Published in final edited form as:

Obesity (Silver Spring). 2010 November ; 18(11): 2204–2211. doi:10.1038/oby.2009.508.

Serum leptin and adiponectin levels and risk of Barrett's esophagus and intestinal metaplasia of the gastroesophageal junction

Olivia M. Thompson^{1,2,3,*}, Shirley A. A. Beresford^{2,4}, Elizabeth A. Kirk^{1,5}, and Thomas L. Vaughan^{2,4}

¹Nutritional Sciences Program, The University of Washington, Seattle, WA

²Division of Public Health Sciences, The Fred Hutchinson Cancer Research Center, Seattle, WA

³Behavioral Research Program, Health Promotion Research Branch, Division of Cancer Control and Population Sciences, The National Cancer Institute, Rockville, MD

⁴Department of Epidemiology, The University of Washington, Seattle, WA

⁵Department of Pathobiology, The University of Washington, Seattle, WA

Abstract

Persons diagnosed with Barrett's esophagus (BE) are at increased risk of developing esophageal adenocarcinoma (EA). Obesity is a major risk factor for both BE and EA. The purpose of this study was to determine the extent to which the adipokines leptin and adiponectin, both of which are deregulated in obese states, mediate the obesity-BE relationship. In this case-control study based in western Washington State, 106 male and 71 female patients newly diagnosed with BE were compared with 112 male and 64 female controls from the general population. Relationships between leptin and adiponectin, obesity, and BE were examined using unconditional logistic regression. Females in the highest tertiles of body mass index and waist circumference were at the greatest risk of BE (adjusted OR=4.3 (95% CI=1.7–10.7), $P_{\text{trend}} < .01$; OR=4.9 (95% CI=1.9–12.5), $P_{\text{trend}} < .01$, respectively) compared to females in the lowest tertiles. Adjustment for leptin and adiponectin attenuated these associations by 43% and 41%, respectively. Similarly, males in the highest tertiles of waist circumference and waist-to-hip ratio were at the greatest risk of BE (adjusted OR=2.1 (95% CI=1.1–4.2), $P_{\text{trend}} = .08$; OR=2.7 (95% CI=1.3–5.7), $P_{\text{trend}} = .01$, respectively) compared to males in the lowest tertiles. However, adjustment for leptin and adiponectin attenuated these associations by only 6% and 8%, respectively. Our study results are consistent with the notion that circulating leptin and adiponectin partially mediate the obesity-BE relationship, particularly in women. Leptin and adiponectin's role in the progression from normal epithelium to BE and on to EA should be further elucidated.

Keywords

Barrett's Esophagus; Esophageal Adenocarcinoma; Leptin; Adiponectin; Obesity

Correspondence: Dr. Olivia M. Thompson, Division of Cancer Control and Prevention Sciences, National Cancer Institute, 6130 Executive Blvd., Room 4074A, MSC 7332, Bethesda, MD 20892-7335, Phone: 301.594.3893, Fax: 301.480.2087, thompsonom@mail.nih.gov.

*The author's present affiliation, which is The National Cancer Institute, is different from those which the work was conducted under, which were The University of Washington and The Fred Hutchinson Cancer Research Center.

Disclosure: None

INTRODUCTION

Esophageal cancer remains a significant global public health problem. It is the eighth most prevalent cancer in the world, accounting for an estimated 462,102 new cases and 385,877 deaths each year (1). Once a relative rarity in the United States (US), esophageal adenocarcinoma (EA) has increased more rapidly than any other cancer over the past 30 years and now represents the most common histologic type of esophageal cancer (2, 3). Most cases of EA develop from a premalignant metaplastic condition termed Barrett's esophagus (BE) that occurs under conditions of chronic gastroesophageal reflux (4). Attention is given to the study of BE not only because patients diagnosed with BE are at high risk of developing EA, but also because of the possibility that modifying behavioral risk factors for BE might be an effective method of preventing the development of EA. Identified risk factors for BE and EA include male sex, white race, advanced age, gastroesophageal reflux disease (GERD), obesity, and cigarette use (4–6).

Obesity in particular is emerging as a strong modifiable behavioral risk factor for BE. Six of eight epidemiologic studies published to date examining the relationship have shown a significant association between obesity and BE (6–13). Furthermore, in a study designed to examine mechanisms by which obesity acts to increase BE risk, Ogunwobi and colleagues (14) established that leptin, an adipokine whose expression and secretion are upregulated in obese states (15–20), was implicated in BE pathophysiology. Recent reports suggest that leptin synergizes with acid to inhibit apoptosis and promote cellular proliferation in Barrett's-derived EA cells, in part, through activation of phosphatidylinositol 3'-kinase (PI3K)/serine/threonine kinase Akt (Akt) (21, 22); that the short form of the leptin receptor is present in Barrett's epithelium (23); and that increased serum leptin is associated with BE risk in men (24).

In a previous report from our community-based case-control study, we observed that obesity significantly increased BE risk (11). In the current analysis, we use data and specimens from this study to examine the extent to which the excess risk associated with measures of obesity is explained by circulating levels of leptin and adiponectin, an adipokine whose expression and secretion are downregulated in obese states (25–28) and has been shown to inhibit leptin-induced EA cell proliferation (29). We compared serum leptin and adiponectin levels of patients newly diagnosed with BE to levels in controls selected from the general population. Consistent with data published from studies of leptin and/or adiponectin and cancer (30, 31), we hypothesized that increased obesity would be associated with increased leptin and decreased adiponectin serum levels, which in turn would lead to an increased risk of BE.

MATERIALS AND METHODS

Study Participants

Cases were defined as adult (20–80 years old) men and women of western Washington State newly diagnosed with BE by biopsy of the tubular esophagus, following upper endoscopy for refractory GERD symptoms between October 1, 1997 and September 30, 2000, as previously described (11). Of the 193 cases who completed the parent study, 177 (92%) completed a blooddraw and had weight and height data, and were therefore included in this report. Consistent with the concept of “ultra-short segment BE” (32–34), cases were defined by the presence of specialized metaplastic epithelium, termed SIM.

Controls were selected from geographic areas in close proximity to those of case participants using a modified version of the Waksberg random-digit dialing (RDD) method (35, 36) where the first five digits of a case participant's residential telephone number are used to

identify potential control participants (37, 38). Controls were matched to cases by age (± 3 years) and sex. Of the 211 population controls who completed the parent study, 176 (83%) completed a blooddraw and had weight and height data, and were therefore included in this study. In the parent study, participants who underwent an upper endoscopy for refractory GERD symptoms but were not diagnosed with BE were included as a second control group. We did not include GERD controls in current analyses, but they were included with the population controls in defining quantiles for continuous variables to be consistent with other reports from the parent study. The Institutional Review Board of the Fred Hutchinson Cancer Research Center (FHCRC) located in Seattle, Washington approved this study.

Data Collection

Measures of obesity included body mass index (BMI; BMI = weight (kg)/height² (m)), waist circumference, and waist-to-hip ratio. Trained FHCRC staff obtained self-reported and measured weight and height values. Staff measured study participants' weight using a UC-300 series Precision Health scale (A&D Weighing, Milpitas, CA) and height using a tape measure, while in usual clothing with shoes removed. We calculated BMI using measured weight and height values wherever possible (three cases and four controls did not have measured values). Using standard procedures, FHCRC staff obtained waist and hip circumference measurements that were used to calculate waist-to-hip ratio.

BMI, waist circumference, and waist-to-hip ratio were each examined in their continuous forms (natural and transformed) and categorized according to sex-specific tertile distributions among the combination of GERD and population controls who partook in the parent study and completed a blooddraw. Among women, BMI was categorized (in kg/m²) as <25.00, 25.00–29.99, and ≥ 30.00 ; waist circumference was categorized (in inches) as <32.00, 32.00–37.99, and ≥ 38.00 ; and waist-to-hip ratio was categorized as <0.80, 0.80–0.84, and ≥ 0.85 . Among men, BMI was categorized (in kg/m²) as <27.00, 27.00–29.99, and ≥ 30.00 ; waist circumference was categorized (in inches) as <37.00, 37.00–40.99, and ≥ 41.00 ; and waist-to-hip ratio was categorized as <0.91, 0.91–0.95, and ≥ 0.96 . Women and men in the lowest categories served as the referent.

Study participants provided additional medical and lifestyle data through in-person, structured interviews with trained interviewers. Known or suspected risk factors analyzed included sex, age (as a continuous variable in years; and categorized, in years, as: 20–39, 40–59, or 60–80), race or ethnicity (non-Hispanic white, Hispanic, or other), educational attainment (categorized, in college years, as: $\leq 1-2$, 3–4, or ≥ 5), annual income (categorized, in US dollars, as: <\$45,000, \$45,000–\$74,999, or $\geq$ \$75,000), and cigarette use (as a continuous variable in pack-years; and ever/never smoked greater than one cigarette per day for ≥ 6 months).

Study participants also provided a 30 ml sample of venous blood upon completion of the parent study. Following blood collection, specimens were immediately transported on ice by courier to the Public Health Sciences Core Laboratory at the FHCRC and processed within 5 hours of receipt. After refrigerated centrifugation, serum specimens were inspected for gross hemolysis or lipemia, aliquotted into cryovials, and stored at -70° C. Serum leptin and adiponectin levels were determined by radioimmunoassay according to the manufacturer's instructions (RIA; Linco Research Inc., St. Charles, MO) at the Northwest Lipid Research Center Laboratory, Seattle, Washington, by laboratory staff blind to study objectives and participants' case or control status.

Serum levels of leptin and adiponectin were each examined in their continuous forms (natural and transformed) and categorized according to sex-specific tertile distributions among the combination of GERD and population controls who partook in the parent study

and completed a blooddraw. Among women, leptin was categorized (in ng/ml) as <13.5, 13.5–25.9, and ≥ 26.0 ; and adiponectin was categorized (in ug/ml) as <11.9, 11.9–18.6, and ≥ 18.7 . Among men, leptin was categorized (in ng/ml) as <4.9, 4.9–9.9, and ≥ 10.0 ; and adiponectin was categorized (in ug/ml) as <7.1, 7.1–11.3, and ≥ 11.4 . Women and men in the lowest categories served as the referent.

Statistical Methods

Participant characteristics were examined using proportions and mean values with corresponding standard deviations and standard errors. To examine relationships between serum levels of leptin and adiponectin and BE, and between obesity and BE we computed odds ratios (ORs) and corresponding 95% confidence intervals (CIs) using unconditional logistic regression in regression models adjusted for age, cigarette use, and leptin or adiponectin. Mediation of the obesity-BE relationship by leptin and/or adiponectin was quantified as a percentage using the following formula (39):

$$100[(OR_{M-} - OR_{M+})/(OR_{M-} - 1)]$$

where OR_{M-} represents the relationship between obesity and BE, without consideration of either adipokine and OR_{M+} represents the relationship between obesity and BE, after adjustment for either adipokine. Tests for linear trends were performed by modeling leptin, adiponectin, BMI, waist circumference, and waist-to-hip ratio in their continuous forms. P-values reported were those that corresponded to linear trends in fully adjusted models. For all analytical tests, a two-sided probability of $p \leq .05$ was considered statistically significant. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Participant characteristics are presented in Table 1. Included in this study were 177 (106 male/71 female) cases and 176 (112 male/64 female) controls. The mean ages of cases and controls were 51.5 ± 12.2 years and 52.6 ± 12.4 years for males, respectively, and 55.8 ± 12.4 years and 56.9 ± 14.1 years for females, respectively. Most of the study participants were non-Hispanic white, and reported earning at least \$45,000 US dollars annually and having some college education. Over 60% of cases reported smoking at least one cigarette per day for 6 months or longer, while less than 50% of controls reported cigarette use. Compared to controls, cases tended to be overweight or obese and had an increased waist circumference and waist-to-hip ratio. Cases had higher leptin and lower adiponectin serum levels compared to controls.

ORs and 95% CIs for serum leptin levels and BE risk, stratified by sex, are presented in Table 2. Serum leptin levels were not significantly associated with BE risk among males, but among females, those in the second and third tertiles of serum leptin level were at increased BE risk (fully adjusted OR=3.4 (95% CI=1.4–8.3); OR=3.1 (95% CI=1.2–8.4) respectively; $P_{\text{trend}}=.03$) compared to those in the first tertile. Furthermore, in a model fit to the combined group of males and females, those in the second and third tertiles of serum leptin level were at increased BE risk (fully adjusted OR=1.8 (95% CI=1.1–3.1); OR=1.9 (95% CI=1.1–3.2) respectively; $P_{\text{trend}}=.03$) compared to those in the first tertile (data not shown).

ORs and 95% CIs for serum adiponectin levels and BE risk, stratified by sex, are presented in Table 3. Serum adiponectin levels were not associated with BE risk in sex-specific models; but in the male and female combined model, those in the third tertile of serum

adiponectin level were at decreased BE risk (fully adjusted OR=0.54 (95% CI=0.31–0.93) $P_{\text{trend}}=.07$) compared to those in the first tertile (data not shown).

ORs and 95% CIs for the various measures of obesity and BE risk attenuated by serum levels of leptin and/or adiponectin, stratified by sex, are presented in Table 4. In males, waist circumference and waist-to-hip ratio were associated with BE risk. Males in the third tertiles of waist circumference and waist-to-hip ratio were at the greatest BE risk (age- and cigarette use-adjusted OR=2.1 (95% CI=1.1–4.2); OR=2.7 (95% CI=1.3–5.7) respectively; waist circumference $P_{\text{trend}}=.08$ and waist-to-hip ratio $P_{\text{trend}}=.01$) compared to males in the first tertiles. Adjustment for serum levels of both leptin and adiponectin attenuated these associations by 6% and 8%, respectively.

In females, BMI and waist circumference were associated with risk of BE. Females in the second and third tertiles of BMI and third tertile of waist circumference were at the greatest BE risk (age- and cigarette use-adjusted OR=3.6 (95% CI=1.5–8.9); OR=4.3 (95% CI=1.7–10.7); OR=4.9 (95% CI=1.9–12.5) respectively; $P_{\text{trend}} < .01$ for both BMI and waist circumference) compared to females in the first tertiles. Adjustment for serum levels of both leptin and adiponectin attenuated these associations by 28%, 43%, and 41%, respectively.

In male and female combined models, BMI, waist circumference, and waist-to-hip ratio were associated with risk of BE. Participants in the third tertiles of BMI, waist circumference, and waist-to-hip ratio were at the greatest BE risk (age-, sex, and cigarette use-adjusted OR=2.3 (95% CI=1.3–3.8); OR=2.8 (95% CI=1.6–4.9); OR=2.4 (95% CI=1.3–4.1) respectively; BMI $P_{\text{trend}}=.01$, waist circumference $P_{\text{trend}} < .01$, waist-to-hip ratio $P_{\text{trend}} < .01$) compared to males and females in the first tertiles. Adjustment for serum levels of both leptin and adiponectin attenuated these associations by 36%, 22%, and 36%, respectively (data not shown).

DISCUSSION

The primary purposes of this study were to determine whether circulating levels of leptin and adiponectin predict risk of BE and to evaluate the extent to which they mediate the relationship between obesity and BE. Our major findings were that: (1) among men and women combined, leptin and adiponectin were significant predictors of BE risk, independent of each other, (2) the associations between the measured adipokine levels and BE risk were substantially stronger among women, and (3) the association between BE risk and obesity was attenuated, but not eliminated, when leptin and adiponectin were considered, by approximately 6–8% (in male models), 28–43% (in female models), and 22–36% (in male and female combined models).

Our finding that increased serum leptin is associated with increased BE risk in men and women combined is in contrast to a finding recently published by Kendall and colleagues (24) from a population-based case-control study conducted in Australia. Compared to males in the lowest quartile of serum leptin, males in the highest quartile were at increased BE risk (OR=2.4; 95% CI=1.1–5.2, in the multivariate-adjusted model), but no associations between serum leptin levels and BE risk were observed in men and women combined or in women separately. Reasons for the discrepant findings between our and Kendall and colleagues' studies are unclear. However, leptin's involvement in cancer pathophysiology in general is supported by numerous studies published in experimental and epidemiologic literature. Garofalo and Surmacz recently published a review of data from pertinent studies (30) examining the relationship of leptin to a variety of cancers including breast, colorectal, prostate, ovarian, endometrial, and lung. In all instances, increased leptin levels were associated with increased cancer risks and/or one or more hallmarks of cancer progression.

Importantly, following publication of Garofalo and Surmacz's review article, Ogunwobi and colleagues (14) published novel data demonstrating that exposure of EA cells to leptin resulted in increased cellular proliferation and inhibition of apoptosis attributable to a cyclooxygenase-2 (Cox-2) dependent, prostaglandin E2 (PGE2) mediated transactivation of the epidermal growth factor receptor (EGFR) and c-Jun NH₂-terminal kinase (JNK).

Adiponectin's involvement in cancer pathophysiology is also supported by a number of epidemiologic and experimental studies. Kelesidis and colleagues recently published a review of articles that examined adiponectin's association with cancers including acute myelogenous leukemia, breast, colorectal, prostate, endometrial, and gastric (31). In all instances, decreased adiponectin levels were associated with increased cancer risks. A recent report from an experimental study of adiponectin and Barrett's-associated EA show that adiponectin (in its globular form), upon binding to and activating the adiponectin receptor-1, inhibits proliferation of leptin-induced EA cells by activating 5'-AMP-activated kinase (AMPK) and serine/threonine phosphatases (29). Thus, downstream signaling events influenced by leptin and/or adiponectin might be expected to alter BE and EA risk.

Several limitations of this study should be noted. Retrospective case-control studies select participants on the basis of the outcome measure, and then obtain past exposure information, and thus are susceptible to recall bias. In this study, very minimal information contributing to the main analyses was obtained by self-report; and the anthropometric and biochemical measurements were obtained objectively and not subject to recall. Selection of appropriate controls for retrospective case-control studies is often a challenge. Selection bias is minimized by the RDD methods employed in the parent study and by our adjustment for covariate data associated with either obesity or BE. However, because we were unable to compare demographic, anthropometric, and metabolic characteristics between responders and non-responders to the control recruitment process, it is possible that those who did participate differ from those who did not participate. A final limitation is that, notwithstanding this study's moderate sample size, we were unable to examine sex differences in BE risk by segment length because of small numbers when subclassification was attempted, and we could not fully consider the effect of participant race or ethnicity on BE risk estimates.

Nevertheless, findings from this study suggest that serum levels of both leptin and adiponectin partially account for the relationship between obesity and BE. While sex-based differences in BE risk need to be further explored in larger studies, results from this study imply that mediation by either adipokine appears to be strongest in women. Future epidemiologic studies are needed to establish the role(s) that leptin and adiponectin play in the progression of BE from normal epithelium, and in the progression to EA from BE. Such studies should explore sex-based differences in BE risk, and consider other factors in the potentially causal pathway explored here, such as exogenous hormone use, diabetic or other chronic disease status, and dietary and physical activity practices, that could moderate either leptin or adiponectin's effect on the obesity-BE relationship.

Acknowledgments

The authors would like to thank Janine Kikuchi and Terri Watson for database management; Tricia Christopherson for management of patient interviews and data collection; Eva Paquette, Kim Hunter, Mike Weygint, and Karen Henniger for interviewing study participants and collecting biospecimens; the many participating gastroenterologists without whom this study could not have been conducted, including Drs. Charles Bedard, Tony Bokorfoush, Robert Sanford, William Hirota, Martin Greene, Richard Tobin, Mitchell Cohen, Willaim Hirota, Steven Lewis, William Putnam, Amy Tsuchida, Alexandra Read, Timothy Little, Robert Durnford, Michael Lyons, Jonathan Kushner, Eric Ormseth, and Spencer Root; and the study participants for their generous contributions of time and commitment to research.

FUNDING

National Cancer Institute (R01 CA72866, 2R25 CA092408-06, K05 CA124911)

REFERENCES

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol*. 2006; 24(14):2137–2150. [PubMed: 16682732]
2. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst*. 2005; 97(2):142–146. [PubMed: 15657344]
3. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin N Am*. 2002; 11:235–256. [PubMed: 12424848]
4. Vaughan, TL. Esophagus. In: Franco, El; Rohn, TE., editors. *Cancer Precursors: Epidemiology, Detection and Prevention*. New York: Springer-Verlag; 2002. p. 96-116.
5. Engel LS, Chow WH, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. *J Natl Cancer Inst*. 2003; 95(18):1404–1413. [PubMed: 13130116]
6. Corley DA, Kubo A, Levin TR, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. *Gastroenterology*. 2007; 133(1):34–41. [PubMed: 17631128]
7. Vaughan TL, Kristal AR, Blount PL, et al. Nonsteroidal anti-inflammatory drug use, body mass index, and anthropometry in relation to genetic and flow cytometric abnormalities in Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev*. 2002; 11(8):745–752. [PubMed: 12163328]
8. El-Serag HB, Kvapil P, Hacken-Bitar J, Kramer JR. Abdominal obesity and the risk of Barrett's esophagus. *Am J Gastroenterol*. 2005; 100(10):2151–2156. [PubMed: 16181362]
9. Stein DJ, El-Serag HB, Kuczynski J, Kramer JR, Sampliner RE. The association of body mass index with Barrett's esophagus. *Aliment Pharmacol Ther*. 2005; 15:22(10):1005–1010.
10. Smith KJ, O'Brien SM, Smithers BM, et al. Interactions among smoking, obesity, and symptoms of acid reflux in Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev*. 2005; 14(11 Pt 1):2481–2486. [PubMed: 16284367]
11. Veugeliers PJ, Porter GA, Guernsey DL, Casson AG. Obesity and lifestyle risk factors for gastroesophageal reflux disease, Barrett esophagus and esophageal adenocarcinoma. *Dis Esophagus*. 2006; 19(5):321–328. [PubMed: 16984526]
12. Edelstein ZR, Farrow DC, Bronner MO, Rosen SN, Vaughan TL. Central adiposity and risk of Barrett's esophagus. *Gastroenterology*. 2007; 39(9):772–778.
13. Anderson LA, Watson RGP, Murphy SJ, et al. Risk factors for Barrett's esophagus and esophageal adenocarcinoma: Results from the FINBAR study. *World J Gastroenterol*. 2007; 13(10):1585–1594. [PubMed: 17461453]
14. Ogunwobi O, Mutungi G, Beales ILP. Leptin stimulates proliferation and inhibits apoptosis in Barrett's esophageal adenocarcinoma cells by cox-2 dependent, PGE2 mediated transactivation of the EGF receptor and JNK activation. *Endocrinology*. 2006; 147(9):401–409.
15. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature*. 1994; 372(6505):425–432. Erratum in: *Nature* 1995;374(6521):479. [PubMed: 7984236]
16. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin levels in normal-weight and obese humans. *N Engl J Med*. 1996; 334(5):292–295. [PubMed: 8532024]
17. Kennedy A, Gettys TW, Watson P, et al. The metabolic significance of leptin in humans: sex-based differences in relationship to adiposity, insulin sensitivity, and energy expenditure. *J Clin Endocrinol Metab*. 1997; 82(4):1293–1300. [PubMed: 9100610]
18. Saad MF, Damani S, Gingerich RL, et al. Sexual dimorphism in plasma leptin level. *J Clin Endocrinol Metab*. 1997; 82(2):579–584. [PubMed: 9024258]
19. Isidori AM, Strollo F, More M, et al. Leptin and aging: correlation with endocrine changes in male and female healthy adult populations of different body weights. *J Clin Endocrinol Metab*. 2000; 85(5):1954–1962. [PubMed: 10843181]

20. Monti V, Carlson JJ, Hunt SC, Adams TD. Relationship of ghrelin and leptin hormones with body mass index and waist circumference in a random sample of adults. *Am Diet Assoc.* 2006; 106(6): 822–828.
21. Beales ILP, Ogunwobi OO. Leptin synergistically enhances the anti-apoptotic and growth-promoting effects of acid in EA oesophageal adenocarcinoma cells in culture. *Mol Cell Endocrinol.* 2007; 274:60–68.
22. Beales ILP, Ogunwobi OO, Cameron E, El-Amin K, Mutungi G, Wilkinson M. Activation of Akt is increased in the dysplasia-carcinoma sequence in Barrett's oesophagus and contributes to increased proliferation and inhibition of apoptosis: a histopathological and functional study. *BMC Cancer.* 2007
23. Francois F, Roper J, Goodman A, et al. The association of gastric leptin with esophageal inflammation and metaplasia. *Gut.* 2007
24. Kendall BJ, Macdonald GA, Hayward NK, et al. Leptin and the risk of Barrett's oesophagus. *Gut.* 2008
25. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). *Biochem Biophys Res Commun.* 1996; 16;221(2):286–289.
26. Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun.* 1999; 257(1):79–83. [PubMed: 10092513]
27. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab.* 2001; 86(5): 1930–1935. [PubMed: 11344187]
28. Gavrilu A, Chan JL, Yiannakouris N, et al. Serum adiponectin levels are inversely associated with overall and central fat distribution but are not directly regulated by acute fasting or leptin administration in humans: cross-sectional and interventional studies. *J Clin Endocrinol Metab.* 2003; 88(10):4823–4831. [PubMed: 14557461]
29. Ogunwobi OO, Beales IL. Globular adiponectin, acting via adiponectin receptor-1, inhibits leptin-stimulated oesophageal adenocarcinoma cell proliferation. *Mol Cell Endocrinol.* 2008; 285(1–2): 43–50. [PubMed: 18313838]
30. Garofalo C, Surmacz E. Leptin and cancer. *J Cell Physiol.* 2006; 207(1):12–22. [PubMed: 16110483]
31. Kelesidis I, Kelesidis T, Mantzoros CS. Adiponectin and cancer: a systematic review. *Br J Cancer.* 2006; 94(9):1221–1225. [PubMed: 16570048]
32. Mueller J, Werner M, Stolte M. Barrett's esophagus: histopathologic definitions and diagnostic criteria. *World J Surg.* 2004; 28:148–154. [PubMed: 14727064]
33. Shama P, Sampliner RE. Short segment Barrett's esophagus and intestinal metaplasia of the cardia—it's not al symantics!!! *Am J Gastroenterol.* 1998; 93:2303–2304. [PubMed: 9820428]
34. Spechler SJ. Short and ultrashort Barrett's esophagus—what does it mean? *Semin Gastrointest Dis.* 1997; 8:59–67. [PubMed: 9109693]
35. Waksburg J. Sampling methods for random digit dialing. *J Am Stat Assoc.* 1978; 73:40–46.
36. Robinson LL, Daigle A. Control selection using random digit dialing for cases of childhood cancer. *Am J Epidemiol.* 1984; 120:164–166. [PubMed: 6741917]
37. Sakkinen PA, Severson RK, Ross JA, Robinson LL. Random digit dialing for control selection in childhood cancer studies: the geographic proximity and demographics within matched sets. *Am J Public Health.* 1995; 85:555–557. [PubMed: 7702122]
38. Voigt LF, Davis S, Koepsell TD. Do cases and controls matched on the first eight digits of their telephone number share geographic proximity and socioeconomic characteristics? *Annals of Epidemiology.* 2006; 16(4):299–304. [PubMed: 16242962]
39. Aneshensel, CS. *Elaborating an explanation: antecedent, intervening, and consequent variables: theory-based data analysis for the social sciences.* Thousand Oaks (CA): Pine Forge Press; 2002. p. 158-190.

Table 1

Characteristics of male and female case and control participants

N = 353	Male Cases (n=106) n (%)	Male Controls (n=112) n (%)	Female Cases (n=71) n (%)	Female Controls (n=64) n (%)
Characteristic				
Age (years)				
20–39	17 (16%)	20 (18%)	7 (10%)	6 (9%)
40–59	63 (59%)	64 (57%)	34 (48%)	32 (50%)
60–80	26 (25%)	28 (25%)	30 (42%)	26 (41%)
Race and Ethnicity				
Non-Hispanic White	101 (95%)	98 (87%)	56 (79%)	63 (98%)
Hispanic	3 (3%)	4 (4%)	5 (7%)	0 (0%)
Other	2 (2%)	10 (9%)	10 (14%)	1 (2%)
Educational Attainment				
<3 Years of College	57 (54%)	51 (46%)	43 (60%)	28 (44%)
3–4 Years of College	23 (22%)	34 (30%)	19 (27%)	21 (33%)
≥5 Years of College	26 (24%)	27 (24%)	9 (13%)	15 (23%)
Annual Income^a				
<\$45,000	22 (22%)	24 (23%)	30 (50%)	26 (42%)
\$45,000–\$74,999	40 (40%)	35 (34%)	15 (25%)	15 (24%)
≥\$75,000	38 (38%)	44 (43%)	15 (25%)	21 (34%)
Cigarette Use				
Ever Used	71 (67%)	54 (48%)	44 (62%)	28 (44%)
Never Used	35 (33%)	58 (52%)	27 (38%)	36 (56%)
Body Mass Index (kg/m²)^b				
Tertile 1	30 (28%)	39 (35%)	13 (18%)	30 (47%)
Tertile 2	31 (29%)	36 (32%)	30 (42%)	18 (28%)
Tertile 3	45 (43%)	37 (33%)	28 (40%)	16 (25%)
Waist circumference (inches)^c				
Tertile 1	22 (21%)	35 (32%)	14 (20%)	27 (44%)
Tertile 2	35 (33%)	38 (34%)	25 (36%)	23 (37%)
Tertile 3	49 (46%)	38 (34%)	31 (44%)	12 (19%)
Waist-to-hip ratio^d				
Tertile 1	20 (19%)	39 (35%)	23 (33%)	28 (45%)
Tertile 2	43 (41%)	41 (37%)	19 (27%)	19 (31%)
Tertile 3	43 (41%)	31 (28%)	28 (40%)	15 (24%)
Serum Leptin (ng/ml)^e				
Tertile 1	26 (25%)	35 (31%)	15 (21%)	27 (42%)
Tertile 2	37 (35%)	36 (32%)	33 (47%)	22 (34%)
Tertile 3	43 (41%)	41 (37%)	23 (32%)	15 (24%)
Serum Adiponectin (ug/ml)^f				

N = 353	Male Cases (n=106) n (%)	Male Controls (n=112) n (%)	Female Cases (n=71) n (%)	Female Controls (n=64) n (%)
Tertile 1	35 (33%)	29 (26%)	29 (41%)	19 (30%)
Tertile 2	32 (30%)	34 (30%)	21 (30%)	20 (31%)
Tertile 3	39 (37%)	49 (44%)	21 (30%)	25 (39%)

^a Male n=100 cases and 103 controls. Female n=60 cases and 62 controls.

^b Tertile 1/Tertile 2/Tertile 3: (Male) <27.00/27.00–29.99/>=30.00; (Female) <25.00/25.00–29.99/>=30.00.

^c Male control n=111. Female n=70 cases and 62 controls. Tertile 1/Tertile 2/ Tertile 3: (Male) <37.00/37.00–40.99/>= 41.00; (Female) <32.00/32.00–37.99/>= 38.00.

^d Male control n=111. Female n=70 cases and 62 controls. Tertile 1/Tertile 2/ Tertile 3: (Male) <0.91/0.91–0.95/>= 0.96; (Female) <0.80/0.80–0.84/>= 0.85.

^e Tertile 1/Tertile 2/Tertile 3: (Male) <4.9/4.9–9.9/>= 10.0; (Female) <13.5/13.5–25.8/>= 25.9.

^f Tertile 1/Tertile 2/Tertile 3: (Male) <7.1/7.1–11.3/>= 11.4; (Female) <11.9/11.9–18.6/>= 18.7.

Table 2Odds ratios and 95% confidence intervals for serum leptin and Barrett's esophagus^a

MALES: N = 218			
	Model A	Model B	p^b
Serum Leptin (ng/ml)			.27
Less than 4.9	1.0	1.0	
4.9 – 9.9	1.3 (0.64–2.6)	1.3 (0.62–2.5)	
10.0 or More	1.4 (0.71–2.7)	1.4 (0.69–2.7)	
FEMALES: N = 135			
	Model A	Model B	p^b
Serum Leptin (ng/ml)			.03
Less than 13.5	1.0	1.0	
13.5 – 25.9	3.3 (1.4–7.8)	3.4 (1.4–8.3)	
26.0 or More	3.6 (1.4–9.3)	3.1 (1.2–8.4)	

^a **Model A** was adjusted for continuous age and categorical cigarette use. **Model B** was further adjusted for serum adiponectin in its continuous (log) form.

^b P-values correspond to tests for linear trends when leptin was modeled in its continuous form, in fully adjusted models.

Table 3Odds ratios and 95% confidence intervals for serum adiponectin and Barrett's esophagus^a

MALES: N = 218			p^b
	Model A	Model B	
Serum Adiponectin (ug/ml)			.50
Less than 7.1	1.0	1.0	
7.1 – 11.3	0.73 (0.36–1.5)	0.72 (0.35–1.5)	
11.4 or More	0.57 (0.29–1.1)	0.58 (0.29–1.2)	
FEMALES: N = 135			p^b
	Model A	Model B	
Serum Adiponectin (ug/ml)			.05
Less than 11.9	1.0	1.0	
11.9– 18.6	0.62 (0.26–1.5)	0.74 (0.30–1.8)	
18.7 or More	0.44 (0.18–1.1)	0.49 (0.20–1.2)	

^a **Model A** was adjusted for continuous age and categorical cigarette use. **Model B** was further adjusted for serum leptin in its continuous (log) form.

^b P-values correspond to tests for linear trends when adiponectin was modeled in its continuous form, in fully adjusted models.

Table 4Odds ratios and 95% confidence intervals for obesity, Barrett's esophagus, and serum leptin and adiponectin^a

MALES: N = 218					p ^b
Body Mass Index (kg/m ²)					.45
Model A	Model B	Model C	Model D		
Less than 27.00	1.0	1.0	1.0		
27.00 – 29.99	1.1 (0.54–2.2)	1.4 (0.49–2.2)	1.1 (0.53–2.2)	1.0 (0.48–2.2)	
30.00 or More	1.6 (0.81–3.0)	1.4 (0.61–3.3)	1.5 (0.78–3.0)	1.4 (0.57–3.2)	
Waist circumference (inches)					.08
Less than 37.00	1.0	1.0	1.0	1.0	
37.00 – 40.99	1.4 (0.70–3.0)	1.4 (0.67–3.1)	1.4 (0.67–2.9)	1.4 (0.64–3.1)	
41.00 or More	2.1 (1.1–4.2)	2.1 (0.84–5.0)	2.0 (0.98–4.1)	2.0 (0.80–4.9)	
Waist-to-hip ratio					.01
Less than 0.91	1.0	1.0	1.0	1.0	
0.91 – 0.95	2.0 (0.99–4.1)	2.0 (0.93–4.1)	2.0 (0.97–4.1)	1.9 (0.91–4.1)	
0.96 or More	2.7 (1.3–5.7)	2.6 (1.2–5.9)	2.7 (1.3–5.7)	2.6 (1.1–5.8)	
FEMALES: N = 135					p ^b
Body Mass Index (kg/m ²)					<.01
Model A	Model B	Model C	Model D		
Less than 25.00	1.0	1.0	1.0	1.0	
25.00 – 29.99	3.6 (1.5–8.9)	3.2 (1.2–8.4)	3.3 (1.3–8.4)	2.9 (1.1–7.6)	
30.00 or More	4.3 (1.7–10.7)	3.3 (1.0–10.7)	3.7 (1.0–10.7)	2.9 (0.87–9.5)	
Waist circumference (inches)					<.01
Less than 32.00	1.0	1.0	1.0	1.0	
32.00 – 37.99	1.8 (0.73–4.5)	1.6 (0.62–4.3)	1.5 (0.60–3.9)	1.4 (0.51–3.7)	
38.00 or More	4.9 (1.9–12.5)	3.9 (1.2–12.7)	4.1 (1.6–10.9)	3.3 (0.97–11.1)	
Waist-to-hip ratio					.09
Less than 0.80	1.0	1.0	1.0	1.0	
0.80 – 0.84	1.2 (0.50–2.8)	1.0 (0.39–2.4)	1.1 (0.5–2.6)	0.88 (0.35–2.2)	
0.85 or More	2.1 (0.87–4.9)	1.6 (0.66–4.0)	1.6 (0.7–4.0)	1.3 (0.50–3.3)	

^a**Model A** was adjusted for continuous age and categorical cigarette use. **Model B** was adjusted for continuous age, categorical cigarette use, and serum leptin in its log-transformed continuous form. **Model C** was adjusted for continuous age, categorical cigarette use, and serum adiponectin in its log-transformed continuous form. **Model D** was adjusted for continuous age, categorical cigarette use, and serum leptin and serum adiponectin in their log-transformed continuous forms.

^bThe P-values correspond to tests for linear trends when each obesity variable was modeled in its continuous form, in age- and cigarette use-adjusted models.