help to prevent adenocarcinomas of the esophagus and gastric cardia.

**Table 1**

Characteristics across quartiles of waist-to-hip ratio (WHR) among men and women in the NIH-AARP Diet and health Study (n = 218,854)[1]

| Characteristic | WHR quartiles among men (median) (n = 132,288) | | | | WHR quartiles among women (median) (n = 86,566) | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 (0.88) | 2 (0.93) | 3 (0.96) | 4 (1.02) | 1 (0.73) | 2 (0.78) | 3 (0.83) | 4 (0.90) |
| Number (%) | 33,070 (25.0) | 33,089 (25.0) | 33,092 (25) | 33,037 (25.0) | 21,704 (25.1) | 21,689 (25.1) | 21,567 (24.9) | 21,606 (25.0) |
| Age, mean (SD) | 62.8 (5.3) | 63.3 (5.2) | 63.5 (5.2) | 63.2 (5.2) | 61.7 (5.4) | 62.6 (5.3) | 63.1 (5.2) | 63.5 (5.2) |
| Height (m), mean (SD) | 1.78 (0.1) | 1.78 (0.1) | 1.78 (0.1) | 1.78 (0.1) | 1.63 (0.1) | 1.64 (0.1) | 1.63 (0.1) | 1.63 (0.1) |
| *Race/ethnicity* | | | | | | | | |
| Non-Hispanic white, % | 93.2 | 95.3 | 95.8 | 96.5 | 93.9 | 93.6 | 93.3 | 93.1 |
| Non-Hispanic black, % | 2.9 | 1.4 | 1.2 | 1.1 | 3.8 | 3.3 | 3.3 | 4.1 |
| Hispanic, % | 1.5 | 1.6 | 1.7 | 1.5 | 1.3 | 1.6 | 1.9 | 1.6 |
| Other, % | 2.3 | 1.6 | 1.3 | 0.9 | 1.1 | 1.5 | 1.5 | 1.3 |
| *Education* | | | | | | | | |
| High school or less, % | 15.4 | 16.3 | 17.8 | 20.4 | 23.2 | 25.5 | 29.0 | 31.9 |
| Post high school, % | 8.8 | 9.0 | 9.4 | 10.9 | 10.0 | 10.8 | 11.4 | 11.9 |
| Some college, % | 21.3 | 21.6 | 22.5 | 24.0 | 26.6 | 26.2 | 25.9 | 25.5 |
| College and post graduate, % | 54.5 | 53.1 | 50.2 | 44.7 | 40.2 | 37.5 | 33.7 | 30.7 |
| *Smoking* | | | | | | | | |
| Never smoked, % | 36.2 | 33.7 | 30.9 | 25.9 | 50.5 | 47.1 | 45.7 | 42.0 |
| Former ≤ 20 cigarettes/day, % | 30.4 | 30.5 | 30.1 | 27.7 | 27.4 | 27.6 | 26.8 | 26.0 |
| Former > 20 cigarettes/day, % | 23.0 | 26.2 | 29.1 | 34.6 | 8.9 | 11.1 | 12.6 | 15.0 |
| Current ≤ 20 cigarettes/day, % | 6.7 | 5.6 | 5.6 | 6.0 | 10.3 | 10.6 | 10.6 | 11.3 |
| Current > 20 cigarettes/day, % | 3.8 | 4.1 | 4.4 | 5.9 | 2.9 | 3.6 | 4.3 | 5.7 |
| *Vigorous physical activity* | | | | | | | | |
| Never, % | 1.9 | 2.0 | 2.5 | 3.4 | 3.0 | 3.3 | 4.2 | 6.2 |
| Rarely, % | 7.2 | 8.3 | 9.9 | 13.1 | 10.7 | 12.7 | 14.8 | 18.5 |
| 1–3 time/month, % | 10.1 | 11.2 | 12.5 | 15.0 | 12.0 | 12.8 | 14.6 | 14.8 |
| 1–2 times/week, % | 20.1 | 21.7 | 22.9 | 23.4 | 20.6 | 22.1 | 21.7 | 21.9 |
| 3–4 times/week, % | 32.3 | 31.5 | 30.2 | 26.8 | 30.6 | 29.1 | 27.4 | 24.1 |
| ≥ 5 times/week, % | 28.6 | 25.5 | 22.0 | 18.3 | 23.1 | 20.0 | 17.4 | 14.4 |
| *Activity throughout the day* | | | | | | | | |

| Characteristic | WHR quartiles among men (median) (n = 132,288) | | | | WHR quartiles among women (median) (n = 86,566) | | | |
|---|---|---|---|---|---|---|---|---|
| | **1 (0.88)** | **2 (0.93)** | **3 (0.96)** | **4 (1.02)** | **1 (0.73)** | **2 (0.78)** | **3 (0.83)** | **4 (0.90)** |
| Sit during day, not much walking, % | 5.0 | 5.4 | 6.6 | 8.8 | 6.0 | 6.3 | 6.9 | 8.8 |
| Sit much of day, walk a fair amount, % | 31.4 | 31.1 | 32.5 | 33.7 | 31.2 | 30.9 | 31.5 | 33.7 |
| Stand/walk a lot, no lifting, % | 39.6 | 40.0 | 39.1 | 37.0 | 41.0 | 41.3 | 41.0 | 39.1 |
| Lift/carry light loads, % | 20.3 | 20.1 | 18.9 | 17.5 | 20.1 | 19.9 | 19.0 | 17.0 |
| Heavy work, % | 3.6 | 3.4 | 2.9 | 3.1 | 1.7 | 1.6 | 1.6 | 1.5 |
| Married, Yes, % | 86.3 | 87.0 | 87.1 | 86.7 | 49.0 | 48.4 | 46.8 | 42.8 |
| Self-reported diabetes, % | 6.5 | 7.6 | 8.9 | 11.9 | 2.0 | 3.0 | 4.8 | 11.2 |
| Antacid use, Yes, % | 32.8 | 25.7 | 27.9 | 31.0 | 30.8 | 33.3 | 36.4 | 39.7 |
| Aspirin use, Yes, % | 77.9 | 78.9 | 79.4 | 79.0 | 67.0 | 66.7 | 66.7 | 65.8 |
| NSAID use, Yes,% | 53.2 | 53.9 | 53.5 | 55.1 | 60.7 | 60.4 | 59.8 | 59.7 |
| Calories (kcal), mean (SD) | 1,978 (776) | 1,980 (770) | 2,004 (791) | 2,075 (832) | 1,507 (581) | 1,537 (588) | 1,576 (610) | 1,624 (650) |
| Total fruit (servings/day), mean (SD) | 3.2 (2.5) | 3.1 (2.4) | 3.0 (2.3) | 2.8 (2.3) | 3.1 (2.3) | 3.0 (2.2) | 2.9 (2.3) | 2.9 (2.3) |
| Total vegetables (servings/day), mean (SD) | 4.1 (2.5) | 4.0 (2.4) | 4.0 (2.3) | 4.0 (2.4) | 3.9 (2.5) | 3.8 (2.4) | 3.8 (2.4) | 3.8 (2.4) |
| Total red meat (grams/day), mean (SD) | 69.4 (56.6) | 71.8 (56.0) | 75.9 (57.9) | 84.2 (62.2) | 39.1 (33.7) | 42.2 (35.8) | 45.6 (37.4) | 50.8 (41.1) |
| Total white meat (grams/day), mean (SD) | 62.9 (52.2) | 61.3 (50.3) | 61.5 (49.9) | 62.0 (51.7) | 52.6 (44.6) | 53.9 (45.7) | 54.5 (46.5) | 56.1 (49.1) |
| Alcohol (drinks/day), mean (SD) | 1.1 (2.4) | 1.2 (2.5) | 1.3 (2.8) | 1.4 (3.1) | 0.4 (0.9) | 0.5 (1.0) | 0.5 (1.2) | 0.5 (1.4) |
| *Cancer sites* | | | | | | | | |
| Esophageal adenocarcinoma, *N*(%) | 40 (17) | 45 (19) | 72 (30) | 82 (34) | 0 (0) | 2 (14) | 5 (36) | 7 (50) |
| Gastric cardia adenocarcinoma, *N*(%) | 36 (22) | 33 (21) | 40 (25) | 52 (32) | 5 (17) | 5 (17) | 6 (20) | 14 (47) |
| Gastric non-cardia adenocarcinoma, *N*(%) | 19 (21) | 16 (18) | 19 (21) | 35 (39) | 5 (14) | 8 (22) | 13 (36) | 10 (28) |

*1* some rows or columns may not total 100% due to rounding.

**Table 2**

Pearson Correlation Coefficients for select anthropometric characteristics in the NIH-AARP Diet and health Study (n = 218,854)[1]

| | Characteristic | | | | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Height (m)** | **Weight (kg)** | **BMI (kg/m$^2$)** | **Waist (in)** | **Hip (in)** | **WHR** |
| Height (m) | 1.00 | | | | | |
| Weight (kg) | 0.62 | 1.00 | | | | |
| BMI (kg/m$^2$) | 0.04 | 0.80 | 1.00 | | | |
| Waist (in) | 0.47 | 0.84 | 0.72 | 1.00 | | |
| Hip (in) | 0.14 | 0.64 | 0.72 | 0.65 | 1.00 | |
| WHR | 0.50 | 0.56 | 0.35 | 0.76 | 0.01 | 1.00 |

[1] all $P$<0.0001

**Table 3**

Hazard ratios and 95% confidence intervals of esophageal adenocarcinoma, gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma across categories of anthropometric measures in the NIH-AARP Diet and health Study[1]

| Characteristic[2] | Median by quartile/ category (men/women) | Esophageal adenocarcinoma | | Gastric cardia adenocarcinoma | | Gastric non-cardia adenocarcinoma | |
|---|---|---|---|---|---|---|---|
| | | Cases (n) | Multivariate adjusted HR (95% CI) | Cases (n) | Multivariate adjusted HR (95% CI) | Cases (n) | Multivariate adjusted HR (95% CI) |
| Height (m) | | | | | | | |
| quartile 1 | 1.70/1.57 | 62 | 1.00 (Ref) | 52 | 1.00 (Ref) | 36 | 1.00 (Ref) |
| quartile 2 | 1.78/1.63 | 84 | 1.05 (0.75–1.47) | 45 | 0.66 (0.44–0.99) | 29 | 0.73 (0.44–1.20) |
| quartile 3 | 1.80/1.65 | 38 | 0.90 (0.59–1.36) | 35 | 0.86 (0.55–1.35) | 27 | 1.09 (0.64–1.84) |
| quartile 4 | 1.85/1.73 | 69 | 0.69 (0.47–1.01) | 59 | 0.70 (0.46–1.07) | 33 | 0.84 (0.50–1.42) |
| P for trend | | | 0.09 | | 0.09 | | 0.25 |
| Weight (kg) | | | | | | | |
| quartile 1 | 70.8/55.4 | 41 | 1.00 (Ref) | 28 | 1.00 (Ref) | 20 | 1.00 (Ref) |
| quartile 2 | 79.5/63.6 | 58 | 1.49 (0.99–2.23) | 46 | 1.66 (1.03–2.67) | 35 | 1.93 (1.10–3.38) |
| quartile 3 | 87.2/70.4 | 53 | 1.37 (0.89–2.10) | 44 | 1.53 (0.93–2.51) | 32 | 1.73 (0.96–3.10) |
| quartile 4 | 99.9/84.0 | 101 | 2.66 (1.76–4.02) | 73 | 2.52 (1.55–4.11) | 38 | 1.93 (1.05–3.54) |
| P for trend | | | <0.01 | | <0.01 | | 0.07 |
| BMI (kg/m$^2$) | | | | | | | |
| <18.5 | 18.0/17.9 | 0 | ND | 2 | 2.57 (0.62–10.65) | 1 | 1.34 (0.18–9.79) |
| 18.5–<25 | 23.5/22.5 | 59 | 1.00 (Ref) | 50 | 1.00 (Ref) | 37 | 1.00 (Ref) |
| 25–<30 | 27.0/27.0 | 119 | 1.30 (0.94–1.78) | 79 | 1.15 (0.80–1.65) | 60 | 1.32 (0.86–2.00) |
| 30–<35 | 31.6/31.9 | 64 | 2.28 (1.57–3.30) | 45 | 2.16 (1.41–3.29) | 23 | 1.46 (0.84–2.51) |
| ≥35 | 36.6/37.5 | 11 | 2.11 (1.09–4.09) | 15 | 3.67 (2.00–6.71) | 4 | 0.99 (0.34–2.84) |
| P for trend | | | <0.01 | | <0.01 | | 0.38 |
| Waist circumference (in) | | | | | | | |
| quartile 1 | 34.0/27.8 | 37 | 1.00 (Ref) | 30 | 1.00 (Ref) | 21 | 1.00 (Ref) |
| quartile 2 | 36.5/31.0 | 49 | 1.36 (0.89–2.09) | 38 | 1.32 (0.82–2.14) | 26 | 1.27 (0.71–2.26) |
| quartile 3 | 39.0/34.0 | 79 | 1.51 (1.02–2.25) | 51 | 1.29 (0.82–2.04) | 40 | 1.41 (0.82–2.41) |
| quartile 4 | 43.5/39.0 | 88 | 2.01 (1.35–3.00) | 72 | 2.22 (1.43–3.47) | 38 | 1.46 (0.83–2.55) |
| P for trend | | | <0.01 | | <0.01 | | 0.19 |
| Hip circumference (in) | | | | | | | |

| Characteristic[2] | Median by quartile/ category (men/women) | Esophageal adenocarcinoma | | Gastric cardia adenocarcinoma | | Gastric non-cardia adenocarcinoma | |
|---|---|---|---|---|---|---|---|
| | | Cases (n) | Multivariate adjusted HR (95% CI) | Cases (n) | Multivariate adjusted HR (95% CI) | Cases (n) | Multivariate adjusted HR (95% CI) |
| quartile 1 | 37.0/36.0 | 49 | 1.00 (Ref) | 38 | 1.00 (Ref) | 22 | 1.00 (Ref) |
| quartile 2 | 39.5/39.0 | 62 | 1.27 (0.87–1.85) | 47 | 1.24 (0.81–1.91) | 37 | 1.65 (0.97–2.81) |
| quartile 3 | 41.3/42.0 | 52 | 1.11 (0.75–1.64) | 38 | 1.07 (0.68–1.68) | 28 | 1.31 (0.74–2.30) |
| quartile 4 | 44.0/46.0 | 90 | 1.65 (1.15–2.36) | 68 | 1.71 (1.14–2.58) | 38 | 1.48 (0.86–2.55) |
| P for trend | | | 0.01 | | 0.01 | | 0.37 |
| WHR | | | | | | | |
| quartile 1 | 0.88/0.73 | 40 | 1.00 (Ref) | 41 | 1.00 (Ref) | 24 | 1.00 (Ref) |
| quartile 2 | 0.93/0.78 | 47 | 1.07 (0.70–1.64) | 38 | 0.87 (0.56–1.35) | 24 | 0.95 (0.54–1.67) |
| quartile 3 | 0.96/0.83 | 77 | 1.65 (1.12–2.42) | 46 | 1.00 (0.66–1.53) | 32 | 1.18 (0.69–2.02) |
| quartile 4 | 1.02/0.90 | 89 | 1.81 (1.24–2.64) | 66 | 1.37 (0.92–2.05) | 45 | 1.56 (0.94–2.59) |
| P for trend | | | <0.01 | | 0.08 | | 0.05 |

Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI). BMI = body mass index; ND = no cases in this stratum; WHR = waist-to-hip ratio.

[1]Risk estimates adjusted for age, sex, total energy, antacid use, aspirin use, non-steroidal anti-inflammatory drug use, marital status, diabetes, cigarette smoking, education, ethnicity, alcohol consumption, physical activity, red and white meat intake, and fruit and vegetable intake; also height adjusted for weight and weight adjusted for height.

[2]Anthropometric characteristic categories represent sex-specific quartiles for men and women combined, and BMI uses predefined categories according to the WHO standard definitions: underweight; <18.5 kg/$m^2$, normal; 18.5–<25, overweight; 25–<30, obese; 30–<35; morbidly obese ≥35.

P value for trend across categories is based on the median category values being assigned to each subject within categories and modeled as a continuous variable. ND indicates that there were no cases within this category.

## Table 4

Hazard ratios and 95% confidence intervals of esophageal adenocarcinoma, gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma across mutually adjusted categories of anthropometric measures in the NIH-AARP Diet and health Study[1]

| Characteristic[2] | HR (95% CI) | | |
|---|---|---|---|
| | Esophageal adenocarcinoma | Gastric cardia adenocarcinoma | Gastric non-cardia adenocarcinoma |
| BMI (kg/m$^2$) | | Multivariate + WHR | |
| <18.5 | ND | 2.68 (0.65–11.11) | 1.37 (0.19–10.08) |
| 18.5–<25 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 25–<30 | 1.20 (0.87–1.66) | 1.09 (0.76–1.58) | 1.28 (0.83–1.96) |
| 30–<35 | 1.99 (1.35–2.92) | 1.97 (1.27–3.06) | 1.38 (0.79–2.43) |
| ≥35 | 1.77 (0.90–3.49) | 3.28 (1.76–6.11) | 0.93 (0.32–2.72) |
| P for trend | <0.01 | <0.01 | 0.54 |
| WHR | | Multivariate + BMI | |
| quartile 1 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| quartile 2 | 1.01 (0.66–1.54) | 0.81 (0.52–1.26) | 0.93 (0.53–1.64) |
| quartile 3 | 1.48 (1.00–2.18) | 0.88 (0.57–1.35) | 1.14 (0.67–1.96) |
| quartile 4 | 1.47 (0.99–2.18) | 1.08 (0.71–1.63) | 1.46 (0.86–2.48) |
| P for trend | 0.02 | 0.61 | 0.11 |
| Waist circumference (in) | | Multivariate + hip circumference | |
| quartile 1 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| quartile 2 | 1.36 (0.88–2.11) | 1.28 (0.78–2.09) | 1.27 (0.70–2.29) |
| quartile 3 | 1.52 (0.98–2.34) | 1.21 (0.74–1.99) | 1.41 (0.78–2.55) |
| quartile 4 | 2.03 (1.21–3.39) | 1.98 (1.11–3.53) | 1.46 (0.71–3.03) |
| P for trend | 0.01 | 0.02 | 0.31 |
| Hip circumference (in) | | Multivariate + waist circumference | |
| quartile 1 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| quartile 2 | 1.07 (0.73–1.57) | 1.04 (0.67–1.61) | 1.56 (0.90–2.69) |
| quartile 3 | 0.80 (0.52–1.23) | 0.75 (0.46–1.23) | 1.16 (0.63–2.16) |
| quartile 4 | 0.90 (0.56–1.46) | 0.89 (0.52–1.55) | 1.20 (0.59–2.44) |
| P for trend | 0.48 | 0.54 | 1.00 |

Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI).

[1]Risk estimates adjusted for age, sex, total energy, antacid use, aspirin use, non-steroidal anti-inflammatory drug use, marital status, diabetes, cigarette smoking, education, ethnicity, alcohol consumption, physical activity, red and white meat intake, and fruit and vegetable intake.

[2]WHR, waist circumference and hip circumference characteristic categories represent sex-specific quartiles for men and women combined, and BMI uses predefined categories according to the WHO standard definitions: underweight; <18.5 kg/m$^2$, normal; 18.5–<25, overweight; 25–<30, obese; 30–<35; morbidly obese ≥35.

P value for trend across categories is based on the median category values being assigned to each subject within categories and modeled as a continuous variable.

ND indicates that there were no cases within this category.