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ORIGINAL CONTRIBUTIONS

Proton Pump Inhibitors Are Associated with Reduced Incidence of Dysplasia in Barrett's Esophagus

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BACKGROUND AND AIMS: Esophageal acid exposure is important in the pathogenesis of Barrett's esophagus (BE), and possibly in the progression of BE to dysplasia and carcinoma. The aim of this study is to compare the development of dysplasia in BE patients treated with or without proton pump inhibitor (PPI) or histamine 2-receptor antagonist (H2RA).

METHODS: We analyzed prospectively collected data by a single endoscopist on patients with BE in a VA (Veterans Affairs) setting over a 20-yr time period (1981–2000). A pathologist used standard criteria to diagnose BE/dysplasia. Pharmacy information after 1994 was retrieved from a computerized database, and from research files for the period before that. The receipt and the duration of H2RA and/or PPI use was compared between those with and without dysplasia. The incidence of dysplasia was examined in a Kaplan–Meier survival analysis stratified by PPI treatment status, and the risk of dysplasia was examined in a Cox multiple regression analysis controlling for demographic features, length of BE, and the year of BE diagnosis.

RESULTS: We analyzed data for 236 unique veteran patients with a mean age at BE diagnosis of 61.5 yr, 86% Caucasian, and 98% male. During 1,170 patient-yr of follow-up, 56 patients developed dysplasia giving an annual incidence rate of 4.7%. Of those, 14 had high-grade dysplasia. The cumulative incidence of dysplasia was significantly lower among patients who received PPI after BE diagnosis than in those who received no therapy or H2RA; log rank test ($p < 0.001$). Furthermore, among those on PPIs, a longer duration of use was associated with less frequent occurrence of dysplasia. In multivariate analysis, the use of PPI after BE diagnosis was independently associated with reduced risk of dysplasia, hazards ratio: 0.25 (95% CI 0.13–0.47), $p < 0.0001$. Longer segments of BE and Caucasian race were other independent risk factors for developing dysplasia. In general, similar findings were observed when only cases with high-grade dysplasia were analyzed.

CONCLUSIONS: These results indicate that PPI therapy is associated with a significant reduction in the risk of developing dysplasia in patients with BE. However, more studies are required to confirm this finding.

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INTRODUCTION

The change from normal esophageal squamous epithelium to columnar epithelium with goblet cells is termed Barrett's esophagus (BE). BE is thought to represent an epithelial response to chronic exposure to acid reflux. BE is the single most significant risk factor for esophageal adenocarcinoma. In a small number of patients with BE, metaplasia will progress to dysplasia and in even fewer from dysplasia to adenocarcinoma. Recent clinical and basic science data suggest that acid reflux may play a key role in the development of esophageal cancer. However, the role that acid suppression may have on malignant progression is unclear.

There is epidemiological evidence that acid exposure increases the likelihood of adenocarcinoma. Lagergren *et al.*, in a population-based case-control study, found a strong association between reflux symptoms and esophageal adenocarcinoma (1). Once esophageal metaplastic change occurs, progression to dysplasia/adenocarcinoma is observed in patients with more significant acid exposure. Avidan *et al.*, in a retrospective study, observed that patients with high-grade dysplasia and/or adenocarcinoma had more frequent episodes of acid reflux and longer acid contact time in the esophagus than patients with BE alone and patients with erosive esophagitis (2).

The use of profound acid suppression such as that produced by proton pump inhibitor (PPI) has the potential of

modifying the clinical course of gastroesophageal reflux disease (GERD). For example, acid suppression has been shown to effectively prevent the recurrence of erosive esophagitis and/or esophageal strictures (3, 4). Our anecdotal observations also indicate that the incidence of esophageal peptic strictures is declining in recent times.

Whether acid suppression could alter the natural history of metaplasia remains unknown. Many studies have been published on the impact of acid suppression on the length of BE demonstrating little overall change (5–8). Even antireflux surgical therapy has had little impact on the length of BE (9). The role of acid suppression in conjunction with endoscopic ablation of BE has also been evaluated with unclear results (10–12). Few studies have examined the effects of acid suppression on progression of BE to cancer. Clinical evidence suggesting that acid suppression could alter the metaplasia-dysplasia-adenocarcinoma progression has been lacking. Both medical and surgical means of suppressing acid have failed to alter the incidence of esophageal dysplasia/adenocarcinoma in a consistent manner (13). The aim of this study is to compare the development of dysplasia in a cohort of patients with BE who received acid suppressive therapy *versus* those patients who did not receive therapy.

METHODS

This study is a retrospective analysis of a prospectively characterized cohort of patients with BE diagnosed between 1981 and 2000 at the Southern Arizona VA Healthcare System. A single experienced endoscopist (RES) has been responsible for performing endoscopy and collecting information on therapy of newly referred patients with diagnosed or suspected BE over the past 20 yr. A cohort of patients with documented BE has been followed in a prospective fashion obtaining medical information through scheduled patient interviews and scheduled endoscopy with systematic biopsies. The demographic, clinical, therapeutic, endoscopic, and histological information are maintained in BE study research files. For this study, manual review of all research files was performed. Written informed consent approved by the Human Subjects Protection Program of the University of Arizona Health Sciences Center was obtained.

Criteria for the diagnosis of BE were endoscopic identification of the squamocolumnar junction proximal to the gastroesophageal junction and targeted biopsies with histology revealing columnar epithelium with goblet cells. These findings had to be present on two consecutive endoscopies at least six months apart. The length of BE was defined as the difference between the lengths of the gastroesophageal junction and squamocolumnar junction from the incisors teeth. BE of all lengths were included in the current analysis.

The following variables were available in the Barrett's research files on all patients included in this analysis: date of birth, date of first diagnosis, gender, race (Caucasian, African-American, Hispanic, other), the presence of intestinal metaplasia of the gastric cardia, the length of BE at the time of the diagnosis, vital status, presence of dysplasia, or cancer. Dysplasia was defined using standard criteria (14). Given the variability of histologic definition of BE and dysplasia over the past 20 yr, a single gastrointestinal pathologist (AB) using standard definitions reviewed all histologic specimens for diagnosis of BE and dysplasia. All indeterminate cases of dysplasia were not used for the purpose of this analysis. In 1990, this pathologist began reviewing all BE histologic slides prospectively at regular sessions. Specimens that had been acquired prior to 1990 were reviewed and investigated using the same standard criteria for dysplasia, in several sessions. The pathologist was blinded to previous interpretation, demographics, and the use of acid suppressive therapy.

In 1994, the pharmacy at the Southern Arizona VA Healthcare System started a computerized database in which information of prescription and dispension of medications has been maintained. Using the VA pharmacy database, prescription and dispensing data for histamine 2 receptor antagonists (H2RA) (cimetidine, ranitidine, famotidine, nizatidine), and PPI (omeprazole, lansoprazole, rabeprazole; the only PPIs available at this VA) among veterans with newly diagnosed BE were abstracted. Prior to 1994 the information on the medications was abstracted from the research files. The duration (days) of nonoverlapping dispensing episodes of use for each category of medication was calculated. The initial endoscopy where BE was diagnosed was used as the reference point. Patients were identified as receiving prescriptions "prior to" or "after" the initial diagnostic endoscopy. The dosage each patient received was based on relief of reflux symptoms. When a PPI came on formulary in 1990, this medication became the antisecretory therapy of choice to control reflux symptoms in BE patients.

Patients with dysplasia or esophageal adenocarcinoma diagnosed at or before the time of BE diagnosis were excluded. Patients with no recorded second endoscopy following the initial BE diagnosis were also excluded since they did not meet the study definition of BE.

Statistical Analyses

The proportions of patients using H2RA, PPI, or both were examined in those with and without dysplasia. Univariate Cox proportional hazards (PH) models were used to compare the duration of use of PPI, H2RA, or both among patients who developed dysplasia and those who did not. Other possible predictors of dysplasia were also compared between these two groups including age, ethnicity, the mean length of BE at the time of diagnosis, and the time period of BE diagnosis.

Several variables were examined as potential predictors of using PPI following BE diagnosis and were examined in a multiple logistic regression analysis; these variables included age, gender, race, year of BE diagnosis, and length of BE segment. Wald χ^2 test was used to calculate the odds ratios and the accompanying 95% confidence intervals.

The cumulative incidence of dysplasia was examined in a Kaplan–Meier survival analysis stratified by the receipt of antisecretory therapy. Differences in the incidence rates of dysplasia were examined using the log rank test. The follow-up time for each patient started at the time of BE diagnosis and

ended at the time of the last upper endoscopy through October 2002. Patients were censored for developing adenocarcinoma or dying.

The effect of using acid suppressive therapy on risk of developing dysplasia was also examined in a multivariate Cox proportional hazards model that adjusted for the length of BE at the time of diagnosis, the year of BE diagnosis, and demographic features. Parameter estimates and standard errors obtained from these models were used to calculate hazard ratios (HR) and their accompanying 95% confidence intervals. Log-log calculations were made to test for the proportional hazards assumption, which was met in all models.

RESULTS

We identified 288 patients of whom 52 were excluded because they presented with BE and either dysplasia (n = 21) or adenocarcinoma (n = 10) at their initial endoscopy, or had no follow-up endoscopy after their initial endoscopy (n = 21). There were 236 unique patients with documented BE first diagnosed between 1981 and 2000 (Table 1) who were included in this analysis. The mean age at the time of diagnosis was 61.5 yr (standard deviation, SD = 10.5). Most patients were Caucasian (211, 89%), 21 were Hispanic (9%), 3 African-American (1%), and 1 Native American (1%). The majority (98%) were men. Intestinal metaplasia (IM) of the cardia was present in 19 (8%). Ablation therapy or esophagectomy was employed in 6 (10.7%) of patients who developed dysplasia during the study period; this proportion was not significantly different from those who received ablation therapy and did not develop dysplasia (14.4%). Six patients of 236 with BE developed esophageal adenocarcioma (EAC) during follow-up. Of those, two patients had prior diagnosis of dysplasia and were both receiving PPI after BE diagnosis, and four more patients developed cancer after dysplasia; two were receiving PPI after BE diagnosis, one H2RA, and one received neither.

After the diagnosis of BE was established, 155 patients (66%) were dispensed a PPI, 149 (63%) an H2RA (68 received only PPI, 62 only H2RA, and 87 both), and 21 (8%) received neither. Several possible predictors of using PPIs after BE diagnosis (age, gender, race, length of BE, and year of BE diagnosis) were examined in a logistic regression analysis. Younger age at the time of BE diagnosis ($p = 0.01$), more recent time of BE diagnosis ($p < 0.0001$), and shorter segment of BE ($p = 0.01$) were significant predictors of using PPI (*vs* using an H2RA only or no antisecretory therapy). The deviance, Pearson, and Hosmer and Lemeshow goodness of fit tests were conducted on the regression model and were nonsignificant ($p \geq 0.05$).

Among 236 patients with BE, a total of 56 patients developed dysplasia during a total follow-up duration of 1,170 patient yr. The incidence rate of dysplasia was 4.7% per yr. Dysplasia was low-grade in 42 and high-grade in 14 patients. The associations between developing dysplasia and demographic features were examined in univariate Cox PH models (Table 1). There was no significant difference in age or the time period at BE diagnosis between those who did or did not develop dysplasia. Being Caucasian and having a longer BE segment at the time of initial BE diagnosis was a significant predictor of the future development of dysplasia.

Dysplasia developed in 9 of 19 patients on no PPI or H2RA, 25 of 64 patients on H2RA, and 22 of 155 on PPI therapy after the BE diagnosis. In the Kaplan–Meier survival analysis (Fig. 1), the cumulative incidence of dysplasia was significantly lower among patients with BE who received PPI therapy after diagnosis (n = 155) than those who either received an H2RA or no antisecretory therapy after BE diagnosis (n = 81); $p < 0.001$ for log rank test. The 5-yr incidence rates of dysplasia were 11% and 37%, and the 10-yr incidence rates were 21% and 58% for patients on PPI, and those not on PPI, respectively. The median time to dysplasia was 4.9 yr for patients on PPIs, and 2.3 for patients not on PPI.

Table 1. Characteristics of Patients with and without Dysplasia

Variable	Any Dysplasia (n = 56)	High-Grade Dysplasia (n = 14)	No Dysplasia (n = 180)	*p*-Value (Any Dysplasia *vs* no Dysplasia)	*p*-value (HGD *vs* no Dysplasia)
Age at time of BE diagnosis mean (SD)	62.2 (9.8)	60.2 (9.6)	61.5 (10.8)	0.15	0.98
Caucasian	55 (98%)	14 (100%)	156 (87%)	0.01	0.99
Men	56 (100%)	14 (100%)	176 (98%)	0.26	0.99
BE diagnosis 1990 and after	18 (32%)	4 (29%)	111 (62%)	0.11	0.26
Length of BE (cm), median (I.Q.R)	6.0 (4.0, 9.0)	6.0 (4.0, 9.0)	3.0 (2.0, 5.0)	0.0001	0.0073
Duration of PPI use after BE diagnosis (yr) median (I.Q.R)	0* (0, 0.79)	0* (0, 0.78)	1.9 (0, 4.6)	<0.0001	0.0055
Duration of H2RA use after BE diagnosis (yr) median (I.Q.R)	0.8 (0, 3.0)	0.8 (0, 2.5)	0.9 (0, 5.4)	<0.0001	0.0125
Duration of follow-up to last EGD (yr) median (I.Q.R)	7.2 (4.0, 11.0)	5.3 (1.8, 13.4)	4.3 (2.0, 7.7)	<0.0001	0.0004

Veteran patients with newly diagnosed BE between 1981 and 2000 (total 234). None of these patients had dysplasia or esophageal adenocarcinoma at the onset of follow-up. All patients had at least one follow-up endoscopy with intestinal metaplasia. Comparison of patients who developed dysplasia to those who did not is shown. *P*-values were calculated from univariate Cox PH models. HGD: High-grade dysplasia.

*Since >60% did not receive PPI, median is 0, the mean (SD) is 1.0 (1.9) yr for any dysplasia, and 0.8 (1.5) for high-grade dysplasia.

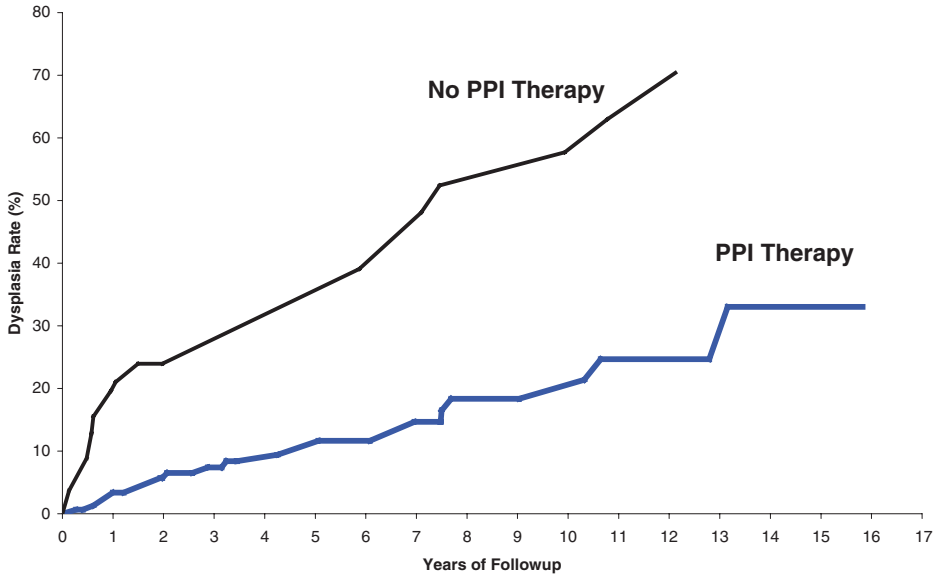

Figure 1. Kaplan–Meier curves illustrating the incidence of dysplasia with and without PPI therapy. The incidence rates of dysplasia among patients with BE stratified by PPI use after BE diagnosis. Results of Kaplan Meier survival analysis stratified by PPI therapy status (either PPI or no; the latter includes H2RA or no antisecretory therapy); p for log rank test <0.0001.

The effect of PPI therapy on the development of dysplasia was examined in a Cox multiple regression model that adjusted for length of BE, year of BE diagnosis, age at time of diagnosis, gender, and race (Table 2). The use of PPI after the diagnosis of BE was associated with 75% reduction in the risk of dysplasia. Of the other covariates, longer segments of BE and Caucasian race were independent risk factors for developing dysplasia. For example, there was an 8% increased risk of dysplasia with each centimeter increase in BE length. There were no significant effects of age or time of initial BE diagnosis on the risk of dysplasia. The use of H2RA following BE diagnosis (irrespective of PPI) was not associated with significant change in the risk of dysplasia of any grade (HR 1.29; $p = 0.47$), or high-grade dysplasia.

In a separate model that adjusted for age, gender, race, length of BE, and time of BE diagnosis, we examined the effect of receiving only PPI after BE diagnosis (n = 68), only H2RA (n = 62), or both (n = 87) on the incidence of dysplasia. The use of PPI only was associated with reduced risk of dysplasia (adjusted odds ratio: 0.13, 0.03–0.50, $p = 0.002$), as well as the use of both PPI and H2RA (0.33, 0.11–0.99; $p = 0.04$), but not the use of H2RA alone (0.62, 0.20–1.97; $p = 0.40$).

Lastly, since referral practice might have changed after the introduction of PPI in VA in 1990, we examined the effect of PPI on dysplasia among 129 patients diagnosed with BE after 1989. In that analysis, the protective effect of PPI use persisted (HR = 0.20, $p = 0.01$).

Similar findings were observed if only high-grade dysplasia patients were considered. The median duration of PPI therapy dispensed after the initial endoscopy was also significantly longer among patients who did not develop high-grade dysplasia ($p = 0.0015$); data not shown. The incidence of high-grade dysplasia was also examined in Cox PH models. Due to the small number of cases with high-grade dysplasia (n = 14), we could not examine more than two variables at one time. In univariate models, the use of PPI after BE diagnosis (HR = 0.18, $p = 0.002$), or PPI use after BE diagnosis was also associated with reduced risk of HGD (HR = 0.12, $p = 0.002$). This effect was not significantly changed after adjusting for age, length of BE, or year of BE diagnosis.

Table 2 Cox Multiple Regression Analysis of Risk Factors for Developing Dysplasia in Patients with BE

Variable	Hazard Ratio	95% Confidence Interval	p-Value
Use of PPI after BE diagnosis	0.25	0.13–0.47	<0.0001
Period of BE diagnosis 1990 and after*	1.63	0.79–3.36	0.19
Age at BE diagnosis (per 10 yr)	1.06	0.74–1.52	0.66
Non-Caucasian race (*vs* Caucasian)	0.12	0.02–0.88	0.04
Length of BE (cm) at diagnosis	1.08	1.00–1.17	0.04

*Categorical variable (1/0), with 1 = BE diagnosed 1990 and after.

DISCUSSION

This study indicates that patients with BE who did not develop dysplasia were more likely to receive PPI therapy and more likely to receive such therapy for a longer period of time than patients who developed dysplasia. PPI therapy was associated with a decrease in the incidence of dysplasia when compared to patients treated with H2RA or no therapy. Further, when controlling for several factors in a multivariate

analysis, the association between PPI use and reduced incidence of dysplasia was independent of demographic features, year of BE diagnosis, and the initial length of BE. These findings suggest that acid suppression can alter the progression of metaplasia to dysplasia.

The results of this study are strengthened by several factors. First, this large sample of BE consisted of all newly diagnosed consecutive patients seen by the same investigator (RES) over two decades, thus minimizing the variability of diagnosis. Second, strict and consistent criteria were used throughout the study period to make the formal diagnosis of BE and dysplasia. A single experienced gastrointestinal pathologist (AB) interpreted all histopathology slides thus eliminating the possibility of interobserver bias. This pathologist has been involved in BE-related research for more than 10 yr (10, 15–19). Third, the results are robust. Several analyses were conducted aiming at adjusting for the possible confounding variables. For example, the time of BE diagnosis could be associated with different medication practices. The length of BE is also associated with future risk of dysplasia with greater risk in longer segments. Demographic features such as age, race, and gender could also be associated with difference in health-care seeking behavior as well as adherence to therapy. The significant inverse association between PPI therapy and dysplasia persisted in multiple regression analyses that adjusted for time of diagnosis, length of BE, as well as important demographic features.

There are potential limitations to the study related to its sources of pharmacy data, retrospective design, and the use of dysplasia as an end point. First, the ascertainment of therapy might have been incomplete for patients who prefer to use non-VA pharmacies as their source of medications. Given the significantly reduced charges for medications in the VA Healthcare System, especially PPI (up to 10-fold difference as compared to non-VA), it is unlikely that many patients will resort to this option. Adherence to medications could vary and is unknown in this study. We used two separate sources of pharmacy data: VA pharmacy at the Southern Arizona VA Healthcare System which began keeping electronic records in 1994; but prior to that the Barrett's research charts were reviewed for prospectively collected information on patients' antireflux medications. However, these limitations are likely to result in nondifferential errors rather than a systematic bias affecting one treatment group. Second, given the observational nonrandomized nature of the study, one has to be cautious in making a causal inference between PPI use and reduction of dysplasia. For example, the results could be confounded by what determines the use of a PPI *versus* an H2RA. More recent time of diagnosis was found to be an independent determinant of the use of PPI in our study, and this conforms with our impression from clinical practice. However, the findings persisted after controlling for the year of BE diagnosis. Lastly, although the presence and grade of dysplasia were defined by a single experienced pathologist, we have not examined intraobserver variation. Dysplasia, especially low-grade, has a variable natural history, and therefore the implication of reducing the incidence of dysplasia is not clear. The number of patients who developed dysplasia (n = 52), or those who were not on PPI or H2RA (8%) were relatively small; however the issue of study power is less relevant in the presence of statistically significant differences that were found. We were unable to examine the effect of antisecretory therapy on the incidence of the more important endpoint, adenocarcinoma, due to the small number of cases. Only two cases of esophageal adenocarcinoma were diagnosed during follow-up without passing through our main outcome, dysplasia; both patients had received PPI after BE diagnosis and before cancer diagnosis.

There is a molecular basis for the role of acid reflux exposure in malignant progression of BE. Cyclooxygenase-2 (COX-2) is believed to play important roles in cell proliferation and inhibition of apoptosis (20). Progressive overexpression of COX-2 is seen in metaplasia, dysplasia, and adenocarcinoma. In *ex vivo* studies pulses of acid (and bile) cause an increase in COX-2 expression (21). Proliferating cell nuclear antigen (PCNA) is an indicator used to identify a higher rate of cell proliferation in metaplastic epithelium with high-grade dysplasia as compared to nondysplastic epithelium (22). The increased cellular proliferation rate is believed to increase the probability of malignant clonal expansion. With PCNA as an indicator, acid suppression has been shown to decrease cellular proliferation and potentially, malignant progression (23). In a rat model, esophageal exposure to acid reflux produces chromosomal damage in epithelial cells primarily through lipid peroxidation (24). This genetic instability leads to perturbation of the cell cycle and abnormal cell proliferation (*i.e.,* cancer).

Biochemically, chronic inflammation predisposes epithelial cells to malignant transformation via two related mechanisms (25). First, inflammation induces cell death, which in turn leads to rapid cell turnover, thus increasing DNA susceptibility to mutagens. Second, inflammatory cells contain reactive oxygen species that act as mutagens. This combination can promote tumor growth. In addition, inflammation increases the expression of cell growth promoters such as transformation growth factor-alpha (TGF-α). TGF-α is found in normal gastrointestinal epithelial cells but is overexpressed in Barrett's metaplasia, as well as inflamed colonic epithelium. TGF-α is believed to be play an essential role in cell proliferation and progression to adenocarcinoma (26). Therapy to reduce inflammation (acid suppression) could theoretically alter the progression of inflammation-induced malignant transformation.

Previous studies have failed to show changes in progression of dysplasia despite acid suppression therapy. Buttar *et al.* performed a retrospective cohort study on patients with high-grade dysplasia and found that patients without acid suppression therapy (medical or surgical) had 2.5 times the risk of developing adenocarcinoma compared to those on therapy (27). This association could not be confirmed when examined in a multivariate analysis. Even surgical antireflux therapy (28–30) has failed to show an alteration in the

development of dysplasia or adenocarcinoma. Parrilla *et al.* randomized 101 BE patients to either medical therapy (H2RA or PPI) or antireflux surgery and found no significance difference in progression to dysplasia (30). Recently, a meta-analysis of surgical and medical antireflux therapies in patients with BE was performed in which the authors found no difference in progression to adenocarcinoma in either group (13). Effective antireflux surgery would be expected to have an impact on neoplastic progression in patients with BE if the timing of the surgery were appropriate.

The timing of acid suppressive therapy may be important. Carlson *et al.* found that once p53 overexpression occurred in metaplastic cells, progression to dysplasia was more likely to occur despite acid suppressive therapy (31). This suggests that once genetic instability has occurred progression is likely despite suppressing reflux. This may account for the inconsistent benefit of acid suppression in previous studies.

Other studies have found an incidence of dysplasia ranging from 3.8% to10.3% per yr regardless of therapy (32, 33). These studies had a mean follow-up of 2 to 5 yr. Unfortunately, the use of acid suppressive medication was poorly reported. The duration and type of medications used in patients with dysplasia was not clearly defined.

The histologic diagnosis of dysplasia is challenging because of differing criteria and poor interobserver reproducibility (34). Criteria from Riddell and colleagues (14) were used to diagnosis and grade dysplasia throughout the study period. A single gastrointestinal pathologist reviewed all histologic slides for patients included in this study. This insured that dysplasia was diagnosed on a consistent basis in all patients regardless of time of diagnosis or type of medical therapy.

The results of this observational study suggest that PPI therapy can alter the progression of BE to dysplasia. Although prospective randomized trials are required for a more definite proof of this observation, it is unlikely that future prospective studies will include a treatment arm that would withhold PPI therapy from symptomatic patients. Rather, studies comparing timing of therapy in the molecular progression to dysplasia, and dose adjustment in response to esophageal acid exposure (*i.e.,* esophageal pH studies) are the likely future directions of PPI therapy in BE.

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