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Interactions between smoking, obesity and symptoms of acid reflux in Barrett's esophagus

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Abstract

Background—Barrett's esophagus (BE), a metaplastic precursor to esophageal adenocarcinoma, is becoming increasingly prevalent in many populations. Clinical studies suggest acid reflux causes BE, however no population-based estimates of risk have been reported and the role of other health factors in modifying risk is unclear.

Methods—We conducted a population-based case-control study in Brisbane, Australia. Cases were 167 patients with histologically-confirmed BE diagnosed between February and December, 2003. Age- and sex-matched controls (n = 261) were randomly selected from a population register. Data on exposure to self-reported symptoms of acid reflux, smoking, obesity and other factors were collected through self-completed questionnaires followed by telephone interview. Risks of BE and BE with dysplasia associated with these exposures were estimated by the odds ratio (OR) and 95% confidence interval (95% CI), both crude and adjusted for other factors.

Results—Self-reported weekly episodes of acid reflux were associated with greatly increased risks of BE (adjusted OR 29.7 [12.2-72.6]) and BE with dysplasia (OR 59.7 [18.5-193]). Smoking was also associated with risk of BE. We found evidence of interactions between symptoms of acid reflux and smoking and obesity. Obese people with self-reported symptoms of acid reflux had markedly higher risks of BE (OR 34.4 [6.3-188]) than people with reflux alone (OR 9.3 [1.4 – 62.2]) or obesity alone (OR 0.7 [0.2 – 2.4]). Similarly, those reporting both acid reflux symptoms and smoking were at substantially higher risks of BE (OR 51.4 [14.1-188]) than those reporting acid reflux or smoking alone.

Conclusions—While history of symptoms of acid reflux is the principle factor associated with BE, risks are substantially increased by obesity and smoking.

Keywords

Barrett's esophagus; esophageal cancer; risk factors; case-control study; obesity

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Introduction

Barrett's esophagus (BE) is a metaplastic change of the lower esophagus in which the normal squamous epithelium is replaced by mucin-secreting columnar epithelium resembling the lining of the small intestine [1]. BE is of considerable interest because patients with this type of metaplasia have markedly increased risks of developing adenocarcinoma of the esophagus compared with the general population; BE patients with dysplastic changes are at even higher risk of cancer [2-4].

Until recently, adenocarcinoma of the esophagus was a rare disease, however the incidence of this cancer has increased sharply during the past three decades in the United States [5], several European countries [6,7] and Australia [8]. Several reports suggest that BE has also become more common recently [3,9]. The reasons for these increases in BE and adenocarcinoma of the esophagus are largely unknown. Increased opportunities for detection through widespread availability of endoscopies may partially explain the rise in BE, although this could not explain the increasing incidence and mortality rates for adenocarcinoma. The most likely explanation is that the increases in esophageal metaplasia and neoplasia are real and reflect increasing exposure to the underlying causal factors.

There is general acceptance, based upon clinical observation and animal models, that chronic reflux of acid into the lower esophagus is the principal cause of BE [1]. Little is known about the role of other environmental and clinical factors that might explain the rising prevalence of BE. While population-based studies of esophageal adenocarcinoma have implicated such common factors as smoking [10,11], obesity [12,13] and various medications [14] in the development of that disease, few comparable studies of BE have been reported. Thus, it remains to be established whether these factors play a role in metaplasia or whether they are involved independently in the development of cancer. Here, we present the findings of an investigation into the causes of BE without dysplasia (hereafter “BE”), as well as BE complicated by dysplasia (“BE with dysplasia”).

Methods

We conducted a population-based study in which data collected from patients with BE were compared with similar data collected from a set of controls. Approval to undertake the study was obtained from the human research ethics committees of the Queensland Institute of Medical Research and major hospitals in Brisbane, Australia.

Study participants

Patients eligible for inclusion in this analysis were people aged 18 to 79 years with a diagnosis of histologically-confirmed BE between 1 February and 31 December, 2003. BE was defined as the presence of specialized intestinal metaplasia (columnar epithelium with goblet cells) in a biopsy taken from the esophagus by upper gastrointestinal endoscopy, regardless of the length of involvement [15]. Patients with specialized intestinal metaplasia detected only in biopsies taken from the gastric cardia were not eligible for inclusion.

All patients meeting the eligibility criteria were prospectively identified at the two major private pathology laboratories and the single public pathology laboratory serving metropolitan Brisbane (population 1.5 million) during the study period. (A third small private laboratory commenced diagnostic services during the ascertainment period, but did not have the resources to participate).

To comply with Australian privacy laws, pathology laboratories were able to release patient contact details to study investigators only after first obtaining written permission from the

patients concerned. For all eligible patients diagnosed through the private pathology laboratories, a notice explaining the study was automatically generated in the computerized report to the treating doctor. If no objection was forthcoming, the pathology laboratory wrote to each patient requesting permission to release their contact details to the investigators; a second letter was sent in the event of non-response. For patients diagnosed through the public laboratory, a letter signed by the Chief Health Officer for Queensland was mailed to each potential case participant. If no contact was made after two mail outs, then these potential cases were deemed "non-responders" and no further attempts were made to contact them. This analysis was restricted to patients with new diagnoses of BE or BE with dysplasia during the ascertainment period; we excluded all those with a previous diagnosis of BE who did not have a first diagnosis of dysplasia during that time ("prevalent cases").

Control participants from the same geographic region were randomly selected from the Australian Electoral Roll (enrolment is compulsory by law), broadly matched by age (in 5 year age groups) and sex to this case series and a parallel case series of patients with esophageal cancer. Control participants were contacted in a similar manner to cases, except that the initial approach came directly from the study investigators.

We obtained written informed consent from case patients and control participants to take part. Those who did not speak English or were too ill to participate were excluded.

Data collection

Data were collected from participants through structured, self-completed questionnaires, followed by standard telephone interviews conducted by trained research nurses. Items on the questionnaire asking about recent gastro-intestinal symptoms were from recent prevalence surveys in Australian populations [16,17]; items asking about historical reflux exposures were based on those used in previous case-control studies of esophageal adenocarcinoma [18,19]. Thus, participants were asked if they had ever experienced acid reflux, defined as "a sour taste from acid or bile rising up into the mouth or throat". If so, they were asked to report their age when these symptoms were first experienced, as well as the frequency of episodes in the past year (or year before diagnosis for cases). Participants were also asked to report reflux frequency at each of four periods (ages 10 to 19 years, 20 to 29 years, 30 to 49 years, 50 to 79 years, as applicable). We collected information about height and weight (current and heaviest ever). Participants were asked whether, over their whole life, they had ever smoked more than 100 cigarettes, cigars or pipes; positive responses elicited further questions about how much they usually smoked on a typical day, and how many years they had smoked. We asked participants to report their frequency of use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) and acetoaminophen during the past 5 years.

We obtained pathology reports and request forms relating to the index biopsy for all consenting cases, from which we determined the location of the biopsy, the date of diagnosis and the presence or absence of dysplasia.

Statistical analyses

Our primary aim was to separately estimate the relative risks of BE and BE with dysplasia associated with self-reported symptoms of acid reflux, and to examine interactions with obesity and smoking. We calculated body mass index (BMI) at current age and at the time of greatest weight by dividing weight in kilograms by the square of height in meters. We used standard BMI categories for analysis (<18.5 kg/m^2 "underweight", 18.5 to 24.9 kg/m^2 "normal", 25 to 29.9 kg/m^2 "overweight", ≥ 30 kg/m^2 "obese"). Among smokers, we derived the number of pack-years of tobacco exposure by dividing the number of cigarettes smoked on a typical day by 20, and multiplying by the total number of years smoked.

We calculated the odds ratio (OR) and 95% confidence interval (95% CI) associated with each exposure using unconditional multivariable logistic regression analysis using the logistic procedure in SAS version 9.1 (SAS Institute Inc., Cary NC). Our approach was to firstly fit simple models which contained single terms for each of the exposures of interest, adjusted only for exact age in years and sex to account for the frequency matching. From these analyses, we developed a list of factors which were either statistically significantly associated with BE, or else were of interest *a priori*. We then included all of these exposures in a saturated model, and conducted a supervised elimination procedure to examine the effects of removing terms from the model one at a time. For each categorical variable, design variables were parameterized using the reference cell coding method with the unexposed or lowest category taken as the reference category. Factors which were collinear were not considered together in the model. Final models included terms for exact age in years, sex, frequency of symptoms of acid reflux in the current age range (never, monthly, weekly or more often), smoking (pack-years), BMI (as a continuous variable) and frequency of NSAID use in the past five years (never, occasionally, 2-3 times per month, weekly or more often). Terms excluded from the final model were past history of peptic ulcers and past history of gastritis.

We examined whether the association with symptoms of acid reflux was modified by other risk factors (i.e. biological interaction) [20] in further analyses restricted to case participants with BE and controls. We classified participants according to their frequency of self-reported reflux in their current age range (never, monthly, weekly or more often) by maximum BMI (normal, overweight, obese), and separately by smoking history (never smoker, ever smoker). Risks for each category of joint exposure were estimated relative to the absolute reference category (people with no reflux who were never smokers or people with no reflux who were normal weight) in a multivariable logistic regression analysis controlling for age, sex and smoking or maximum BMI.

Statistical significance was determined at $\alpha = .05$, and all tests for statistical significance were two-sided.

Results

From 770 potentially eligible patients with BE or BE with dysplasia approached by the pathology laboratories, 609 (79%) responded, of whom 500 agreed to the release of their contact details and 109 refused. Non-responders (mean age 54 years) were younger than responders (58 years), but did not differ by gender. Of 500 patients approached by the investigators, 5 were unable to be further contacted, 4 declined to participate, and 42 withdrew after initially agreeing to participate. We excluded those who did not speak English or were too ill to take part (n=2), leaving 447 BE patients (58% of all potential cases originally approached). Those with a previous diagnosis of BE who did not have a diagnosis of dysplasia during the ascertainment period (“prevalent cases” n=237) were excluded. We also excluded a further 42 patients whose clinical records indicated that their biopsies were taken at the esophago-gastric junction. Thus the final analysis comprised patients who were newly diagnosed with BE (n=117) or BE with dysplasia (n=50).

Of 521 potentially eligible control participants sampled from the electoral roll, 51 were not able to be contacted and 12 were excluded because they were deceased (n=5), too ill (n=4), or unable to speak English (n=3). Of the remaining 458 people, 149 (33%) declined the invitation and 309 (67%) accepted. Completed questionnaires were returned by 261 of 309 (84%) of those who accepted [50% of all potential controls originally selected from the roll]. Characteristics of cases and controls are presented in Table 1.

Patients with BE were almost 5-fold more likely than controls to report a history of acid reflux symptoms; the adjusted odds ratio for patients with dysplastic BE was considerably higher

(OR 13.5, 95% CI 4.6-39.5) (Table 2). Those who reported at least monthly episodes of acid reflux symptoms in the previous year were at three- to four-fold increased risks of being diagnosed with both BE and BE with dysplasia, compared with 30-fold increased risks of BE associated with at least weekly symptoms of reflux. Because episodes of reflux symptoms in the past year may have precipitated medical investigation and thus be associated with diagnosis of BE, we investigated the frequency of reflux symptoms at different age groups in relation to risk of BE. Self-reported symptoms of acid reflux were uncommon between ages 10 to 19 years; thereafter, the prevalence of acid reflux symptoms increased with age among both cases and controls (Table 2). For both BE and BE with dysplasia, the strongest associations were observed with symptoms of acid reflux experienced after age 50 years.

Cigarette smoking was associated with two- to three-fold increased risks of BE and BE with dysplasia, and this persisted after adjustment for other factors. There was no evidence that the strength of association increased with cumulative smoking history (Table 3).

While 46% and 28% of population control participants were currently overweight or obese respectively, obesity was more common among patients with BE and BE with dysplasia, although this was only statistically significant on crude analysis among patients with BE with dysplasia (Table 3). The magnitudes of the associations with obesity were attenuated and no longer statistically significant in fully adjusted models.

Use of aspirin and other NSAIDs during the past 5 years was common among population controls (77%), patients with BE (72%) and BE with dysplasia (76%) (Table 3). Frequency of use varied somewhat between cases and controls, but overall, there was no evidence that these medications were associated with BE or BE with dysplasia. In contrast, weekly use of acetaminophen during the past 5 years was more than twice as likely among BE patients, and almost five times as likely among BE patients with dysplasia compared with controls. Following adjustment for use of NSAIDs, obesity and smoking, the association with acetaminophen was reduced for BE, whereas a negative association with use of NSAIDs became apparent, albeit of marginal statistical significance.

We re-classified participants according to their joint history of acid reflux symptoms and smoking to investigate biologic interaction under an additive model. People who had ever smoked but who reported no recent symptoms of acid reflux had about 2-fold higher risks of BE than never smokers with no self-reported reflux symptoms (Table 4). Among people reporting monthly or weekly reflux symptoms, smokers had statistically significantly higher risks of BE than non-smokers. Highest risks of BE were observed among smokers with at least weekly episodes of reflux (OR 51.4, 95% CI 14.1 – 188).

Similar analyses were conducted to examine interactions between BMI and symptoms of acid reflux (Table 4). In the absence of reflux symptoms, overweight and obese people were at no higher risk of BE than those of normal body weight. Among people reporting a history of acid reflux symptoms however, those who were overweight or obese had statistically significantly higher risks of BE than those in the normal weight range. More than 30-fold increased risks of BE were observed for obese people who reported weekly symptoms of reflux (OR 34.4, 95% CI 6.3-188) compared with people in the normal weight range with no history of reflux.

Discussion

This population-based study has shown that frequent symptoms of reflux are associated with increased risks of BE, and that these risks are substantially elevated by smoking and obesity. The strong association observed between symptoms of acid reflux and BE accords with hospital-based case-control studies [21-23], although we are not aware of any population-based estimates of risk with which to compare these findings. Our data suggest that people who report

experiencing at least weekly symptoms of acid reflux have substantially higher risks of BE than those with less frequent episodes. Moreover, we found that symptoms of acid reflux experienced at older ages conferred substantially higher risks of BE than symptoms at younger ages, despite the increasing prevalence of reflux episodes with increasing age among the control group. While all participants may have selectively recalled symptoms experienced at older ages in preference to early life, the progressively higher risks of BE associated with reflux at successively older ages suggest that biased recall is unlikely to explain all of this effect. It might also be argued that the association with acid reflux is explained by detection bias, in which people with frequent symptoms of acid reflux are more likely to undergo upper endoscopy and hence be diagnosed with BE than people without symptoms of acid reflux. This argument is difficult to sustain in the light of the universally larger associations with acid reflux we observed for BE with dysplasia than for BE without dysplasia.

Obesity has been shown to be a determinant of acid reflux [24-26] and has also been linked with esophageal adenocarcinoma [13,27]. In that context, our observation of modestly higher prevalence of obesity among BE patients is perhaps not surprising. One interpretation is that the association between obesity and BE is simply mediated by the effects of acid reflux, as suggested by the attenuated risk estimates for obesity after adjusting for the presence of reflux in the multivariate model. However, our finding that the presence of both self-reported history of acid reflux and obesity led to considerably higher risks than predicted under additive models of biologic interaction [20] suggests that obesity plays a further role in the development of BE, over and above its likely role in promoting acid reflux. Obesity has been associated with increased risks of many types of human cancer [28], and various biologic mediators (such as steroid hormones, insulin and growth factors) have been proposed to explain the finding [29, 30]. Similar mechanisms may also underlie esophageal metaplasia and neoplasia.

We found that smokers had higher risks of BE than non-smokers, although there was no evidence that longer duration or greater intensity of smoking materially altered the risk of disease. Similar patterns of association have been observed between smoking and adenocarcinoma of the esophagus [10,11]. In the absence of acid reflux symptoms, smokers were at no higher risk of BE than non-smokers, whereas when reflux was present, smoking substantially increased the risks of developing BE. These data suggest that smoking is neither necessary nor sufficient to induce BE, but rather potentiates the metaplastic changes initiated by acid reflux.

While regular use of NSAIDs has been associated with reduced risks of esophageal adenocarcinoma and BE [31-33], we found little evidence to support this contention on univariate analysis. Rather, we found that whereas BE patients reported similar levels of NSAID use as population controls, they reported substantially higher levels of acetaminophen use. After mutual adjustment for other factors, the association with acetaminophen was no longer statistically significant, although patients with dysplastic BE remained considerably more likely than controls to report frequent use of acetaminophen. Despite this observation, we have no reason to believe the association with acetaminophen to be causal, and the most likely explanation for our finding is residual negative confounding due to acid reflux. If residual confounding does underlie this finding, it calls into question the previously observed protective effect of NSAIDs on BE and esophageal adenocarcinoma, particularly as such findings have provided a rationale for clinical trials [34,35].

Several aspects of the study design lend credence to the findings. Patients newly diagnosed with BE were prospectively identified and ascertained from across an entire region and compared to controls sampled from a population register. We are not aware of any previous studies of BE that have sampled newly diagnosed cases and controls in such a way, hence these are likely to be the first population-based estimates of risk for this condition. Cases were rapidly

recruited after their initial diagnosis, reducing the likelihood that their recall and reporting of past exposures was influenced by prolonged knowledge of their condition. Biased recall would also be unlikely to account for the interactions with smoking and obesity that we observed.

Ascertaining cases through pathology laboratories allowed us to systematically identify BE patients from the source population, and also ensured standard application of histologic inclusion criteria [15]. However we were unable to separately examine associations according to extent of involvement of the esophagus as length of BE (as opposed to biopsy site) was not routinely reported by the large number of community endoscopists in this population-based study. While there is some evidence that length of BE is an important determinant of prognosis, there is general consensus that "short" and "long" segment BE represent a continuum of the same pathologic process [36]. It is unlikely that these entities have sufficiently different causes to invalidate the strong associations observed here.

One potential limitation is that because control participants were sampled from the general population, we cannot exclude the possibility that some may have had undiagnosed BE. While this would lead to error in the risk estimates, the magnitude of the error will be small given that the most extreme upper estimates of the population prevalence of BE are no higher than 12% [1]. Moreover, such a bias would tend to make the control series, on average, more similar to the case series and thus would only serve to attenuate any observed associations.

A potentially more serious error for causal inference might arise if people who are diagnosed with BE because they have undergone endoscopy and biopsy do not represent all people with BE (diagnosed and undiagnosed). Thus, an association might be observed between acid reflux and BE simply because people with acid reflux are more likely to undergo endoscopy, and thus be more likely to be diagnosed with BE. Countering this conjecture are the observations that BE is rare in endoscopy series of healthy volunteers [37] and, in population studies, BE is diagnosed in less than 10% of patients with severe reflux who present for endoscopy [38]. These data mitigate the likelihood of a "bottom of the iceberg" pool of undiagnosed patients whose BE etiology differs from that of diagnosed BE patients [39].

Rates of participation in population studies have been falling over time, leading to concerns about unrepresentative samples and potentially biased estimates of risk [40]. To address this issue, we compared self-reported prevalences of key exposures in our control series with those reported by the Australian National Health Survey conducted in 2001. We found very similar prevalences of smoking, obesity and use of medications and conclude that the control series was representative of the Australian community from which the cases arose [41].

In summary, these data confirm the clinical impression that self-reported history of acid reflux is strongly associated with BE and BE with dysplasia, and suggest that smoking and obesity potentiate the effects of acid reflux. From a public health perspective, these data raise the prospect that quitting smoking and losing weight merit further investigation as potential adjuncts in the control of BE.

Study of Digestive Health Investigators

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Abbreviations

BE, Barrett's esophagus; BMI, Body Mass Index; CI, Confidence Interval; N, Number; NSAIDs, non-steroidal anti-inflammatory drugs; OR, Odds Ratio; %, Percentage.

References

1. Falk GW. Barrett's esophagus. Gastroenterology 2002;122:1569–91. [PubMed: 12016424]
2. Murray L, Watson P, Johnston B, et al. Risk of adenocarcinoma in Barrett's oesophagus: population based study. Br Med J 2003;327:534–5. [PubMed: 12958113]
3. Conio M, Cameron AJ, Romero Y, et al. Secular trends in the epidemiology and outcome of Barrett's oesophagus in Olmsted County, Minnesota. Gut 2001;48:304–9. [PubMed: 11171817]
4. Shaheen NJ. Advances in Barrett's Esophagus and Esophageal Adenocarcinoma. Gastroenterology 2005;128:1554–66. [PubMed: 15887151]
5. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. Semin Oncol 1999;26:2–8. [PubMed: 10566604]
6. Vizcaino AP, Moreno V, Lambert R, Parkin DM. Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973-1995. Int J Cancer 2002;99:860–8. [PubMed: 12115489]
7. Botterweck AA, Schouten LJ, Volovics A, et al. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. Int J Epidemiol 2000;29:645–54. [PubMed: 10922340]
8. Lord RV, Law MG, Ward RL, et al. Rising incidence of oesophageal adenocarcinoma in men in Australia. J Gastroenterol Hepatol 1998;13:356–62. [PubMed: 9641297]
9. Prach AT, MacDonald TA, Hopwood DA, Johnston DA. Increasing incidence of Barrett's oesophagus: education, enthusiasm, or epidemiology? Lancet 1997;350:933. [PubMed: 9314878]
10. Lagergren J, Bergstrom R, Lindgren A, Nyren O. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. Int J Cancer 2000;85:340–6. [PubMed: 10652424]
11. Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 1997;89:1277–84. [PubMed: 9293918]
12. Brown LM, Swanson CA, Gridley G, et al. Adenocarcinoma of the esophagus: role of obesity and diet. J Natl Cancer Inst 1995;87:104–9. [PubMed: 7707381]
13. Chow WH, Blot WJ, Vaughan TL, et al. Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 1998;90:150–5. [PubMed: 9450576]
14. Lagergren J, Bergstrom R, Adami HO, Nyren O. Association between medications that relax the lower esophageal sphincter and risk for esophageal adenocarcinoma. Ann Intern Med 2000;133:165–75. [PubMed: 10906830]

15. Sampliner RE. Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus. Am J Gastroenterol 2002;97:1888–95. [PubMed: 12190150]
16. Westbrook JI, Talley NJ, Westbrook MT. Gender differences in the symptoms and physical and mental well-being of dyspeptics: a population based study. Qual Life Res 2002;11:283–91. [PubMed: 12074265]
17. Westbrook JI, Talley NJ. Empiric clustering of dyspepsia into symptom subgroups: a population-based study. Scand J Gastroenterol 2002;37:917–23. [PubMed: 12229966]
18. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825–31. [PubMed: 10080844]
19. Chow WH, Finkle WD, McLaughlin JK, et al. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. JAMA 1995;274:474–7. [PubMed: 7629956]
20. Rothman KJ. Modern Epidemiology. 1986
21. Conio M, Filiberti R, Blanchi S, et al. Risk factors for Barrett's esophagus: a case-control study. Int J Cancer 2002;97:225–9. [PubMed: 11774268]
22. Campos GM, DeMeester SR, Peters JH, et al. Predictive factors of Barrett esophagus: multivariate analysis of 502 patients with gastroesophageal reflux disease. Arch Surg 2001;136:1267–73. [PubMed: 11695971]
23. Lieberman DA, Oehlke M, Helfand M. Risk factors for Barrett's esophagus in community-based practice. GORGE consortium. Gastroenterology Outcomes Research Group in Endoscopy. Am J Gastroenterol 1997;92:1293–7. [PubMed: 9260792]
24. Talley NJ, Quan C, Jones MP, Horowitz M. Association of upper and lower gastrointestinal tract symptoms with body mass index in an Australian cohort. Neurogastroenterol Motil 2004;16:413–9. [PubMed: 15305996]
25. Nilsson M, Johnsen R, Ye W, et al. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. JAMA 2003;290:66–72. [PubMed: 12837713]
26. Delgado-Aros S, Locke GR 3rd, Camilleri M, et al. Obesity is associated with increased risk of gastrointestinal symptoms: a population-based study. Am J Gastroenterol 2004;99:1801–6. [PubMed: 15330922]
27. Vaughan TL, Davis S, Kristal A, Thomas DB. 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]
28. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–38. [PubMed: 12711737]
29. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579–91. [PubMed: 15286738]
30. Adami HO, Trichopoulos D. Obesity and mortality from cancer. N Engl J Med 2003;348:1623–4. [PubMed: 12711736]
31. Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. Gastroenterology 2003;124:47–56. [PubMed: 12512029]
32. Farrow DC, Vaughan TL, Hansten PD, et al. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiol Biomarkers Prev 1998;7:97–102. [PubMed: 9488582]
33. Morgan G, Vainio H. Barrett's oesophagus, oesophageal cancer and colon cancer: an explanation of the association and cancer chemopreventive potential of non-steroidal anti-inflammatory drugs. Eur J Cancer Prev 1998;7:195–9. [PubMed: 9696927]
34. Jankowski J, Moayyedi P. Re: Cost-effectiveness of aspirin chemoprevention for Barrett's esophagus. J Natl Cancer Inst 2004;96:885–7. [PubMed: 15173278]
35. Heath EI, Canto MI, Wu TT, et al. Chemoprevention for Barrett's esophagus trial. Design and outcome measures. Dis Esophagus 2003;16:177–86. [PubMed: 14641306]
36. Sharma P, McQuaid K, Dent J, et al. A critical review of the diagnosis and management of Barrett's esophagus: the AGA Chicago Workshop. Gastroenterology 2004;127:310–30. [PubMed: 15236196]

37. El-Serag HB, Petersen NJ, Carter J, et al. Gastroesophageal reflux among different racial groups in the United States. Gastroenterology 2004;126:1692–9. [PubMed: 15188164]

38. Nandurkar S, Locke GR 3rd, Murray JA, et al. Rates of Endoscopy and Endoscopic Findings among People with Frequent Symptoms of Gastroesophageal Reflux in the Community. Am J Gastroenterol 2005;100:1459–65. [PubMed: 15984966]

39. Shaheen N. Is there a “Barrett's iceberg?”. Gastroenterology 2002;123:636–9. [PubMed: 12145816]

40. Rogers A, Murtaugh MA, Edwards S, Slattery ML. Contacting controls: are we working harder for similar response rates, and does it make a difference? Am J Epidemiol 2004;160:85–90. [PubMed: 15229121]

41. Australian Bureau of Statistics. National Health Survey 2001: Summary of Results. Australian Bureau of Statistics; Canberra: 2002.

Table 1

Characteristics of study participants

	Controls (n = 261) n	%	BE (n = 117) n	%	BE with dysplasia (n = 50) n	%
Gender						
Male	172	66	75	64	42	84
Female	89	34	42	36	8	16
Age						
Mean (± SD)*	63 ± 11		56 ± 13		63 ± 10	

* standard deviation

Table 2

Odds Ratios for BE and dysplastic BE associated with history of acid reflux

	Controls		BE			BE with dysplasia	
Exposure	**N=261**	**N=117**	**Crude OR (95% CI)***	**Adjusted OR (95% CI)†**	**N=50**	**Crude OR (95% CI)***	**Adjusted OR (95% CI)†**
Acid reflux ever							
No	50%	16%	1.0	1.0	6%	1.0	1.0
Yes	50%	84%	4.9 (2.8-8.6)	4.8 (2.7-8.5)	94%	15.3 (4.6-50.5)	16.9 (5.0-57.2)
Acid reflux past year							
Never	62%	21%	1.0	1.0	17%	1.0	1.0
Monthly	35%	36%	3.0 (1.7 – 5.4)	2.9 (1.6 – 5.4)	35%	3.6 (1.5-8.7)	4.1 (1.6-10.5)
Weekly	3%	43%	32.3 (13.4 – 78.1)	29.7 (12.2 – 72.6)	48%	51.5 (16.9-157)	59.7 (18.5-193)
Acid reflux age 10-19 yrs							
Never	94%	91%	1.0	1.0	86%	1.0	1.0
Monthly	5%	7%	0.8 (0.3-2.3)	0.8 (0.3-2.3)	7%	1.2 (0.3-4.6)	1.2 (0.3-4.7)
Weekly	1%	2%	0.9 (0.1-7.0)	1.7 (0.2-16.8)	7%	6.7 (1.2-38.4)	13.2 (1.8-98.5)
Acid reflux age 20-29 yrs‡							
Never	87%	69%	1.0	1.0	67%	1.0	1.0
Monthly	11%	20%	1.7 (0.9-3.4)	1.7 (0.9-3.4)	17%	1.9 (0.8-4.7)	2.1 (0.8-5.3)
Weekly	2%	11%	5.0 (1.5-17.4)	6.7 (1.7-26.6)	15%	15.4 (3.8-70.0)	24.5 (4.8-124)
Acid reflux age 30-49 yrs§							
Never	75%	44%	1.0	1.0	31%	1.0	1.0
Monthly	22%	32%	1.8 (1.0-3.2)	1.7 (0.9-3.0)	40%	3.5 (1.6-7.5)	3.6 (1.6-8.1)
Weekly	3%	24%	8.7 (3.6-21.4)	9.9 (3.8-25.5)	29%	21.2 (7.2-62.7)	27.3 (8.5-87.4)
Acid reflux age 50-79 yrs‖							
Never	56%	25%	1.0	1.0	5%	1.0	1.0
Monthly	40%	45%	2.3 (1.2-4.6)	2.2 (1.1-4.4)	55%	14.3 (3.2-62.9)	14.8 (3.3-66.5)
Weekly	5%	31%	12.5 (4.9-31.9)	13.5 (5.0-37.0)	40%	89.7 (17.6-457)	96.7 (18.2-514)
Acid reflux for current age group							
Never	55%	21%	1.0	1.0	9%	1.0	1.0
Monthly	40%	43%	2.7 (1.5-4.7)	2.5 (1.4-4.6)	49%	7.2 (2.4-21.8)	7.5 (2.5-22.9)
Weekly	5%	36%	19.1 (8.5-43.2)	19.9 (8.4-46.7)	42%	59.1 (16.8-208)	62.2 (16.8-230)

*Odds ratio and 95% confidence intervals adjusted for exact age in years and sex

†Odds ratio and 95% confidence intervals adjusted for exact age in years, sex, BMI (continuous), pack years smoked (continuous), NSAID use

‡Analysis restricted to participants aged ≥ 25 years

§Analysis restricted to participants aged ≥ 35 years

‖Analysis restricted to participants aged ≥ 55 years

Table 3

Odds ratios for BE and BE with dysplasia associated with smoking, obesity and NSAIDs

	Controls	BE			BE with dysplasia		
Exposure	**N=261**	**N=117**	**Crude OR (95% CI)***	**Adjusted OR (95% CI)†**	**N=50**	**Crude OR (95% CI)***	**Adjusted OR (95% CI)†**
Cigarette smoking intensity (pack-years)							
None	46%	27%	1.0	1.0	18%	1.0	1.0
25 or less	28%	44%	2.5 (1.5-4.4)	3.1 (1.6-6.0)	44%	3.7 (1.6-8.5)	3.8 (1.4-10.3)
More than 25	26%	29%	2.1 (1.1-3.8)	2.2 (1.1-4.5)	38%	2.9 (1.2-6.9)	3.3 (1.2-9.5)
Maximum BMI (kg/m^2)							
18.5 – 24.9	25%	22%	1.0	1.0	12%	1.0	1.0
25 - 29.9	46%	36%	1.0 (0.5-1.7)	0.9 (0.5-1.8)	45%	1.7 (0.6-4.4)	1.3 (0.5-3.9)
≥ 30	28%	42%	1.7 (0.9-3.2)	1.5 (0.7-3.1)	43%	2.9 (1.1-7.7)	2.1 (0.7-6.4)
Aspirin/NSAIDS (frequency of use in past 5 years)							
Never	23%	27%	1.0	1.0	24%	1.0	1.0
Occasionally	32%	32%	0.7 (0.4-1.4)	0.8 (0.4-1.5)	36%	1.0 (0.4-2.2)	0.9 (0.4-2.4)
<2-3/month	12%	11%	0.6 (0.3-1.3)	0.8 (0.3-1.9)	2%	0.1 (0.0-1.1)	0.1 (0.0-1.0)
≥ 1/week	34%	29%	0.8 (0.4-1.5)	0.6 (0.3-1.3)	38%	1.1 (0.5-2.6)	0.8 (0.3-2.1)
Acetominophen (frequency of use in past 5 years)							
Never	17%	13%	1.0	1.0	6%	1.0	1.0
Occasionally	51%	43%	0.9 (0.4-1.7)	0.7 (0.3-1.5)	48%	2.4 (0.7-8.3)	2.6 (0.6-11.4)
<2-3/month	19%	21%	0.9 (0.4-2.1)	1.0 (0.4-2.3)	20%	3.0 (0.7-11.9)	4.1 (0.8-20.8)
≥ 1/week	14%	24%	1.9 (0.8-4.1)	1.3 (0.5-3.1)	26%	5.0 (1.3-19.3)	3.1 (0.6-15.1)

* Odds ratio and 95% confidence intervals adjusted for exact age in years and sex

† Odds ratio and 95% confidence intervals adjusted for exact age in years, sex, frequency of acid reflux symptoms in current age group, BMI (continuous), pack years smoked (continuous), NSAID use

Table 4

Odds ratios for BE associated with frequency of acid reflux, cross-classified by smoking and maximum obesity

	Frequency of episodes of acid reflux in current age group								
	Never			Monthly			Weekly		
	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)
Smoking (pack years)*									
Never smoker	25%	7%	1.0	19%	9%	1.9 (0.7-5.5)	2%	8%	16.9 (4.2-67.5)
Ever smoker	31%	15%	2.4 (0.9-6.8)	20%	34%	7.3 (2.8-19.4)	2%	27%	51.4 (14.1-188)
Maximum BMI†									
18.5 to 24.9 kg/m^2	14%	8%	1.0	11%	8%	1.1 (0.4-3.7)	1%	5%	9.3 (1.4-62.2)
25 to 29.9 kg/m^2	27%	8%	0.6 (0.2-1.7)	18%	18%	1.7 (0.6-1.6)	3%	12%	7.9 (2.3-27.6)
≥ 30 kg/m^2	15%	6%	0.7 (0.2-2.4)	12%	18%	2.5 (0.9-7.0)	1%	18%	34.4 (6.3-188)

*Odds ratio and 95% confidence intervals adjusted for age (continuous), sex, BMI (continuous)

†Odds ratio and 95% confidence intervals adjusted for age (continuous), sex, pack years smoked (continuous)