Interactions among Smoking, Obesity, and Symptoms of Acid Reflux in Barrett's Esophagus

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Abstract

Background: **Barrett's esophagus, a metaplastic precursor to esophageal adenocarcinoma, is becoming increasingly prevalent in many populations. Clinical studies suggest acid reflux causes Barrett's esophagus; 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 Barrett's esophagus diagnosed between February and December 2003. Age-matched 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 Barrett's esophagus and Barrett's esophagus 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 Barrett's esophagus (adjusted OR, 29.7; 95% CI, 12.2-72.6) and Barrett's esophagus with dysplasia (OR, 59.7; 95% CI, 18.5-193). Smoking was also associated with risk of Barrett's esophagus. 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 Barrett's esophagus (OR, 34.4; 95% CI, 6.3-188) than people with reflux alone (OR, 9.3; 95% CI, 1.4-62.2) or obesity alone (OR, 0.7; 95% CI, 0.2-2.4). Similarly, those reporting both acid reflux symptoms and smoking were at substantially higher risks of Barrett's esophagus (OR, 51.4; 95% CI, 14.1-188) than those reporting acid reflux or smoking alone.**

Conclusions: **Although history of symptoms of acid reflux is the principle factor associated with Barrett's esophagus, risks are substantially increased by obesity and smoking.** (Cancer Epidemiol Biomarkers Prev 2005;14(11):2481–6)

Introduction

Barrett's esophagus 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). Barrett's esophagus 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; Barrett's esophagus 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 Barrett's esophagus has also become more common recently (3, 9). The reasons for these increases in Barrett's esophagus and adenocarcinoma of the esophagus are largely unknown. Increased opportunities for detection through widespread availability of endoscopies may partially explain the increase in Barrett's esophagus, 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 Barrett's esophagus (1). Little is known about the role of other environmental and clinical factors that might explain the rising prevalence of Barrett's esophagus. Although 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 Barrett's esophagus 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 Barrett's esophagus without dysplasia, as well as Barrett's esophagus complicated by dysplasia (''Barrett's esophagus with dysplasia'').

Materials and Methods

We conducted a population-based study in which data collected from patients with Barrett's esophagus 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

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histologically confirmed Barrett's esophagus between February 1 and December 31, 2003. Barrett's esophagus 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 nonresponse. 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 ''nonresponders,'' and no further attempts were made to contact them. This analysis was restricted to patients with new diagnoses of Barrett's esophagus or Barrett's esophagus with dysplasia during the ascertainment period; we excluded all those with a previous diagnosis of Barrett's esophagus 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 (enrollment 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 gastrointestinal 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 10-19, 20-29, 30-49, and 50-79 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 >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 nonsteroidal anti-inflammatory drugs (NSAID) 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 Barrett's esophagus and Barrett's esophagus with dysplasia associated with self-reported symptoms of acid reflux and to examine interactions with obesity and smoking. We calculated the 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''; 18.5-24.9 kg/m^2, ''normal''; 25-29.9 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 first 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 Barrett's esophagus, 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 5 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; ref. 20) in further analyses restricted to case participants with Barrett's esophagus 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, and obese), and separately by smoking history (never smoker and 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 $\alpha = 0.05$, and all tests for statistical significance were two sided.

Results

From 770 potentially eligible patients with Barrett's esophagus or Barrett's esophagus with dysplasia approached by the pathology laboratories, 609 (79%) responded, of whom 500 agreed to the release of their contact details and 109 refused. Nonresponders (mean age, 54 years) were younger than responders (58 years) but did not differ by gender. Of 500

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

Abbreviation: BE, Barrett's esophagus.

patients approached by the investigators, five were unable to be further contacted, four 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 Barrett's esophagus patients (58% of all potential cases originally approached). Those with a previous diagnosis of Barrett's esophagus 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 esophagogastric junction. Thus, the final analysis comprised patients who were newly diagnosed with Barrett's esophagus (n = 117) or Barrett's esophagus 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 Barrett's esophagus were almost 5-fold more likely than controls to report a history of acid reflux symptoms; the adjusted OR for patients with dysplastic Barrett's esophagus was considerably higher (OR, 15.3; 95% CI, 4.6-50.5; Table 2). Those who reported at least monthly episodes of acid reflux symptoms in the previous year were at 3- to 4-fold increased risks of being diagnosed with both Barrett's esophagus and Barrett's esophagus with dysplasia, compared with 30-fold increased risks of Barrett's esophagus 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 Barrett's esophagus, we investigated the frequency of reflux symptoms at different age groups in relation to risk of Barrett's esophagus. 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 Barrett's esophagus and Barrett's esophagus with dysplasia, the strongest associations were observed with symptoms of acid reflux experienced after age 50 years.

Cigarette smoking was associated with 2- to 3-fold increased risks of Barrett's esophagus and Barrett's esophagus 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).

Although 46% and 28% of population control participants were currently overweight or obese respectively, obesity was more common among patients with Barrett's esophagus and Barrett's esophagus with dysplasia; however, this was

Table 2. ORs for BE and dysplastic BE associated with history of acid reflux

Exposure	Controls (%), n = 261	BE			BE with dysplasia		
		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 y							
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 y‡							
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 y§							
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 y‖							
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)

Abbreviation: BE, Barrett's esophagus.
*ORs and 95% CIs adjusted for exact age (y) and sex.
†ORs and 95% CIs adjusted for exact age (y), sex, BMI (continuous), pack-years smoked (continuous), and NSAID use.
‡Analysis restricted to participants ages ≥25 y.
§Analysis restricted to participants ages ≥35 y.
‖Analysis restricted to participants ages ≥55 y.

Table 3. ORs for BE and BE with dysplasia associated with smoking, obesity, and NSAIDs

Exposure	Controls (%), n = 261	BE			BE with dysplasia		
		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	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)
≥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 y)							
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/mo	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/wk	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 y)							
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/mo	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/wk	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)

Abbreviation: BE, Barrett's esophagus.
*ORs and 95% CIs adjusted for exact age (y) and sex.
†ORs and 95% CIs adjusted for exact age (y), sex, frequency of acid reflux symptoms in current age group, BMI (continuous), pack-years smoked (continuous), and NSAID use.

only statistically significant on crude analysis among patients with Barrett's esophagus 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 Barrett's esophagus (72%) and Barrett's esophagus 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 Barrett's esophagus or Barrett's esophagus with dysplasia. In contrast, weekly use of acetaminophen during the past 5 years was more than twice as likely among Barrett's esophagus patients and almost five times as likely among Barrett's esophagus patients with dysplasia compared with controls. Following adjustment for use of NSAIDs, obesity, and smoking, the association with acetaminophen was reduced for Barrett's esophagus, whereas a negative association with use of NSAIDs became apparent, albeit of marginal statistical significance.

We reclassified participants according to their joint history of acid reflux symptoms and smoking to investigate the biological 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 Barrett's esophagus 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 Barrett's esophagus than nonsmokers. Highest risks of Barrett's esophagus 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 Barrett's esophagus 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 Barrett's esophagus than those in the normal weight range. More than 30-fold increased risks of Barrett's esophagus 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.

Table 4. ORs 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† (kg/m^2)									
18.5-24.9	14	8	1.0	11	8	1.1 (0.4-3.7)	1	5	9.3 (1.4-62.2)
25-29.9	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	15	6	0.7 (0.2-2.4)	12	18	2.5 (0.9-7.0)	1	18	34.4 (6.3-188)

Abbreviation: BE, Barrett's esophagus.
*ORs and 95% CIs adjusted for age (continuous), sex, and BMI (continuous).
†ORs and 95% CIs adjusted for age (continuous), sex, and pack-years smoked (continuous).

Discussion

This population-based study has shown that frequent symptoms of reflux are associated with increased risks of Barrett's esophagus, and that these risks are substantially elevated by smoking and obesity. The strong association observed between symptoms of acid reflux and Barrett's esophagus 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 Barrett's esophagus than those with less frequent episodes. Moreover, we found that symptoms of acid reflux experienced at older ages conferred substantially higher risks of Barrett's esophagus than symptoms at younger ages, despite the increasing prevalence of reflux episodes with increasing age among the control group. Although all participants may have selectively recalled symptoms experienced at older ages in preference to early life, the progressively higher risks of Barrett's esophagus 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 Barrett's esophagus 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 Barrett's esophagus with dysplasia than for Barrett's esophagus 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 Barrett's esophagus patients is perhaps not surprising. One interpretation is that the association between obesity and Barrett's esophagus 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 biological interaction (20) suggests that obesity plays a further role in the development of Barrett's esophagus, 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 biological 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 Barrett's esophagus than nonsmokers, 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 Barrett's esophagus than nonsmokers, whereas when reflux was present, smoking substantially increased the risks of developing Barrett's esophagus. These data suggest that smoking is neither necessary nor sufficient to induce Barrett's esophagus but rather potentiates the metaplastic changes initiated by acid reflux.

Although regular use of NSAIDs has been associated with reduced risks of esophageal adenocarcinoma and Barrett's esophagus (31-33), we found little evidence to support this contention on univariate analysis. Rather, we found that although Barrett's esophagus 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 Barrett's esophagus 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 Barrett's esophagus 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 Barrett's esophagus were prospectively identified and ascertained from across an entire region and compared with controls sampled from a population register. We are not aware of any previous studies of Barrett's esophagus 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 Barrett's esophagus 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 Barrett's esophagus (as opposed to biopsy site) was not routinely reported by the large number of community endoscopists in this population-based study. Although there is some evidence that the length of Barrett's esophagus is an important determinant of prognosis, there is general consensus that ''short'' and ''long'' segments of Barrett's esophagus 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 Barrett's esophagus. Although 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 Barrett's esophagus 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 Barrett's esophagus, because they have undergone endoscopy and biopsy, do not represent all people with Barrett's esophagus (diagnosed and undiagnosed). Thus, an association might be observed between acid reflux and Barrett's esophagus simply because people with acid reflux are more likely to undergo endoscopy and thus be more likely to be diagnosed with Barrett's esophagus. Countering this conjecture are the observations that Barrett's esophagus is rare in endoscopy series of healthy volunteers (37) and, in population studies, Barrett's esophagus is diagnosed in <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 Barrett's esophagus etiology differs from that of diagnosed Barrett's esophagus patients (39).

Rates of participation in population studies have been decreasing 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 Barrett's esophagus and Barrett's esophagus 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 Barrett's esophagus.

Appendix A. Study of Digestive Health Investigators

Queensland Institute of Medical Research, Brisbane Australia: David C. Whiteman MBBS, Ph.D.; Adele C. Green MBBS Ph.D.; Nicholas K. Hayward Ph.D.; Peter G. Parsons Ph.D.; Sandra J. Pavey Ph.D.; David M. Purdie Ph.D.; and Penelope M. Webb Ph.D.

University of Queensland, Brisbane, Australia: David Gotley MD, FRACS and B. Mark Smithers MBBS, FRACS.

The University of Adelaide, Adelaide, Australia: Glyn G. Jamieson MS, FRACS.

Flinders University, Adelaide, Australia: Paul Drew Ph.D. and David I. Watson MD, FRACS.

Mayne Pathology, Sydney, Australia: Andrew Clouston Ph.D., FRCPA.

Appendix B. Study of Digestive Health Research Staff

Project Manager: Suzanne O'Brien RN, MPH; Research Scientist: Derek Nancarrow Ph.D.; Research nurses: Andrea McMurtrie RN, Linda Terry RN MPH, Michael Connard B.Sc. (Hons), Deborah Roffe RN, Lorelle Smith EN, and Marian Martin RN.

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