Published in final edited form as:

Dis Esophagus. 2015 April ; 28(3): 283–290. doi:10.1111/dote.12185.

Personal and family history of cancer and the risk of Barrett's esophagus in men

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Abstract

The association between Barrett's esophagus (BE) and a personal or family history of cancer other than gastroesophageal remains unknown. To evaluate the effect of personal and family history of certain cancers and cancer treatments on the risk of BE, we analyzed data from a Veterans Affairs case-control study that included 264 men with definitive BE (cases) and 1486 men without BE (controls). Patients with history of esophageal or gastric cancer were excluded. Patients underwent elective esophagogastroduodenoscopy (EGD) or a study EGD concurrently with screening colonoscopy to determine BE status. Personal and family history of several types of cancer was obtained from self-reported questionnaires, supplemented and verified by electronic medical-record reviews. We estimated the association between personal and family history of cancer or radiation/chemotherapy, and BE. Personal history of oropharyngeal cancer (1.5% vs. 0.4%) or prostate cancer (7.2% vs. 4.4%) was more frequently present in cases than controls. The association between BE and prostate cancer persisted in multivariable analyses (adjusted OR 1.90; 95% CI 1.07-3.38, $P=0.028$) while that with oropharyngeal cancer (adjusted OR 3.63; 95% CI 0.92-14.29, $P=0.066$) was attenuated after adjusting for retained covariates of age, race, GERD, hiatal hernia, and PPI use. Within the subset of patients with cancer, prior treatment with radiation or chemotherapy was not associated with BE. There were no significant differences between cases and controls in the proportions of subjects with several specific malignancies in first- or second-degree relatives. In conclusion, the risk of BE in men may be elevated with prior personal history of oropharyngeal or prostate cancer. However, prior cancer treatments and family history of cancer were not associated with increased risk of BE. Further studies are needed to elucidate if there is a causative relationship or shared risk factors between prostate cancer and BE.

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Keywords

Barrett's esophagus; Esophageal adenocarcinoma; Prostate cancer; Sex hormones; Radiation-induced esophageal damage

Introduction

Barrett's esophagus (BE), an acquired condition characterized by the presence of intestinal metaplasia of the lower esophagus, is the precursor lesion for esophageal adenocarcinoma. BE patients have an estimated overall 0.2% annual risk of progression to adenocarcinoma, which is several fold higher than the general population.^{1, 2} BE is not associated with specific symptoms and requires endoscopy for diagnosis; therefore, identifying risk factors for BE is important for targeted BE screening and, eventually, esophageal cancer prevention.

In 2012, there were approximately 13.7 million Americans living with active or prior history of cancer.³ Cancer survivors are at an approximately 14% higher risk of developing a second primary malignancy than the general population.⁴ Studies have reported the familial clustering of gastroesophageal reflux disease (GERD), BE and esophageal adenocarcinoma;⁵⁻⁸ however, we know little regarding the association between BE and personal or family history of cancer other than gastroesophageal. Studies investigating prior cancer treatments (radiation therapy and/or chemotherapy) and increased risk of BE/EAC have yielded conflicting results.⁹⁻²⁰ To that end, using data from a large case-control study among US veterans, we investigated the relationship between personal and family history of various types of cancer, as well as cancer treatments, on the risk of developing BE.

Methods

Study design and participants

This case-control study of BE risk factors was performed at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC), in Houston, Texas. The study was approved by the Institutional Review Boards for MEDVAMC and Baylor College of Medicine. Details of this study population were previously described.²¹

Briefly, study participants were recruited between February 15, 2008, and December 14, 2012, from among consecutive eligible patients aged 40 to 80 undergoing an elective esophagogastroduodenoscopy (EGD) for any indication, and consecutive patients aged 50-80 attending 1 of 7 selected primary care clinics at the MEDVAMC. The primary care patients were eligible for a screening colonoscopy and agreed to undergo the study EGD during the same clinical visit as their colonoscopy. None of the primary care patients were primarily referred for EGD. The elective endoscopy and primary care groups combined represent all patients both symptomatic or not, who, if they had BE, would be diagnosed at the Houston VA (i.e., the source population for BE). In both groups, we excluded patients with a previous history of esophageal or gastric surgery or cancer, active systemic treatment for any cancer, significant liver disease, history of major stroke or mental disorder, or current use of anticoagulants.

BE cases comprised patients from the elective endoscopy group or the primary care group with specialized small-intestinal epithelium in the histopathological examination of at least 1 biopsy obtained from endoscopically suspected BE areas. Patients with endoscopically suspected BE without specialized intestinal metaplasia on biopsy were not considered in this analysis. Presence and length of BE was recorded at the study EGD according to the Prague C & M classification,²² and two expert pathologists reviewed all slides for endoscopically-suspected BE to determine the presence of specialized intestinal epithelium.

Ascertaining personal and family history of cancer and cancer treatments

Study participants completed a computer-assisted survey administered by a research assistant before their study EGD. The survey contained questions about personal history of cancer, including multiple cancer types; age and year of cancer diagnosis; history of chemotherapy; and history of any cancer in first- and second-degree relatives, specified by type. The VA electronic medical records were reviewed for all study participants to verify self-reported presence or absence of cancer and radiation or chemotherapy history. History, treatment, pathology, or imaging results that were consistent with reported malignancy in the medical record were considered. Medical records were also used to extract the anatomic location of radiation therapy. In cases of disagreement between self-report and medical records, we considered information in the latter to be more valid.

We also collected information from the survey about smoking history, alcohol consumption, GERD symptoms, and use of proton pump inhibitors (PPIs), aspirin, or nonsteroidal anti-inflammatory drugs (NSAIDs). Never smokers were defined as those who had smoked less than 100 cigarettes over their entire life. Participants were classified as positive for *Helicobacter pylori* infection if organisms were seen on histopathological examination of any of the study's gastric biopsies or if review of medical records revealed previously positive biopsies, serum antibodies, or prior treatment. Body mass index (BMI), waist circumference, and waist-to-hip ratio (WHR) values were measured for each participant.

Statistical analysis

The analyses were limited to men. The main exposures were personal or family history of nongastroesophageal cancers and prior cancer treatments (radiation therapy, chemotherapy, and combination chemoradiotherapy). Using bivariate and multivariate logistic regression, we compared the proportions of patients with each exposure between BE cases and all controls combined, as well as between BE cases and each control group separately. Analysis of cancer treatments was conducted among the subgroup of participants with history of cancer.

We calculated odds ratios (OR) and 95% confidence intervals (95% CI), using unconditional logistic-regression models. Forward stepwise selection was used to construct multiple regression models, using variables with a P value < 0.1 in the unadjusted analysis. These variables included age at study recruitment, race (white, black, other), GERD symptom duration and severity, presence of hiatal hernia (none, <3 cm, ≥3 cm), WHR, and PPI use. To examine the effect of possible confounding or explanatory variables, we examined sequential adding of several variables into the models, examining the association between

BE and both oropharyngeal and prostate cancer. All analyses were conducted using SPSS version 20 (IBM Corp.).

Results

In total, 264 BE cases and 1486 combined controls (1038 endoscopy controls and 448 primary care controls) were included in this analysis. The mean age of participants was 60.9 years, most were white (65.8%), and all were men. BE cases were significantly more likely to be white, have hiatal hernias, a history of GERD or PPI use, or WHR 0.9. However, they were significantly less likely to have had *H. pylori* infections than combined controls (Table 1). The average time from cancer diagnosis to study enrollment was not significantly different between cases and controls, 8.86 years and 8.93 years, respectively.

Association between BE and personal history of cancer

A greater proportion of BE cases had a personal history of any cancer (17%) than the combined control group (12.3%; $P=0.036$) (Table 2), the endoscopy control group (12.5%; $P=0.055$), and the primary care control group (11.8%; $P=0.017$). However, no association between history of all cancer types combined and BE was found on stepwise multivariable analysis with retained covariates of race, GERD, and PPI use (combined control group; adjusted OR 1.24; 95% CI 0.86-1.80) (data not shown).

When analyzed by specific cancer types, bivariate analysis showed significant associations between BE and personal history of 2 cancer types: oropharyngeal cancer (unadjusted OR 3.80; 95% CI 1.06-13.54) and prostate cancer (unadjusted OR 1.70; 95% CI 1.00-2.88) (Table 3). In our study population, there were 10 patients with history of oropharyngeal cancer and 84 patients with history of prostate cancer. Other types of cancer examined that were not significantly associated with BE included bladder, colorectal, hematological, kidney, lung, and skin (Table 2).

To examine the effect of possible confounding or explanatory variables, we examined sequential adding of several variables into the models, examining the association between BE and both oropharyngeal and prostate cancer. After adjustment for age, race, GERD, PPI use, WHR, smoking, and alcohol consumption, the association between BE and prostate cancer persisted whereas the adjusted association between BE and oropharyngeal cancer was no longer statistically significant at the 0.05 level (Table 3).

Associations between BE and previous personal cancer treatment

In the subgroup of participants with a personal history of cancer ($n=228$), 53 underwent radiation therapy, 9 received radiation near the esophageal field, 23 received chemotherapy, 11 received combination chemoradiotherapy, and 20 received hormonal therapy for prostate cancer (one in combination with chemotherapy). BE was not more common in those who underwent prior cancer treatments (Table 4). There was no significant association between hormonal therapy and BE.

Associations between BE and family history of cancer

There were no significant associations between BE and history of cancer in first- or second-degree relatives, either for overall history of any cancer or for cancers at individual sites including brain, bladder, colorectal, hematological, kidney, lung, liver, oropharyngeal, prostate, or skin cancers (Table 5).

Discussion

We evaluated the possible effect of personal history of cancer, cancer treatment, and family history of cancer on the risk of BE. On bivariate analysis, there were higher proportions of BE in those with prior history of oropharyngeal and prostate cancer. When adjusted for age, race, GERD, PPI use, alcohol, tobacco use, and WHR, patients with BE had a significant 1.96 higher odds of having a history of prostate cancer than controls. On the contrary, oropharyngeal cancer was not an independent risk factor for BE after adjustment for the same confounders as above (Table 3). Additionally, there was no significant association between history of bladder, colorectal, hematological, kidney, lung, or skin cancer and BE. Lastly, there was no significant association between family history of cancer and risk of BE.

An important finding from our study and one previous report,²³ was the higher rate of BE in patients with history of prostate cancer. Our significant association between prostate cancer and BE became even more prominent after controlling for known BE risk factors (unadjusted OR 1.70; 95% CI 1.00-2.88, P value 0.05 increased to adjusted OR 1.96; 95% CI 1.10-3.47, P value 0.022) (Table 3). Pines et al. recently reported in a case-control study of 3,669 patients with BE and 14,676 controls, a 1.99 relative risk of prostate cancer history in BE patients ($P < 0.001$).²³ The higher prevalence of BE and EAC in men compared to women has been well described,^{24, 25} however differences in known risk factors such as GERD, obesity, and tobacco do not seem to account entirely for the gender discrepancy.²⁶

Several epidemiologic studies suggest that obesity increases the risk of higher stage prostate cancer and a more aggressive course.²⁷ Obesity is also a known risk factor for BE and EAC.²⁸⁻³⁰ In our study population, WHR 0.9 was an independent risk factor for BE, in line with prior analyses in this cohort.²¹ However, the association between prostate cancer and BE was independent of WHR in our combined as well as primary care control groups, but not in the endoscopy control group. Patients in the endoscopy group were more likely to be similar to BE cases with respect to GI symptoms, some cancer risk factors (smoking, alcohol, *H. pylori*), and cancer history than asymptomatic primary care controls. Therefore, important differences in cancer history were more likely to be missed in the comparison between BE cases and endoscopy controls.

There is emerging evidence that sex hormones may play a role,³¹ possibly explaining the link between prostate cancer and BE. Previous studies have identified androgen receptors in both normal and adenocarcinoma esophageal tissue;^{32, 33} Nevertheless, it is not clear to what degree androgen or anti-androgen effects influence the development of BE or EAC. As prostate cancer is an androgen-sensitive malignancy, one study looked at 36,627 men with prostate cancer and observed their rates of developing EAC. They found a reduced risk of EAC in prostate cancer patients, compared to that expected in the general population

(standardized incidence ratio (SIR) 0.7; 95% CI 0.5-0.95). Interestingly, these men had no increased or decreased risk of developing esophageal squamous cell cancer.³⁴ The suggestion that factors predisposing to prostate cancer or the hormonal cancer treatments themselves reduce the risk of EAC is not in line with our findings of a higher rate of BE in prostate cancer patients. It is possible that prostate cancer treatments slow the progression of BE to EAC. Our current body of knowledge regarding the influence of sex hormones on the risk of BE remains limited, and our study did not find an association between hormonal therapy for prostate cancer and risk of BE. The mechanisms underlying a possible link between BE and prostate cancer require further study.

A well-described association between BE and oropharyngeal cancer was supported by our bivariate analysis results; however, after adjustment for potential risk factors, there was no significant association between BE and oropharyngeal cancer (Table 3). Several mechanisms could explain the possible association between BE and aerodigestive-tract cancers found in our study, as well as in a few previous studies.^{35, 36} GERD, the established BE risk factor,^{24, 37} has been implicated as a predisposing factor to developing chronic laryngitis and laryngeal cancer.^{35, 38} A recent cross-sectional study reported that 30% of oropharyngeal cancer patients who never used tobacco or alcohol have GERD symptoms.³⁸ Tobacco has been strongly linked to oropharyngeal cancer³⁹ but not strongly or consistently with BE or esophageal adenocarcinoma.²⁴ A third possible mechanism is shared genetic mutations, such as those in tumor suppressor gene *p53*.⁴⁰

Another possible link between BE and oropharyngeal cancer is infection with human papillomavirus (HPV), a suggested risk factor for head and neck cancer.⁴¹⁻⁴³ While some studies have suggested higher rates of HPV in esophageal tissue samples of those with BE,⁴⁴⁻⁴⁶ two North American case-control studies found no difference in the prevalence of HPV in esophageal tissue samples between patients with BE and healthy controls.^{47, 48} We previously tested HPV status in a subsample of our study participants (39 cases and 127 controls) and found no HPV by immunohistochemistry in any of the samples in either group. Furthermore, no sample had HPV DNA detected via PCR.⁴⁸

In our study, the association between BE and oropharyngeal cancer, while persisting in magnitude (risk estimate is relatively stable), loses statistical significance when adjusting for several potential confounding or explanatory variables. This finding suggests a role for shared risk factors such as GERD, tobacco use, and radiation.

It is possible that local radiotherapy increases the risk of BE. Several studies report increased risk of esophageal squamous cell carcinoma in those with prior history of radiation therapy to the mediastinum;⁹⁻¹² however, no such evidence supports an increased risk of BE or esophageal adenocarcinoma in these patients. In our study, although radiation therapy among BE cases was greater than in controls, this difference was not significant. In a sub-analysis of 181 exclusively white men with history of cancer, the association between esophageal radiation and BE was statistically significant, though limited by a small population size of only 9 patients who received radiation therapy near the esophageal field (3 cases and 6 controls). Lastly, adjusting for radiation attenuated the association between BE and laryngeal cancer suggesting it may explain some of this association.

Our results do not support that chemotherapy or chemoradiotherapy is a risk factor for BE. Some studies suggest an association between systemic chemotherapy and increased risk of BE,¹³⁻¹⁷ while others have found no such association.^{18, 19} Our study differs from previous reports in our deliberate exclusion of patients undergoing active cancer treatment, to avoid confusing transient mucosal damage for BE. It is possible that some of the BE-like changes in previous studies were transient chemotherapy- or radiotherapy-related changes that do not persist in the long term.^{17, 18}

Few studies have examined the association between family history of specific cancers other than esophageal or gastric and the risk of developing BE. In one Italian case- control study of 272 BE patients, 456 esophagitis patients, and 517 controls with normal endoscopic findings and no reflux symptoms, the investigators report that the proportions of participants with 1 relative with cancer were not significantly different among the groups (53%, 51%, and 48%, respectively). There was also no significant difference in family history of any cancer type, including esophageal or gastric, among the 3 groups.⁴⁹ Similarly, our study showed that cancer history in first- or second- degree relatives was not significantly different in BE patients compared with controls.

This study had important limitations. The study population was comprised of only men, and most were in their 7th decade of life; therefore, the findings may not be generalizable to other groups. In addition, the temporality of the timing of cancer and development of BE is unclear because of the nature of our study design. Our sample size (264 BE cases, 1486 controls; of whom 228 individuals have a history of cancer) is adequate to find associations of potential clinical significance. However, the statistical power to find differences was limited by the small number of cases with several individual cancer types, and therefore these associations may have been missed. Our study may have also missed associations between BE and cancers associated with particularly poor outcomes, as we looked solely at rates of BE among cancer survivors. We also did not have information as to the type or dose of chemotherapeutic agents. However, the internal validity of the study was high; as we were able to show the previously established BE risk factors of white race,^{24, 37, 50} male gender,^{24, 50} hiatal hernia,⁵¹ and GERD.^{24, 37}

In conclusion, our findings suggest an association between previous history of oropharyngeal or prostate cancer and increased risk of having BE. Further studies are needed to elucidate if there is a causative relationship or shared risk factors between prostate cancer and BE, which may have implications for current screening practices.

Acknowledgments

Funding: This work is funded in part by National Institutes of Health (NIH) grant from the National Cancer Institute R01 116845, the Houston VA HSR&D Center of Excellence (CIN 13-413), and the Texas Digestive Disease Center NIH DK58338. Dr. El-Serag is also supported by National Institute of Diabetes and Digestive and Kidney Diseases K24-04-107. The opinions expressed reflect those of the authors and not necessarily those of the Department of Veterans Affairs, the US government, the NIH or Baylor College of Medicine. The NIH had no role in the design and conduct of the study, the collection, management, analysis and interpretation of the data, or the preparation, review or approval of the manuscript.

References

1. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of Adenocarcinoma among Patients with Barrett's Esophagus. *N Engl J Med*. 2011; 365:1375–83. [PubMed: 21995385]
2. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst*. 2011; 103:1049–57. [PubMed: 21680910]
3. American Cancer Society Facts & Figures. [Accessed August 18, 2013] 2013. Available at <<http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf>>
4. Curtis, RE.; Freedman, DM.; Ron, E., et al. New malignancies among cancer survivors: SEER cancer registries, 1973-2000. National Cancer Institute; Bethesda (MD): 2006.
5. Romero Y, Cameron AJ, Locke GR, et al. Familial aggregation of gastroesophageal reflux in patients with Barrett's esophagus and esophageal adenocarcinoma. *Gastroenterology*. 1997; 113:1449–56. [PubMed: 9352846]
6. Trudgill NJ, Kapur KC, Riley SA. Familial clustering of reflux symptoms. *Am J Gastroenterol*. 1999; 94:1172–78. [PubMed: 10235188]
7. Crabb DW, Berk MA, Hall TR, et al. Familial gastroesophageal reflux and development of Barrett's esophagus. *Ann Intern Med*. 1985; 103:52–4. [PubMed: 4003988]
8. Fahmy N, King JF. Barrett's esophagus: An acquired condition with genetic predisposition. *Am J Gastroenterol*. 1993; 88:1262–65. [PubMed: 8338095]
9. Audebert A, Sauvanet A, Mauvais F, et al. Radiation-induced esophageal carcinoma: report of 11 cases. *Ann Chir*. 2002; 127:289–96. [PubMed: 11980302]
10. Shimizu T, Matsui T, Kimura O, et al. Radiation-induced esophageal cancer: a case report and a review of the literature. *Jpn J Surg*. 1990; 20:97–100. [PubMed: 2304291]
11. Ahsan H, Neugut AI. Radiation therapy for breast cancer and increased risk for esophageal carcinoma. *Ann Intern Med*. 1998; 128:114–7. [PubMed: 9441571]
12. Taal BG, Aleman BMP, Lebesque JV, et al. The management of radiation-associated oesophageal carcinoma: a report of 16 cases. *Eur J Cancer*. 1993; 294:1114–9. [PubMed: 7686020]
13. Dahms BB, Greco MA, Strandjord SE, et al. Barrett's esophagus in three children after antileukemia chemotherapy. *Cancer*. 1987; 60:2896–900. [PubMed: 3479229]
14. De Mingo L, Garcia C, Morato P, et al. Barrett's esophagus and chemotherapy, a case report. *Eur J Pediatr Surg*. 1999; 9:327–30. [PubMed: 10584194]
15. Schiavetti A, Di Nardo G, Ingrosso A, et al. Barrett esophagus in long-term survivors of childhood solid tumors. *J Pediatr Hematol Oncol*. 2011; 33:559–61. [PubMed: 21900834]
16. Sartori S, Nielsen I, Trevisani L, et al. Barrett's esophagus after antineoplastic chemotherapy. *Endoscopy*. 1990; 22:152. [PubMed: 2357940]
17. Sartori S, Nielsen I, Indelli M, et al. Barrett esophagus after chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF): an iatrogenic injury? *Ann Intern Med*. 1991; 114:210–11. [PubMed: 1984745]
18. Herrera JL, Uzel C, Martino R, et al. Barrett's esophagus: lack of association with adjuvant chemotherapy for localized breast carcinoma. *Gastrointest Endosc*. 1992; 38:551–53. [PubMed: 1397909]
19. Peters FT, Sleijfer DT, van Imhoff GW, et al. Is chemotherapy associated with development of Barrett's esophagus? *Dig Dis Sci*. 1993; 38:923–26. [PubMed: 8482192]
20. Shields HM, Recht A, Wang HH. Exposure to both radiation and chemotherapy increases the risk of Barrett's and multilayered epithelium. *Dig Dis Sci*. 2009; 54:2143–2149. [PubMed: 19093207]
21. Kramer J, Fischbach L, Richardson P, et al. Waist-to-hip ratio, but not body mass index, is associated with an increased risk of Barrett's esophagus in white men. *Clin Gastroenterol Hepatol*. 2013; 11:373–81. [PubMed: 23220167]
22. Sharma P, Dent J, Armstrong D, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. *Gastroenterology*. 2006; 131:1392–9. [PubMed: 17101315]

23. Pines G, Dickman R, Niv Y, et al. Extraesophageal malignancies among patients with Barrett esophagus. *J Clin Gastroenterol*. Mar 15.2013 Epub ahead of print.
24. Wong A, Fitzgerald RC. Epidemiologic risk factors for Barrett's esophagus and associated adenocarcinoma. *Clin Gastroenterol Hepatol*. 2005; 3:1–10. [PubMed: 15645398]
25. Vizcaino AP, Moreno V, Lambert R, et al. Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973-1995. *Int J Cancer*. 99:860–868. [PubMed: 12115489]
26. Lofdahl HE, Lu Y, Lagergren J. Sex-specific risk factor profile in oesophageal adenocarcinoma. *Br J Cancer*. 2008; 99(9):1506–1510. [PubMed: 18841152]
27. Fowke JH, Motley SS, Concepcion RS, Penson DF, Barocas DA. Obesity, body composition, and prostate cancer. *BMC Cancer*. Jan 18.2012 12:23. doi: 10.1186/1471-2407-12-23. [PubMed: 22257467]
28. Corley DA, Kubo A, Levin TR, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. *Gastroenterology*. 2007; 133:34–41. [PubMed: 17631128]
29. Akiyama T, Yoneda M, Maeda S, Nakajima A, Koyama S, Inamori M. Visceral obesity and the risk of Barrett's esophagus. *Digestion*. 2011; 83:142–145. [PubMed: 21266807]
30. Nelsen EM, Kirihaara Y, Takahashi N, Shi Q, Lewis JT, Namasivayam V, Buttar NS, Dunagan KT, Prasad GA. Distribution of body fat and its influence on esophageal inflammation and dysplasia in patients with Barrett's esophagus. *Clin Gastroenterol Hepatol*. 2012; 10:728–734. [PubMed: 22433923]
31. Cronin-Fenton DP, Murray LJ, Whiteman DC, et al. Reproductive and sex hormonal factors and oesophageal and gastric junction adenocarcinoma: a pooled analysis. *Eur J Cancer*. 2010; Jul(11): 2067–76. [PubMed: 20456945]
32. Tihan T, Harmon JW, Wan X, et al. Evidence of androgen receptor expression in squamous and adenocarcinoma of the esophagus. *Anticancer Res*. 2001; 21(4B):3107–14. [PubMed: 11712819]
33. Awan AK, Iftikhar SY, Morris TM, et al. Androgen receptors may act in a paracrine manner to regulate oesophageal adenocarcinoma growth. *Eur J Surg Oncol*. 2007; 33(5):561–8. [PubMed: 17254742]
34. Cooper SC, Croft S, Day R, Thomson CS, et al. Patients with prostate cancer are less likely to develop oesophageal adenocarcinoma: could androgens have a role in the aetiology of oesophageal adenocarcinoma? *Cancer Causes Control*. 2009
35. Price JC, Jansen CJ, Johns ME. Esophageal reflux and secondary malignant neoplasia at laryngoesophagectomy. *Arch Otolaryngol Head Neck Surg*. 1990; 116:163–64. [PubMed: 2297405]
36. Vrabec DP. Multiple primary malignancies of the upper aerodigestive system. *Ann Otol Rhinol Laryngol*. 1979; 88:846–54. [PubMed: 517930]
37. Anderson LA, Watson RG, Murphy SJ, et al. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. *World J Gastroenterol*. 2007; 13:1585–94. [PubMed: 17461453]
38. Dahlstrom KR, Little JA, Zafereo ME, et al. Squamous cell carcinoma of the head and neck in never smoker-never drinkers: a descriptive epidemiologic study. *Head Neck*. 2008; 30:75–84. [PubMed: 17694557]
39. Hashibe M, Brennan P, Benhamou S, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst*. 2007; 99(10): 777–789. [PubMed: 17505073]
40. Bennett WP. P53 alterations in progenitor lesions of the bronchus, esophagus, oral cavity, and colon. *Cancer Detect Prev*. 1995; 19:503–11. [PubMed: 8925519]
41. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst*. 2000; 92:709–20. [PubMed: 10793107]
42. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011; 29:4294–301. [PubMed: 21969503]

43. Sturgis EM, Ang KK. The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms. *J Natl Compr Canc Netw*. 2011; 9:665–73. [PubMed: 21636538]
44. Rajendra S, Robertson IK. Similar immunogenetics of Barrett's oesophagus and cervical neoplasia: is HPV the common denominator? *J Clin Pathol*. 2010; 63:1–3. [PubMed: 20026700]
45. Shields HMZF, Antonioli DA, Doos WG, Kim S, Spechler SJ. Detection by scanning electron microscopy of a distinctive esophageal surface cell at the junction of squamous and Barrett's epithelium. *Dig Dis Sci*. 1993; 38:97–108. [PubMed: 8420766]
46. Acevedo-Nuño EG-OA, Vázquez-Camacho G, Balderas-Peña Luz Ma A, Moreno-Villa H, Montoya-Fuentes H. Human papillomavirus DNA and protein in tissue samples of oesophageal cancer, Barrett's oesophagus and oesophagitis. *Anticancer Res*. 2004; 24:1319–23. [PubMed: 15154668]
47. Iyer A, Rajendran V, Adamson CS, Peng Z, Cooper K, Evans MF. Human papillomavirus is detectable in Barrett's esophagus and esophageal carcinoma but is unlikely to be of any etiologic significance. *J Clin Virol*. 2011; 50:205–8. [PubMed: 21169053]
48. El-Serag HB, Hollier JM, Gravitt P, Alsarraj A, Younes M. Human papillomavirus and the risk of Barrett's esophagus. *Dis Esophagus*. Jul; 2013 26(5):517–21. [PubMed: 22891654]
49. De Ceglie A, Filiberti R, Blachi S, et al. History of cancer in first degree relatives of Barrett's esophagus patients: a case-control study. *Clin Res Hepatol Gastroenterol*. 2011; 35:831–38. [PubMed: 21924696]
50. Rogers E, Goldkind S, Iseri O, et al. Adenocarcinoma of the lower esophagus. A disease primarily of white men with Barrett's esophagus. *J Clin Gastroenterol*. 1986; 8:613–18. [PubMed: 3805655]
51. Miholic J, Hafez J, Lenglinger J, et al. Hiatal hernia, Barrett's esophagus, and long-term symptom control after laparoscopic fundoplication for gastroesophageal reflux. *Surg Endosc*. Nov; 2012 26(11):3225–31. [PubMed: 22648102]

Table 1
Demographic, clinical and life style characteristics in cases and all controls

		BE cases (N=264)	Controls (N=1486)	P value *
Variable		n (%)	n (%)	
Age, years				
	Mean (SD)	61.45 (7.59)	60.80 (7.78)	0.212
Race				
	White	231 (87.5)	920 (61.9)	<0.001
	Black	30 (11.4)	524 (35.3)	
	Other	3 (1.1)	42 (2.8)	
GERD				<0.001
	No symptoms	100 (37.9)	820 (55.2)	
	< 5 years	24 (9.1)	108 (7.3)	
	5-9 years	19 (7.2)	130 (8.7)	
	10 years	119 (45.1)	415 (27.9)	
	Missing	2 (0.8)	13 (0.9)	
Hiatal hernia				<0.001
	No	34 (12.9)	566 (38.1)	
	Yes (≤ 3 cm)	104 (39.4)	587 (39.5)	
	Yes (>3 cm)	124 (47.0)	327 (22)	
	Missing	2 (0.8)	6 (0.4)	
BMI				
	Mean (SD)	30.13 (5.38)	30.38 (11.59)	0.728
Waist hip ratio				0.001
	Less than 0.9	18 (6.8)	203 (13.7)	
	Greater than or equal to 0.9	245 (92.8)	1245 (83.8)	
Tobacco smoking				0.367
	Never smoker	58 (22.0)	385 (25.9)	
	0 – 29.9 pack-years	90 (34.1)	501 (33.7)	
	30 pack-years	104 (39.4)	538 (36.2)	
	Missing	12 (4.5)	62 (4.2)	
Alcohol drinking				0.791
	Non-drinker	20 (7.6)	110 (7.4)	
	Ex-drinker	98 (37.1)	575 (38.7)	
	Current drinker	140 (53.0)	745 (50.1)	
	Missing	6 (2.3)	56 (3.8)	
<i>Helicobacter pylori</i> status				<0.001
	Negative	204 (77.3)	970 (65.3)	
	Positive	46 (17.4)	455 (30.6)	

		BE cases (N=264)	Controls (N=1486)	<i>P</i> value*
Variable		n (%)	n (%)	
	Missing	14 (5.3)	61 (4.1)	
Ever used PPIs				<0.001
	No	74 (28)	705 (47.4)	
	Yes	184 (69.7)	723 (48.7)	
	Missing	6 (2.3)	58 (3.9)	
Aspirin or NSAIDs in the last year				0.881
	No	97 (36.7)	562 (37.8)	
	Yes	140 (53)	794 (53.4)	
	Missing	27 (10.2)	130 (8.7)	

BE, Barrett's esophagus; SD, standard deviation; GERD, gastroesophageal reflux disease; BMI, body mass index; PPI, proton pump inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs.

* Missing values not included in analysis.

Table 2
The distribution of personal history of previous cancer between Barrett's esophagus cases and all controls

Cancer Type		BE cases N=264 (%)	Controls N=1486 (%)	P value
All Cancers				0.036
	No	219 (83.0)	1303 (87.7)	
	Yes	45 (17.0)	183 (12.3)	
Bladder				0.388
	No	264 (100.0)	1475 (99.3)	
	Yes	0 (0)	11 (0.7)	
Colorectal				0.976
	No	262 (99.2)	1475 (99.3)	
	Yes	2 (0.8)	11 (0.7)	
Hematological ¹				
	No	262 (99.2)	1479 (99.5)	0.552
	Yes	2 (0.8)	7 (0.5)	
Kidney				
	No	263 (99.6)	1482 (99.7)	0.760
	Yes	1 (0.4)	4 (0.3)	
Lung				0.953
	No	263 (99.6)	1480 (99.6)	
	Yes	1 (0.4)	6 (0.4)	
Oropharyngeal				
	No	260 (98.5)	1480 (99.6)	0.040
	Yes	4 (1.5)	6 (0.4)	
Prostate				
	No	245 (92.8)	1421 (95.6)	0.048
	Yes	19 (7.2)	65 (4.4)	
Skin				0.724
	No	248 (93.9)	1404 (94.5)	
	Yes	16 (6.1)	82 (5.5)	
Other ²				0.838
	No	263 (99.6)	1479 (99.5)	
	Yes	1 (0.4)	7 (0.5)	

¹ Hematological cancers include lymphoma, leukemia and myelodysplastic disorders.

² Other cancers include brain, bone, liver, sarcoma, testicular, thymus, and thyroid cancers.

Table 3
Association between Barrett's esophagus and personal history of oropharyngeal and prostate cancer. The analyses are adjusted for several potential confounding or explanatory variables and presented for comparisons between cases and combined control group as well as separate control groups

Cancer Type	BE cases vs. All controls		BE cases vs. Endoscopy controls		BE cases vs. Primary care controls	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Oropharyngeal Cancer						
Unadjusted	3.80 (1.06-13.54)	0.040	3.98 (0.99-16.01)	0.052	7.35 (0.82-66.11)	0.075
Adjusted for:						
Age	3.80 (1.07-13.58)	0.040	3.90 (0.97-15.71)	0.056	7.52 (0.83-67.77)	0.072
Age, race	3.02 (0.83-10.99)	0.094	3.37 (0.81-14.03)	0.095	4.83 (0.54-43.56)	0.161
Age, race, GERD, PPI	2.92 (0.77-11.09)	0.115	3.22 (0.76-13.71)	0.113	3.56 (0.32-39.65)	0.301
Age, race, smoking	3.18 (0.87-11.63)	0.081	3.65 (0.87-15.27)	0.077	4.50 (0.50-40.89)	0.181
Age, race, alcohol	3.01 (0.83-10.97)	0.095	3.33 (0.80-13.82)	0.098	4.76 (0.53-43.14)	0.165
Age, race, radiation near esophagus	4.59 (0.55-38.45)	0.160	9.27 (0.71-120.52)	0.089		1.00
Age, WHR	3.76 (1.05-13.44)	0.041	4.32 (1.05-17.70)	0.042	3.34 (0.61-18.39)	0.166
Age, race, WHR	2.97 (0.82-10.84)	0.099	3.57 (0.85-14.98)	0.083	2.07 (0.37-11.45)	0.404
All variables*	5.76 (0.61-54.69)	0.127	10.28 (0.72-146.71)	0.086		1.00
Prostate Cancer						
Unadjusted	1.70 (1.00-2.88)	0.050	1.53 (0.89-2.65)	0.126	2.40 (1.20-4.82)	0.014
Adjusted for:						
Age	1.62 (0.95-2.77)	0.076	1.41 (0.81-2.46)	0.220	2.23 (1.11-4.51)	0.025
Age, race	1.80 (1.03-3.13)	0.038	1.57 (0.89-2.79)	0.122	2.38 (1.12-5.04)	0.024
Age, race, GERD, PPI	1.80 (1.02-3.16)	0.042	1.59 (0.89-2.83)	0.120	3.27 (1.41-7.59)	0.006
Age, race, smoking	1.97 (1.13-3.44)	0.018	1.70 (0.95-3.04)	0.072	2.49 (1.16-5.32)	0.019
Age, race, alcohol	1.81 (1.04-3.15)	0.037	1.56 (0.87-2.77)	0.133	2.46 (1.15-5.26)	0.020
Age, WHR	1.65 (0.96-2.82)	0.069	1.44 (0.82-2.52)	0.201	2.32 (1.15-4.69)	0.019
Age, race, WHR	1.85 (1.06-3.23)	0.030	1.61 (0.90-2.88)	0.106	2.49 (1.17-5.32)	0.018
All variables*	1.96 (1.10-3.47)	0.022	1.70 (0.94-3.07)	0.080	3.61 (1.53-8.55)	0.003

BE, Barrett's esophagus; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; WHR, waist hip ratio.

* All variables include age, race, GERD, PPI use, smoking, alcohol use, WHR and radiation therapy near esophagus for oropharyngeal cancer analysis, and age, race, GERD, PPI use, smoking, alcohol use, and WHR for prostate cancer analysis.

Table 4
Associations between Barrett's esophagus and cancer treatments among cancer patients

Personal History n/N (%)		BE cases (N=45)	Controls (N=183)	Bivariate OR (95% CI)	P value*	Multivariate OR (95% CI)	P value*
Radiation therapy					0.481		0.206
	No	24 (53.3)	127 (69.4)				
	Yes	11 (24.4)	42 (23.0)	1.33 (0.60-2.95)		1.78 (0.73-4.36)	
	Missing	10 (22.2)	14 (7.7)				
Radiation nearesophageal field ^I					0.218		0.057
	No	32 (71.1)	163 (89.1)				
	Yes	3 (6.7)	6 (3.3)	2.45 (0.59-10.39)		5.24 (0.95-28.82)	
	Missing	10 (22.2)	14 (7.7)				
Chemotherapy					0.709		0.871
	No	41 (91.1)	161 (88.0)				
	Yes	4 (8.9)	19 (10.4)	0.81 (0.260-2.50)		1.11 (0.32-3.82)	
	Missing	0 (0)	3 (1.6)				
Chemoradiation					0.457		0.513
	No	34 (75.6)	159 (86.9)	0.45 (0.056-3.66)		0.48 (0.05-4.30)	
	Yes	1 (2.2)	10 (5.5)				
	Missing	10 (22.2)	14 (7.7)				

^I Radiation near the esophageal field was given for treatment of oropharyngeal and lung cancers. BE, Barrett's esophagus.

* Missing values not included in analysis.

Table 5
Associations between Barrett's esophagus and family history of cancer in first-and second-degree relatives

		First-Degree Relatives			Second-Degree Relatives		
Cancer Type, n/N (%)		BE cases N=264	Controls (All) N=1486	P value *	BE cases N=264	Controls (All) N=1486	P value *
All cancers				0.683			0.553
	No	145 (54.9)	796 (53.6)		231 (87.5)	1319 (88.8)	
	Yes	119 (45.1)	690 (46.4)		33 (12.5)	167 (11.2)	
Brain				1.000			1.000
	No	260 (98.5)	1459 (98.2)		263 (99.6)	1480 (99.6)	
	Yes	4 (1.5)	27 (1.8)		1 (0.4)	6 (0.4)	
Bladder				0.182			1.000
	No	261 (98.9)	1479 (99.5)		264 (100)	1485 (99.9)	
	Yes	3 (1.1)	7 (0.5)		0 (0)	1 (0.1)	
Colorectal				0.346			0.298
	No	242 (91.7)	1386 (93.3)		262 (99.2)	1459 (98.2)	
	Yes	22 (8.3)	100 (6.7)		2 (0.8)	27 (1.8)	
Hematological ¹				1.00			0.480
	No	260 (98.5)	1460 (98.3)		263 (99.6)	1483 (99.8)	
	Yes	4 (1.5)	26 (1.7)		1 (0.4)	3 (0.2)	
Kidney				0.074			0.151
	No	261 (98.9)	1482 (99.7)		263 (99.6)	1486 (100)	
	Yes	3 (1.1)	4 (0.3)		1 (0.4)	0 (0)	
Lung				0.956			1.000
	No	238 (90.2)	1338 (90.0)		261 (98.9)	1467 (98.7)	
	Yes	26 (9.8)	148 (10.0)		3 (1.1)	19 (1.3)	
Liver				0.808			1.000
	No	260 (98.5)	1457 (98.0)		264 (100)	1485 (99.9)	
	Yes	4 (1.5)	29 (2.0)		0 (0)	1 (0.1)	
Oropharyngeal				1.000			1.000
	No	263 (99.6)	1476 (99.3)		264 (100)	1485 (99.9)	
	Yes	1 (0.4)	10 (0.7)		0 (0)	1 (0.1)	
Prostate				0.177			0.603
	No	255 (96.6)	1404 (94.5)		264 (100)	1479 (99.5)	
	Yes	9 (3.4)	82 (5.5)		0 (0)	7 (0.5)	
Skin				0.214			1.000
	No	255 (96.6)	1454 (97.8)		263 (99.6)	1480 (99.6)	
	Yes	9 (3.4)	32 (2.2)		1 (0.4)	6 (0.4)	

¹ Hematological cancers include lymphoma, leukemia and myelodysplastic disorders. BE, Barrett's esophagus.

* Chi square, and Fisher Exact (if number of observations in any cell is <5) tests were used.

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