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Assessment of Familiality, Obesity, and Other Risk Factors for Early Age of Cancer Diagnosis in Adenocarcinomas of the Esophagus and Gastro-esophageal Junction

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Abstract

BACKGROUND AND AIMS—Adenocarcinomas of the esophagus and adenocarcinomas of the gastroesophageal junction are postulated to be complex genetic diseases. Combined influences of environmental factors and genetic susceptibility likely influence the age at which these cancers develop. The aim of this study was to determine whether familiality and other recognized risk factors are associated with the development of these cancers at an earlier age.

METHODS—A structured validated questionnaire was utilized to collect self reported data on gastro-esophageal reflux symptoms, risk factors for Barrett’s esophagus (BE) and family history, including age of cancer diagnosis in affected relatives from probands with BE, adenocarcinoma of the esophagus, or adenocarcinoma of the gastro-esophageal junction, at five tertiary care academic hospitals. Medical records of all relatives reported to be affected were requested from hospitals providing this cancer care to confirm family histories. Familiality of BE/cancer, obesity (defined as

body mass index > 30), gastro-esophageal reflux symptoms, and other risk factors were assessed for association with a young age of cancer diagnosis.

RESULTS—A total of 356, 216 non-familial and 140 familial, cancers were studied. The study population consisted of 292 (82%) men and 64 (18%) women. Mean age of cancer diagnosis was no different comparing familial and non-familial cancers, 62.6 yrs vs. 61.9 yrs, $p = 0.70$. There were also no significant differences in symptoms of gastroesophageal reflux, body mass index, race, gender, and smoking history between familial and non-familial cancers. Mean age of cancer diagnosis was significantly younger comparing those who were obese one year prior to diagnosis with those who were non-obese, mean age 58.99 yrs vs. 63.6 yrs, $p = 0.008$. Multivariable modeling of age at cancer diagnosis showed that obesity 1 year before diagnosis was associated with a younger age of cancer diagnosis ($p=0.005$) after adjustment for heartburn and regurgitation duration.

CONCLUSIONS—Obesity is associated with the development of esophageal and gastro-esophageal junctional adenocarcinomas at an earlier age. Familial cancers arise at the same age as non-familial cancers and have a similar risk factor profile.

Barrett's esophagus (BE) and its associated cancers – esophageal adenocarcinoma (EAC) and gastro-esophageal junctional adenocarcinoma (GEJAC) -- are associated with chronic gastro-esophageal reflux disease (GERD).^{1–3} Furthermore, these conditions are identified predominantly in white men.^{3–6} Obesity appears to be another important risk factor for these cancers, independent of GERD.^{7–10} Familial Barrett's esophagus (FBE), the aggregation of BE and its associated cancers in families, is a newly recognized syndrome, which suggests that BE and its associated cancers are complex genetic diseases.^{11–15}

Guidelines for screening and surveillance of BE are based on existing knowledge of these risk factors.¹⁶ Age is also a predictor of BE and its subsequent progression to cancer, which guides diagnostic interventions. For complex diseases such as cancer, age of disease onset is generally thought to be related to combined influences of duration of environmental exposures and genetic susceptibility. Thus, EAC and GEJAC may develop at an earlier age in FBE families than the general population. Subjects with an inherited susceptibility may also react to exposures known to be associated with the development of metaplastic epithelium (e.g., obesity or gastro-esophageal reflux) at an earlier age. The identification of factors that lead to earlier age of disease onset should help guide decisions regarding endoscopic screening and surveillance and also provide insights into the mechanisms of carcinogenesis.

The primary aim of this study was to identify risk factors associated with an earlier age of diagnosis of EAC and GEJAC. Specifically, the goals were to compare incidence age of diagnosis and other associated risk factors between FBE and non-FBE cancers and to determine if duration of GERD symptoms, obesity, and other recognized risk factors were associated with an earlier age of cancer diagnosis.

METHODS

Recruitment

This study was conducted using data obtained from an ongoing multi-center familial Barrett's esophagus (FBE) study registered at clinicaltrials.gov, identifier NCT00288119, whose ultimate goal is the identification of susceptibility genes. Eligible probands with established or newly diagnosed BE, EAC, or GEJAC were recruited at 5 tertiary care academic hospitals in the United States as previously described.^{11,12} The BE probands themselves were not part of the present analysis but any relatives of these BE probands reported with EAC or GEJAC were included and were classified as familial cancers. Recruitment periods differed at the different hospitals depending on available personnel and institutional review board approval and ranged from 6 months to 7 years but included all eligible patients seen in the endoscopy

suite during the respective recruitment period. The study group for this analysis was restricted to subjects with cancer, probands or relatives, and also included patients from a previously published report on the prevalence of FBE.¹²

Family History

Probands, defined as the first known affected member in a family, who consented to study participation were administered a FBE questionnaire that elicited information about reflux symptoms (patterned on the validated Mayo GERQ¹⁷), and other relevant exposures including obesity, and a detailed family history of BE, esophageal cancer, and other cancers. Individuals self reported their heights and weights at present and at 1, 5, 10, and 20 years prior to enrolment. Probands were asked to obtain permission for contacting first degree family members and any other affected relatives. FBE questionnaires were also administered to relatives who consented to participate. If an affected relative with reported cancer was deceased, then the next of kin was asked to complete relevant portions of the questionnaire, specifically age of cancer diagnosis. Endoscopic screening was then offered to any family member who filled out the FBE questionnaire and had not had previous upper endoscopy.¹⁸ Attempts were made to obtain the endoscopic and histological diagnosis for all family members reported to have BE or esophageal cancer. Institutional review boards for human investigation at each individual hospital participating in the study have approved this protocol.

Definitions

For probands as well as relatives, the definition of BE required clear documentation of measurements of affected segment of tubular esophagus in the endoscopy report and documented presence of intestinal metaplasia on biopsy. EAC was defined by documented histology plus a mass predominantly involving the tubular esophagus and GEJAC was defined by documented histology plus a mass predominantly involving the gastro-esophageal junction. All biopsies from within the institution were reviewed by a designated gastrointestinal pathologist. Endoscopy and pathology records were requested from outside hospitals for relatives reported to have esophageal cancer or BE. Body mass index [BMI = weight/height² in units of kg/(m²)] was calculated and obesity was defined as BMI $\geq$ 30.

Probands and families were classified as confirmed FBE diagnosis when the diagnosis of BE, EAC, or GEJAC was ascertained in the proband and at least one affected relative. Probands were classified as having non-familial disease if they reported no affected family member and BE was not diagnosed in any family member who subsequently agreed to a screening endoscopy. Probands and families were classified as possible FBE diagnosis when the proband reported an affected family member but medical records on the family member could not be obtained. Probands were classified as false positive FBE diagnosis when the proband reported an affected family member with BE or EAC/GEJAC who did not meet ascertainment criteria for BE or EAC/GEJAC, respectively, upon review of medical records.

Probands and family members with EAC/GEJAC who were members of confirmed or possible FBE families were grouped as “FBE” and probands with no family history or false positive FBE diagnosis were grouped as “non-FBE” for analysis.

Statistical Analysis

Sample size calculations were performed to test a primary hypothesis of a difference in incidence age of cancers for individuals with a family history compared to individuals without a family history. A standard deviation of 12.21 years for age-at-onset was assumed using information from the 1996 Surveillance, Epidemiology and End Results (SEER) tumor registry on rates of EAC given age and gender categories (for whites only). Because it is difficult to determine FBE/“sporadic” status with certainty without identification of the susceptibility gene

(s), power was computed assuming misclassification rates from 0 to 20% in both directions. Assuming a minimum sample size of 80 FBE cancers, the power is $\geq 65\%$ to detect a difference in mean age-at-onset of 5 years, and $\geq 99\%$ to detect a difference in mean age-at-onset of 10 years for misclassification rates up to 20% at a significance level (α) of 0.05. The goal was to accrue a minimum of 80 cancers in the FBE group for whom the incidence age of cancer diagnosis was available.

Only subjects with cancer, EAC or GEJAC, were included in the analysis. Differences in age at diagnosis and other risk factors such as GERD symptoms, gender, race, smoking, and obesity were compared between the FBE cancer group and the non-FBE cancer group. Fisher's exact tests were used to compare categorical variables generating 2-sided p-values and the Kruskal-Wallis test was used to compare average age at diagnosis generating two-sided p-values between the FBE cancers and non-FBE cancers groups. P-values < 0.05 were considered statistically significant. Obesity was initially examined by comparing the calculated current BMI (in kg/m^2), as well as BMI reported 1, 5, 10, and 20 years prior to diagnosis between groups. Obesity was then defined as $\text{BMI} \geq 30$ and compared as a binary categorical variable between the FBE and non-FBE groups. In order to investigate which relevant clinical and/or demographic variables are associated with age at esophageal cancer diagnosis, mixed linear models were used allowing for adjustment for familial correlations of BE/EAC/GEJAC. Akaike's Information Criterion (AIC), defined as the $-2 \log$ likelihood of the model plus 2 times the number of estimated parameters, was calculated and used to compare statistical models. Lower values of AIC signify the better fitting preferred models when comparing models that have used the same number of subject information. Statistical Analysis Software (Version 9.1, SAS, Inc., Cary, NC, 2003) were used for analyses and the Statistical Package for Social Sciences software (SPSS, Inc. for Windows, Version 11.0, Chicago, IL) was used for generating graphs.

RESULTS

Classification of Esophageal and Junctional Cancers

The familial study from which the study cohort is derived successfully recruited 1011 of 1916 (53%) eligible probands with BE, EAC, or GEJAC seen during the study period. A total of 356 individuals with cancer (256 EAC, 45 GEJAC, and 55 whose location could not be clearly determined) were identified. Questionnaires were completed by 192 subjects in the non-FBE cancer group and 56 subjects in the FBE cancer group. The non-FBE cancers group consisted of 216 probands with cancer who had no family history of BE or EAC/GEJAC. The 140 subjects in the FBE cancers group consisted of 54 probands with EAC/GEJAC and 86 relatives reported to have esophageal cancer. There were no significant differences in gender or race between the non-FBE and the FBE group. Stage information was available for 147 cancers in the non-FBE group and 44 cancers in the FBE group (Table 1). There was no significant difference in cancer stage distribution between the 2 groups.

Age of Cancer Diagnosis in Familial Cancers

Age of cancer diagnosis was known in 320 subjects with mean age = 62.1 yrs (S.D. = 12.9 yrs, range, 22–89 yrs). There was no significant difference in age of cancer diagnosis between the non-FBE vs. the FBE group, mean age 61.9 vs. 62.6 yrs, $p = 0.70$ (Table 1 and Figure 1A). There was also no significant difference in age of cancer diagnosis when the non-FBE group was compared with those in the FBE group whose familial status was confirmed, mean age 61.9 vs. 61.1 yrs, $p = 0.18$ (Figure 1B). The study cohort included 27 cancers that occurred in families with 3 or more affected individuals. The mean age of diagnosis of cancer for these 27 subjects was 64.8 years and was no earlier than the remainder of the group.

Symptoms and Exposures in Familial Cancers

There was no significant difference in the proportion of non-FBE cancer patients and the FBE cancer patients who reported heartburn (60% vs. 67%, $p = 0.44$) or regurgitation (64% vs. 66%, $p = 0.88$) prior to cancer diagnosis (Table 1). There were also no significant differences in frequency, duration, or severity of heartburn or regurgitation as assessed by the FBE questionnaire between the non-FBE and the FBE cancer groups. Weight and height measurements were obtained on 198 subjects in the non-FBE group and 54 subjects in the FBE group. At time of diagnosis, 36 (16.7%) of the non-FBE subjects were obese vs. 17 (12.1%) of the FBE group, $p = 0.24$ (Table 1). Furthermore, there was no significant difference in the percent of subjects who were obese at 1 year, 5 years, 10 years, and 20 years prior to diagnosis, between the non-FBE and FBE cancer groups. The proportions of non-FBE and FBE cancers that smoked (73% vs. 74%, $p = 1.0$) and drank alcohol (83% vs. 80%, $p = 0.68$) were also not significantly different.

Affect of Obesity and Other Risk Factors on Age at Cancer Diagnosis

In order to further examine the association between known risk factors for BE associated cancers and age at cancer diagnosis, mixed linear models were used to adjust for familial correlation of BE and cancer (Table 2). In univariable analyses, family history of BE was not associated with age of cancer diagnosis, neither was heartburn duration, regurgitation duration or trouble swallowing duration. However, obesity ($\text{BMI} \geq 30$) 1-year before, 5-years before and 10-years before diagnosis were significantly associated with a younger age at cancer diagnosis (Table 2). Mean age of cancer diagnosis in patients who were obese one year before cancer diagnosis was 58.99 years compared to 63.6 years for those who were not obese (Figure 2). Multivariable modeling (Table 3) showed an association between obesity ($\text{BMI} \geq 30$) 1-year prior to diagnosis and younger age at cancer diagnosis that was further strengthened after adjustment for heartburn duration and regurgitation duration ($\text{BMI} < 30$ age at diagnosis 63.68 compared to $\text{BMI} \geq 30$ age at diagnosis 58.81), while this multivariable effect was not seen with obesity ($\text{BMI} \geq 30$) 5-years or 10-years before diagnosis. Therefore the multivariable model with obesity 1-year before diagnosis and heartburn duration and regurgitation duration provided the best fitting model for age at cancer diagnosis in this study population.

DISCUSSION

Obesity is increasingly recognized as an important risk factor for the development of Barrett's esophagus (BE) and its associated adenocarcinomas, which could partially explain the rising incidence of these diseases in the United States and other countries.^{7–10,19–22} Although obesity also contributes to gastro-esophageal reflux,^{23–25} obesity is clearly an independent risk factor for EAC.^{7–10} Central adiposity has also recently been shown to be independently associated with BE.^{19–22} In this study, obesity 1 year previous to diagnosis of cancer was significantly associated with a diagnosis of cancer at an earlier age. This association was further strengthened after adjustment for heartburn and regurgitation symptom duration. In contrast, the duration of GERD symptoms by themselves were not significant predictors of earlier age of cancer diagnosis. In addition, other known BE/EAC risk factors such as male gender, white race, and smoking were not significantly associated with family history or earlier age at cancer diagnosis.

The association of obesity with earlier age of cancer diagnosis could be related to a dietary factor, obesity induced gastro-esophageal reflux, or alterations in metabolic mediators. Obesity has been proposed to be carcinogenic for a variety of cancers.²⁶ General molecular mechanisms for obesity induced carcinogenesis include oxidative stress/DNA damage, non-inflammatory changes in immune function, inflammatory mediators, hormones and growth factors, and metabolic detoxification factors. The specific molecular mechanisms that lead to the

development of esophageal and gastroesophageal junctional cancers at an earlier age in the presence of obesity need to be elucidated.

Familial aggregation often implies a genetic susceptibility to disease but may also be caused by a common environmental exposure within families. In general, familial cancers are presumed to be complex genetic traits, which in some cancers may manifest with an early age of disease onset. The manifestation of a putative susceptibility gene depends on trait definition. Inclusion of Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastro-esophageal junction as part of a single complex trait is justified because of strong evidence that nearly all adenocarcinomas of the esophagus and a substantial proportion of adenocarcinomas of the gastro-esophageal junction arise in Barrett's epithelium.^{1-2,4,27-32} This study demonstrates that age of disease onset for FBE cancers is the same as non-FBE cancers.

Familial aggregation of BE and its associated cancers could represent a genetic susceptibility to metaplastic transformation of the esophagus, a genetic susceptibility to a recognized risk factor such as GERD¹⁻⁴ or obesity,⁷⁻¹⁰ or a common environmental exposure such as smoking or alcohol.³³⁻³⁵ The proportion of FBE cancers reporting GERD symptoms was the same as the proportion of non-FBE cancers with GERD symptoms, suggesting that FBE does not represent a genetic predisposition to gastro-esophageal reflux. Our prior study that measured the prevalence of FBE raised the possibility that FBE probands with cancer may be less obese than non-FBE probands with cancer.¹² However, the present study, which had a larger sample size and included additional relatives of probands as well as probands did not find a significant difference. Thus, FBE is unlikely to represent a genetic susceptibility to obesity. Finally, this study also found no difference in smoking or alcohol use between FBE and non-FBE cancers.

GERD is clearly associated with BE and its associated cancers.¹⁻⁴ Chronic gastroesophageal reflux is believed to be essential to the process of metaplastic transformation. However, it is not clear what role persistent gastroesophageal reflux plays in the progression from metaplasia to cancer once metaplasia has developed. The duration of GERD symptoms was not found to be associated with an earlier age of cancer diagnosis in this study. The study was primarily powered to investigate the association of age of cancer diagnosis with familiarity. It might not have sufficient power to detect an association with GERD. GERD symptoms are also an indirect marker of GERD exposure and might not reflect the extent of exposure. Another possible explanation that needs to be explored is that although GERD plays an important role in the process of metaplastic transformation it is less important in the subsequent progression to cancer.

The results of this study need to be interpreted in the context of the limitations of the study design. Data on several variables were missing (smoking and alcohol history were unavailable in nearly a third of the subjects) for a number of study subjects (see Table 2). Missing data could lead to biased results, especially if there was an unrecognized systematic misclassification of exposures reported by proxy respondents. However, it is unlikely that age of cancer diagnosis would be misreported, even by proxy respondents. Obesity 1 year prior to diagnosis or longer was used for analysis on the assumption that the majority of weight loss associated with cancer diagnosis was within the first year prior to diagnosis. Obesity was assessed by calculated BMI but we had no information on central adiposity, which may be a better measure of the type of obesity that predisposes individuals to BE.¹⁹⁻²² Individuals self reported data collected by the FBE questionnaire including height and weight in the years preceding study enrollment. Overweight individuals are known to underreport weight, which might lead to an underestimation of obesity in this study.³⁶ Data on GERD symptoms were also self reported and were collected using questions from the validated Mayo GERQ developed by Locke et al.¹⁷

This study cohort of cancer patients is part of an ongoing family study. Therefore, it was necessary to adjust for familial correlations in the statistical analysis. Subjects with a reported affected relative whose diagnosis could not be verified despite multiple attempts were classified as part of the FBE group because we have found the false positive rate of reported family history to be less than 10%.¹² The results did not change when the analysis was restricted to the subset of FBE patients in whom the diagnosis in the affected relative was confirmed (Figure 1B). The results also did not change if adenocarcinomas of the gastro-esophageal junction were excluded from analysis (data not shown). Proband and relatives were able to provide information about age of cancer diagnosis for deceased relatives with cancer; however, exposure information was generally missing for these deceased individuals. Complex traits such as FBE may be genetically heterogeneous. Until and unless the genetic variant(s) that confers susceptibility to the development of BE is(are) identified, there is a strong likelihood that some individuals in this study without a genetic susceptibility were misclassified as FBE and others with a genetic susceptibility were misclassified as non-FBE (“apparently sporadic”). The sample size was sufficient for at least a 20% rate of misclassification. Of course, there may be selected variants that are manifested at an earlier age. Therefore, if FBE is truly a complex genetic disease, it is unlikely that any major susceptibility gene is manifested at an earlier age.

In summary, this study found that obesity was associated with earlier age of cancer diagnosis. The molecular mechanisms by which obesity contributes to the development of BE and its progression to cancer need to be investigated. There were no significant differences in age of disease onset and other risk factors between FBE and non-FBE cancers. Within the limitations of unmeasurable misclassification, FBE is unlikely to represent a genetic susceptibility to obesity or gastro-esophageal reflux. The trait is proposed to be a manifestation of genetic variant(s) that confer a susceptibility to metaplastic transformation of the esophageal epithelium perhaps in the presence of inflammation caused by gastro-esophageal reflux and/or obesity. Furthermore, obesity might contribute to the progression of BE to cancer by undefined mechanisms in susceptible individuals. Based on the results of this study, screening and surveillance practices do not need to be modified for age in individuals who are members of FBE families.

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References

1. Shaheen N, Ransohoff DF. Gastroesophageal reflux, barrett esophagus, and esophageal cancer: scientific review. *JAMA* 2002;287(15):1972–81. [PubMed: 11960540]
2. Winters C Jr, Spurling TJ, Chobanian SJ, Curtis DJ, Esposito RL, Hacker JF 3rd, Johnson DA, Cruess DF, Cotelingam JD, Gurney MS, et al. Barrett’s esophagus. A prevalent, occult complication of gastroesophageal reflux disease. *Gastroenterology* 1987;92(1):118–24. [PubMed: 3781178]
3. Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;340(11):825–31. [PubMed: 10080844]

4. Spechler SJ, Goyal RK. Barrett's esophagus. *N Engl J Med* 1986;315:362–71. [PubMed: 2874485]
5. Devesa SS, Blot WJ, Fraumeni JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;83:2049–53. [PubMed: 9827707]
6. Cameron AJ, Lomboy CT. Barrett's esophagus: age, prevalence, and extent of columnar epithelium. *Gastroenterology* 1992;103:1241–5. [PubMed: 1397881]
7. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. *Ann Intern Med* 1999;130:883–90. [PubMed: 10375336]
8. Chow WH, Blot WJ, Vaughan TL, Risch HA, Gammon MD, Stanford JL, Dubrow R, Schoenberg JB, Mayne ST, Farrow DC, Ahsan H, West A, Rotterdam H, Niwa S, Fraumeni JJ. Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1998;90:150–5. [PubMed: 9450576]
9. Brown LM, Swanson CA, Gridley G, et al. Adenocarcinoma of the esophagus: role of obesity and diet. *J Natl Cancer Inst* 1995;87:847–8. [PubMed: 7791237]
10. Vaughan TL, Davis S, Kristal A, et al. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 1995;4:85–92. [PubMed: 7742727]
11. Chak A, Lee T, Kinnard MF, Brock W, Faulx A, Willis J, Cooper GS, Sivak MV Jr, Goddard KA. Familial aggregation of Barrett's esophagus, esophageal adenocarcinoma, and gastroesophageal junctional adenocarcinoma in Caucasian adults. *Gut* 2002;51(3):323–8. [PubMed: 12171951]
12. Chak A, Ochs-Balcom H, Falk G, Grady WM, Kinnard M, Willis JE, Elston R, Eng C. Familiality in Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastroesophageal junction. *Cancer Epidemiol Biomarkers Prev* 2006;15(9):1668–73. [PubMed: 16985029]
13. Groves C, Jankowski J, Barker F, Holdstock G. A family history of Barrett's esophagus: another risk factor? *Scand J Gastroenterol* 2005;40(9):1127–8. [PubMed: 16211720]
14. Sappati Biyyani RS, Chessler L, McCain E, Nelson K, Fahmy N, King J. Familial trends of inheritance in gastro esophageal reflux disease, Barrett's esophagus and Barrett's adenocarcinoma: 20 families. *Dis Esophagus* 2007;20(1):53–7. [PubMed: 17227311]
15. Drowdlic CM, Goddard KA, Chak A, Brock W, Chessler L, King JF, Richter J, Falk GW, Johnston DK, Fisher JL, Grady WM, Lemeshow S, Eng C. Demographic and phenotypic features of 70 families segregating Barrett's esophagus and esophageal adenocarcinoma. *J Med Genet* 2003 Sep;40(9):651–6. Erratum in: *J Med Genet*. 2004;41(1):46. [PubMed: 12960209]
16. Wang KK, Sampliner RE. Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008;103(3):788–97. [PubMed: 18341497]
17. Locke GR, Talley NJ, Weaver AL, Zinsmeister AR. A new questionnaire for gastroesophageal reflux disease. *Mayo Clin Proc* 1994;69:539–47. [PubMed: 8189759]
18. Chak A, Faulx A, Kinnard M, Brock W, Willis J, Wiesner GL, Parrado AR, Goddard KAB. Identification of Barrett's esophagus in relatives by endoscopic screening. *Am J Gastroenterol* 2004;99(11):2107–14. [PubMed: 15554988]
19. El-Serag HB, Kvapil P, Hacken J, Kramer JR. Abdominal obesity and the risk of Barrett's esophagus. *Am J Gastroenterology* 2005;100:2151–6.
20. Edelstein ZR, Farrow DC, Bronner MP, Rosen SN, Vaughan TL. Central adiposity and risk of Barrett's esophagus. *Gastroenterology* 2007;133(2):403–11. [PubMed: 17681161]
21. Corley DA, Kubo A, Levin TR, Block G, Habel L, Zhao W, Leighton P, Quesenberry C, Rumore GJ, Buffler PA. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. *Gastroenterology* 2007;133(1):34–41. [PubMed: 17631128]
22. Edelstein ZR, Farrow DC, Bronner MP, Rosen SN, Vaughan TL. Central adiposity and risk of Barrett's esophagus. *Gastroenterology* 2007 Aug;133(2):403–11. [PubMed: 17681161]
23. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. *JAMA* 2003;290:66–72. [PubMed: 12837713]
24. Murray L, Johnston B, Lane A, Harvey I, Donovan J, Nair P, Harvey R. Relationship between body mass and gastro-esophageal reflux symptoms: The Bristol Helicobacter Project. *Int J Epidemiol* 2003;32:645–50. [PubMed: 12913045]

25. Locke GR 3rd, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ 3rd. Risk factors associated with symptoms of gastroesophageal reflux. *Am J Med* 1999;106:642–9. [PubMed: 10378622]
26. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004 Aug;4(8):579–91. [PubMed: 15286738]
27. MacDonald WC, MacDonald JB. Adenocarcinoma of the esophagus and/or gastric cardia. *Cancer* 1987;60:1094. [PubMed: 3607726]
28. Cameron AJ, Lomboy CT, Pera M, Carpenter HA. Adenocarcinoma of the gastroesophageal junction and Barrett's esophagus. *Gastroenterology* 1995;109:1541–6. [PubMed: 7557137]
29. Hameeteman W, Tytgat GN. Barrett's esophagus: development of dysplasia and adenocarcinoma. *Gastroenterology* 1989;96:1249–56. [PubMed: 2703113]
30. Reid BJ, Blount PL, Rubin CE, Levine DS, Haggitt RC, Rabinovitch PS. Flow-cytometric and histologic progression to malignancy in Barrett's esophagus: prospective endoscopic surveillance of a cohort. *Gastroenterology* 1992;102:1212–9. [PubMed: 1551528]
31. Ruol A, Parenti A, Zaninotto G, Merigliano S, Costantini M, Cagol M, Alfieri R, Bonavina L, Peracchia A, Ancona E. Intestinal metaplasia is the probable common precursor of adenocarcinoma in Barrett's esophagus and adenocarcinoma of the gastric cardia. *Cancer* 2000;88:2520–2528. [PubMed: 10861428]
32. Hirota WK, Loughney TM, Lazas DJ, Maydonovitch CL, Rhol V, Wong RKH. Specialized intestinal metaplasia, dysplasia, and cancer of the esophagus and gastroesophageal junction: prevalence and clinical data. *Gastroenterology* 1999;116:277–85. [PubMed: 9922307]
33. Gammon MD, Schoenberg JB, Ahsan H, Risch HA, Vaughan TL, Chow WH, Rotterdam H, West A, Dubrow R, Stanford JL, Mayne ST, Blot WJ, Farrow DC, Niwa S, Fraumeni JJ. Tobacco, alcohol and socioeconomic status and adenocarcinoma of the esophagus and gastric cardia. *J Natl Cancer Inst* 1997;89:1277–84. [PubMed: 9293918]
34. Lagergren J, Bergstrom R, Lindgren A, et al. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the esophagus and gastric cardia. *Int J Cancer* 2000;85:340–6. [PubMed: 10652424]
35. Kabat GC, Ng SK, Wynder EL. Tobacco, alcohol intake, and diet in relation to adenocarcinoma of the esophagus and gastric cardia. *Cancer Causes Control* 1993;4:123–32. [PubMed: 8481491]
36. Rowland ML. Self-reported weight and height. *Am J Clin Nutr* 1990;52:1125–33. [PubMed: 2239790]

Figure 1A

Figure 1B

Figure 1.

Figure 1A. Histograms of age of diagnosis in Non-FBE (Left) and FBE Cancers (Right) as self reported.

Figure 1B. Histograms of age of diagnosis in Non-FBE (left) and FBE (right) cancers whose status was confirmed by review of endoscopy and/or pathology records of affected relative(s).

Figure 2. Histograms of age of diagnosis in cancer patients without obesity (left) and those with obesity (right) one year before diagnosis.

Table 1

Gender, race, stage, marital status, body mass index, GERD symptoms, and exposure history in Non-FBE and FBE Cancer groups for individuals who answered the study questionnaire.

	Non-FBE Cancers	FBE Cancers	p-value
Average age at cancer diagnosis	61.9 yrs	62.6 yrs	0.70
Gender:			
<i>Men</i>	176 (81.5%)	115 (82.1%)	1.0
<i>Women</i>	40 (18.5%)	25 (17.9%)	
White Race	193/201 (96.0%)	61/61 (100.0%)	0.20
Cancer Stage:			
<i>I</i>	35 (23.8%)	11 (25.0%)	0.88
<i>II</i>	45 (30.6%)	11 (25.0%)	
<i>III</i>	49 (33.3%)	17 (38.6%)	
<i>IV</i>	18 (12.2%)	5 (11.4%)	
Body Mass Index ≥ 30			
<i>At Diagnosis</i>	36 (16.7%)	17 (12.1%)	0.24
<i>1 Yr Previously</i>	58 (29.3%)	20 (37.7%)	0.25
<i>5 Yr Previously</i>	68 (34.9%)	24 (46.2%)	0.15
<i>10 Yr Previously</i>	56 (29.2%)	20 (38.5%)	0.24
<i>20 Yr Previously</i>	38 (20.1%)	14 (27.5%)	0.26
Married?			
<i>No</i>	17.0%	25.8%	0.14
<i>Yes</i>	83.0%	74.2%	
Heartburn Present	116/194 (59.8%)	37/56 (66.1%)	0.44
Heartburn Duration			
<i>None</i>	79 (40.1%)	23 (37.7%)	0.36
<i>< 1 yr</i>	8 (4.1%)	0 (0%)	
<i>1 – 5 yrs</i>	12 (6.1%)	2 (3.3%)	
<i>5 – 10 yrs</i>	14 (7.1%)	3 (4.9%)	
<i>>10 yrs</i>	84 (42.6%)	33 (54.1%)	
Heartburn Frequency			
<i>None</i>	82 (41.8%)	23 (37.7%)	0.73
<i>< monthly</i>	29 (14.8%)	9 (14.8%)	
<i>Monthly</i>	18 (9.2%)	3 (4.9%)	
<i>Weekly</i>	22 (12.2%)	10 (16.4%)	
<i>Several times a week</i>	24 (11.2%)	10 (16.4%)	
<i>Daily</i>	21 (10.7%)	6 (9.8%)	
Heartburn Severity			

	Non-FBE Cancers	FBE Cancers	p-value
<i>None</i>	81 (41.5%)	23 (38.3%)	0.91
<i>Mild</i>	29 (14.9%)	8 (13.3%)	
<i>Moderate</i>	61 (31.3%)	20 (33.3%)	
<i>Severe</i>	24 (12.3%)	9 (15.0%)	
Regurgitation Present	123/192 (64.1%)	37/56 (66.1%)	0.87
Regurgitation Duration			0.55
<i>None</i>	73 (37.1%)	26 (41.9%)	
<i>< 1 yr</i>	28 (14.2%)	4 (6.5%)	
<i>1 – 5 yrs</i>	25 (12.7%)	7 (11.3%)	
<i>5 – 10 yrs</i>	23 (11.7%)	7 (11.3%)	
<i>>10 yrs</i>	48 (24.4%)	18 (29.0%)	
Regurgitation Frequency			0.95
<i>None</i>	75 (38.1%)	26 (41.9%)	
<i>< monthly</i>	40 (20.3%)	13 (21.0%)	
<i>Monthly</i>	25 (12.7%)	9 (14.5%)	
<i>Weekly</i>	25 (10.2%)	5 (9.7%)	
<i>Several times a week</i>	20 (12.7%)	6 (8.1%)	
<i>Daily</i>	12 (6.1%)	3 (4.8%)	
Regurgitation Severity			0.47
<i>None</i>	76 (38.6%)	26 (41.9%)	
<i>Mild</i>	32 (16.2%)	6 (9.7%)	
<i>Moderate</i>	59 (29.9%)	17 (27.4%)	
<i>Severe</i>	30 (15.2%)	12 (21.0%)	
Ever Smoke?			1.0
<i>No</i>	26.7%	26.3%	
<i>Yes</i>	73.3%	73.7%	
Drink Coffee?			0.85
<i>No</i>	19.5%	17.9%	
<i>Yes</i>	80.5%	82.1%	
Drink Alcohol?			0.68
<i>No</i>	16.7%	19.6%	
<i>Yes</i>	83.3%	80.4%	

Kruskal-Wallis test of differences in average age

* Fishers exact test

Table 2

Univariable mixed models of age of esophageal cancer onset adjusting for familial correlation of disease onset between individuals within families.

Variable of Interest	Mean Age in years	p-value of effect	Akaike's Information Criteria (AIC)	# observations used (total 356)
FBE:				
<i>No family history</i>	61.93	0.61	2540.5	320
<i>Family history</i>	62.69			
Gender:				
<i>Men</i>	62.08	0.71	1926.1	320
<i>Women</i>	62.80			
Obesity 1 year ago:				
<i>BMI < 30</i>	63.60	0.008	1895.4	241
<i>BMI ≥ 30</i>	58.99			
Obesity 5 years ago:				
<i>BMI < 30</i>	63.74	0.02	2526.1	320
<i>BMI ≥ 30</i>	59.71			
Obesity 10 years ago:				
<i>BMI < 30</i>	63.61	0.01	2524.2	320
<i>BMI ≥ 30</i>	59.31			
Obesity 20 years ago:				
<i>BMI < 30</i>	63.40	0.11	2525.5	320
<i>BMI ≥ 30</i>	60.39			
Heartburn Duration:				
<i>None</i>	REF	REF	2526.1	320
<i>< 1 yr</i>	63.93	0.68		
<i>1 – 5 yrs</i>	61.88	0.55		
<i>5 – 10 yrs</i>	63.67	0.66		
<i>>10 yrs</i>	63.48	0.50		
Regurgitation Duration				
<i>None</i>	REF	REF	2524.2	320
<i>< 1 yr</i>	60.92	0.39		
<i>1 – 5 yrs</i>	58.56	0.30		
<i>5 – 10 yrs</i>	57.79	0.11		
<i>>10 yrs</i>	58.99	0.36		
Ever Smoke?				
<i>No</i>	62.89	REF	1933.7	245
<i>Yes</i>	62.23	0.72		
Drink Alcohol?				

Variable of Interest	Mean Age in years	p-value of effect	Akaike's Information Criteria (AIC)	# observations used (total 356)
<i>No</i>	65.24	REF	1884.7	241
<i>Yes</i>	61.71	0.09		

* REF – referent group

Table 3

Multivariable mixed models of age of esophageal cancer onset adjusting for heartburn duration, regurgitation duration, and familial correlation of disease onset between individuals within families

Variable of Interest	Mean Age in Years	p-value of effect	Akaike's Information Criteria (AIC)	# observations used (total 356)
Obesity 1 year ago:				
<i>BMI</i> < 30	63.68	0.005	1883.7	245
<i>BMI</i> ≥ 30	58.81			
Obesity 5 years ago:				
<i>BMI</i> < 30	63.72	0.02	1853.5	241
<i>BMI</i> ≥ 30	59.75			
Obesity 10 years ago:				
<i>BMI</i> < 30	63.51	0.02	1818.3	238
<i>BMI</i> ≥ 30	59.55			