The Prevalence of Barrett's Esophagus associated Dysplasia in Puerto Rico

Priscilla Magno, MD, MSc*†‡; Lorena González, MS§; Marcia Cruz-Correa, MD, PhD*†; Erick Suárez, PhD**

Objective: Barrett's esophagus (BE) is the strongest risk factor of esophageal adenocarcinoma (EAC). A previous study found a lower incidence of EAC in Puerto Rico (PR) as compared to other racial/ethnic groups in the United States (US). Notwithstanding, BE epidemiology in PR is unknown. Study aims: i) to determine BE prevalence among individuals with gastroenterological pathology reports from three major anatomic pathology laboratories in PR and ii) to describe the association between dysplastic BE with age and gender.

Methods: Clinic-based study examined data collected from three anatomic pathology laboratories encompassing the majority of gastroenterology practices in PR. Individuals with histology confirmed BE (January 2007-December 2011) were analyzed (n=1,232). We estimated BE prevalence and adjusted odds ratios (AOR) to assess magnitude of association between dysplastic BE with age and gender using logistic regression models.

Results: Overall BE prevalence was 4.4% (95% CI = 4.1–4.6). Most BE patients were males (male-to-female ratio = 2.3:1) with mean age of 64 ± 13 years. Ninety one percent of BE biopsies showed no dysplasia whereas 6.2% had EAC. BE patients age > 74 years had an increased risk of EAC (AOR: 2.38, 95% CI = 1.14–4.94) compared to those < 55 years old. Males had increased EAC risk (AOR: 2.23, 95% CI = 1.23–4.06) compared to females.

Conclusion: BE prevalence in PR is similar to that of non-Hispanic whites and Hispanics in US. The lower occurrence of dysplastic BE in PR could explain EAC incidence disparities between PR and other groups in the US. [*P R Health Sci J 2014;33:184-189*]

Key words: Barrett's esophagus, Esophageal adenocarcinoma, Hispanics, Puerto Rico

Barrett's esophagus (BE) is defined as a condition of the lower esophagus in which the normal squamous epithelium is replaced by columnar epithelium as a result of chronic gastroesophageal reflux (GERD) (1). The diagnosis of BE requires both endoscopic identification of columnar mucosa extending proximally into the tubular esophagus with histological confirmation of metaplastic columnar epithelium with goblet cells in biopsy specimens (2). Men are twice as likely as women to develop BE, with highest incidence observed in Caucasian males over the age of 55 years (3,4). Patients with this condition are at an increased risk of developing esophageal adenocarcinoma (EAC), the most rapidly increasing cancer of the gastrointestinal tract (5-8).

The true prevalence of BE among various populations has been not well established. Prevalence studies vary considerably due to discrepancies in patient selection (symptomatic or asymptomatic GERD patients), endoscopic and histopathology criteria. Reported prevalence in United States (US) cohorts ranges from of 1.46% (9) - 5.6% (10) in asymptomatic patients and 4.39% to 10–15% in patients undergoing upper endoscopy for chronic GERD symptoms (9-11). Fan et al (9) performed a large retrospective review of 4,457 endoscopy reports and found an overall prevalence of 1.7% (4.39% in 410 symptomatic GERD patients and 1.46% in 4047 asymptomatic patients). In addition these investigators reported a prevalence of BE among different racial/ethnic groups in the continental US with symptoms of GERD: 5% in non-Hispanic whites (NHW), 4.4% in US Hispanics, and 2.6% in non-Hispanic blacks (NHB). Racial and ethnic disparities among BE patients in the continental US were also studied by Abrams et al (12) in a single center

*Department of Medicine, Medical Sciences Campus, University of Puerto Rico, San Juan, PR; †University of Puerto Rico Comprehensive Cancer Center, San Juan, PR; ‡Veterans Administration Caribbean Healthcare System, San Juan, PR; §Research Design, Biostatistics and Clinical Research Ethics, Puerto Rico Clinical and Translational Research Consortium, Medical Sciences Campus, University of Puerto Rico, San Juan, PR; **Department of Biostatistics and Epidemiology, Graduate School of Public Health, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico.

M.C.C. has served as a speaker for Abbott Nutrition, received traveling/meeting funds from the American Association for Cancer Research Meeting; and currently receives royalties from Johns Hopkins University. The remaining authors have no conflict of interest to disclose.

Address correspondence to: Priscilla Magno, MD, University of Puerto Rico Comprehensive Cancer Center, PMB 711, 89 De Diego Ave, Suite 105, San Juan, PR 00927-6346. Email: priscilla.magno@upr.edu

retrospective analysis of 2,100 patients who underwent upper endoscopy during a 1-year period. They found a significantly higher prevalence of BE in NHW than US Hispanics (6.1% vs. 1.7%, P = .0002) and NHB (6.1% vs. 1.6%, P = .004).

While the prevalence of BE in Puerto Rico (PR) remains largely unknown, the incidence of EAC has increased in PR. Gonzalez and colleagues (13) reported, based on data of the Puerto Rico Central Cancer Registry, that age-standardized incidence rate of EAC (per 100,000 individuals) increased about 31% in the time periods from 1992-1996 to 2001-2005 among men (P < 0.05) whereas among women no changes were observed (P > 0.05). In addition, these investigators found significant disparities of EAC incidence in PR as compared to other racial/ethnic groups in the US. During the period 2001-2005, lower standardized rates ratios (SRR) of EAC were observed among individuals in PR as compared to US Hispanics (SRR men = 0.50, 95% confidence interval (95%CI): 0.36–0.69; SRR women = 0.73, 95%CI: 0.40–1.36) and non-Hispanic white (SRR men = 0.30, 95%CI: 0.23–0.38; SRR women = 0.43, 95%CI: 0.26–0.63) in the US; however, men and women in PR had about 2.32 and 1.14 times higher incidence rates of EAC, respectively, than non-Hispanic blacks in the US (only significant, P < 0.05, among men). It is uncertain if this lower risk of EAC could be possibly explained by a different prevalence of BE in PR as compared to other racial/ethnic groups in the continental US. The aims of our study were: i) to determine the prevalence of BE with different grades of dysplasia among individuals with gastroenterological pathology reports from the three largest anatomic pathology laboratories in PR and (ii) to describe the magnitude of the association between dysplastic BE and demographic risk factors (age and gender) in PR.

Patients and Methods

Study design and Study population

This study was approved by University of Puerto Rico Medical Sciences Campus Institutional Review Board. We studied archived pathology reports from patients 21 years or older with histopathological diagnosis of BE obtained from the three largest anatomic pathology laboratories in PR (Puerto Rico Pathology, Hato Rey Pathology Laboratory and Southern Pathology Services) between January 2007 and December 2011 (n = 1,232). These laboratories serve the majority of gastroenterologists from private practice and hospitals throughout the entire territory of PR. All three participating laboratories had experienced pathologists evaluating all BE samples for the entire study period. Two of the laboratories have their pathology reports archived in password-protected encrypted electronic databases since early 2000 and one since year 2007. The databases comprised the following de-identified information: gender, age at first BE biopsy reported, date of birth, town of residence, and the presence of dysplasia {i.e., non-dysplastic, low-grade dysplasia (LGD), high-grade dysplasia (HGD), and EAC}. Databases were merged into one password-protected encrypted database for statistical analysis.

Statistical analysis

Descriptive statistics were used for continuous and categorical data for the 2007-2011 period. Data from initial biopsies were used to describe the Barrett's esophagus population of this study. Laboratories processed esophageal biopsies (all esophageal tissues including BE specimens) from approximately 5,625 individuals per year of study period. The prevalence estimation of BE was calculated with 95% CI.

We graphically described the trend of the number of biopsy reports of individuals with BE (including repeated biopsies). Percent changes of the number of biopsy reports per year, during the study period, were included on the graph. Also male to female ratio of BE was calculated per year.

To estimate the magnitude of the association of dysplastic BE and EAC with age and gender, we estimated crude and adjusted odds ratio (AOR) with 95% CIs using a logistic regression model. An interaction assessment was performed with these predictors to validate the AOR's using the likelihood ratio test (14). The logistic regression model was run with tissue pathology results; for individuals with multiple biopsies the more advanced disease was chosen. Statistical analysis was performed using Stata/SE statistical software version 11.0 (Stata Corp., L.P., College Station, TX).

Results

Table 1 shows the socio-demographical description of individuals diagnosed with BE. The majority of these individuals were males (69.5%), aged 65-74 (32.9%), and (~39%) lived at the Metro health region of Puerto Rico. During the 2007-2011 period, the male-to-female ratio of BE patients ranged from 1:8:1 to 2.8:1.

The total number of individuals with esophageal tissue pathology report from 2007 to 2011 from the three laboratories was 28,125. Among these individuals, the prevalence of BE for the 2007-2011 period was 4.4% (95% CI = 4.1 – 4.6). During this period, the highest number of BE diagnosis was observed in 2009 (303 cases) (Table 2).

Most individuals with BE in this study only had one biopsy report (83.8%), 12.3% (151 out of 1,232) had two reports and 3.9% (48 out of 1,232) had three or more reports during the complete study period. Consequently, we ended up with a total of 1,483 BE biopsy reports. The trend analysis showed that the annual percentage of change in the number of biopsy reports of BE patients increased about 3.5% and 17% from 2007 to 2008 and 2010 to 2011, respectively, while a marked reduction was observed from 2009 to 2010 (Figure 1).

Table 1. Demographic characteristics of individuals with Barrett's esophagus biopsies obtained from 2007 to 2011 (n=1,232)

	n (%)
Gender *(Missing values = 1)*	
Male	856 (69.5)
Female	375 (30.5)
Age *(Missing values = 2)*	
(Mean ± SD)	64.9 ± 12.8
21-54	244 (19.8)
55-64	300 (24.4)
65-74	405 (32.9)
≥75	281 (22.9)
Health region *(Missing values = 112)*	
Metro	436 (38.9)
Ponce	269 (24.0)
Caguas	154 (13.8)
Bayamon	147 (13.1)
Other regions*	114 (10.2)

*Includes the regions of Fajardo, Arecibo, and Mayagüez

Table 3 shows the prevalence of tissue dysplasia and EAC at initial biopsies of individuals with BE during 2007-2011 period. From the 16.2% of BE patient that had multiple biopsies reported, 186 patients had non-dysplastic BE, 8 had LGD, and 5 had HGD diagnosed in the first biopsy report. Two cases, one patient with non-dysplastic BE and one patient with HGD, were diagnosed with EAC in follow-up biopsies. BE patients older than 74 years old had more than two-fold (AOR: 2.38, 95% CI: 1.14 – 4.94) the odds of having EAC than those younger than 55 years old, once we adjusted by gender ($P < 0.05$). About the same odds were shown when we compared men to women (Table 4). The odds of having a HGD or LGD were higher among men than women and among the older age groups (65-74 and ≥ 75) than those younger than 55 years, but none were significant ($P > 0.05$; Table 4).

Table 2. Prevalence of Barret's esophagus among individuals with esophageal biopsies from 2007 to 2011*

Year	Prevalence (%)	95% Confidence Interval
2007	4.3	3.7 – 4.8
2008	4.7	4.2 – 5.3
2009	5.4	4.8 – 6.0
2010	3.4	2.9 – 3.8
2011	4.1	3.6 – 4.7
2007-2011	4.4	4.1 – 4.6

*Based on annual reports of all esophageal biopsies reported by three major pathology laboratories in Puerto Rico.

Discussion

Our retrospective review of histopathology reports found an overall estimated BE prevalence of 4.4%. Despite the great variability of BE prevalence reported in the literature, our estimated prevalence of BE (3.4% to 5.4%) was found to be similar to that reported for both symptomatic GERD patients (1.46%-4.39%) (9,10) and asymptomatic GERD patients (5.6%) in the US (10). Although clinical information regarding patient symptoms was not available for our analysis, esophageal biopsy samples were taken from individuals who underwent endoscopic interventions for the evaluation of gastrointestinal symptoms. The predominant demographic profile of our cohort, males aged 65-74, confirms prior observations of an older male predominance in BE (5).

The significant disparities of EAC incidence observed in PR with lower incidence rates of EAC as compared to other racial/ethnic groups in the US is not supported by a different prevalence of BE in our population. The overall estimated BE in PR is similar to that reported in a large cohort of symptomatic GERD patients for NHW (5% - 6.1%), and US Hispanics (4.4%) and higher than NHB (1.6% - 2.56%) (9). These findings could explain the higher risk of developing EAC in PR over NHB but not the lower risk of EAC in PR as compared to NHW and US Hispanics as described by Gonzalez and colleagues (13). As an unexpected finding in our study, only 8.9% were diagnosed with EAC or BE with dysplasia. This finding differs greatly from one of the largest multicenter outcomes study in the US with 2,816 patients, which reported a higher prevalence of

Table 3. Histological assessment of dysplasia in Barrett's esophagus reports (n=1,232)

	n (%)
Initial biopsy *(Missing values = 8)*	
No dysplasia	1,114 (91.2)
LGD	18 (1.5)
HGD	14 (1.2)
EAC	76 (6.2)

LGD = Low Grade Dysplasia, HGD = High Grade Dysplasia , EAC = Esophageal Adenocarcinoma

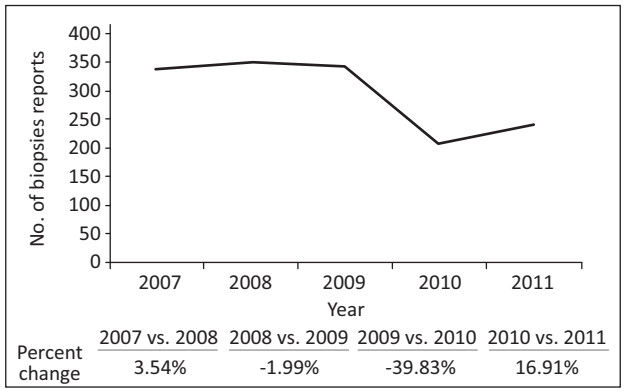

Figure 1. Overall biopsy reports from individuals with Barrett's esophagus from 2007 to 2011 (n=1,483, repeated biopsies included).

Table 4. Magnitude of the association of Barrett's esophagus dysplasia and EAC with risk factors*

Characteristics	EAC†		HGD/LGD†	
	OR (95% CI)	AOR (95%CI)	OR (95% CI)	AOR (95% CI)
Age (in years)				
≤54	1.00	1.00	1.00	1.00
55-64	1.36 (0.63 – 2.94)	1.39 (0.64 – 3.02)	0.95 (0.32 – 2.87)	0.96 (0.32 – 2.90)
65-74	1.21 (0.58 – 2.54)	1.24 (0.59 – 2.61)	1.62 (0.63 – 4.20)	1.64 (0.63 – 4.26)
≥75	2.14 (1.03 – 4.43)‡	2.38 (1.14 – 4.94)‡	1.45 (0.52 – 4.05)	1.51 (0.54 – 4.23)
Gender				
Female	1.00	1.00	1.00	1.00
Male	2.09 (1.15 – 3.77)‡	2.23 (1.23 – 4.06)‡	1.28 (0.62 – 2.66)	1.32 (0.63 – 2.74)

EAC = Esophageal Adenocarcinoma, HGD/LGD = High Grade Dysplasia/Low Grade Dysplasia, OR = Odds Ratio, AOR = Adjusted Odds ratio. *Among individuals with multiple biopsies, results from more advanced disease were used for these analyses; †No interaction was found between age and gender (P > 0.05); ‡Results were significant (P < 0.05)

LGD (14%), and HGD/EAC (11%) at index endoscopy (15). Similarly Gaddam et al (16) found a prevalence of dysplastic BE of approximately 19% among 3,515 BE patients most of them NHW. By comparison, while the estimated prevalence of BE in our population is similar to those reported for NHW and US Hispanics, our lower prevalence of dysplastic BE mucosa could possibly explain the lower risk of developing EAC in PR. Environmental and/or pharmacological factors associated with a lower prevalence of dysplasia/EAC such as intake of anti-inflammatory drugs (17, 18), and hydroxyl-methyl-CoA reductase inhibitors (statins) (19, 20) must be also examined in our BE patients.

The risk factors for esophageal malignancy in BE patients has been studied. EAC is more common in BE patients 75 years and older (Hazard ratio: 12.95% CI: 8.0-18), and male patients with BE have twice the risk of females (OR 2.29; 95% CI 1.15- 4.59) to develop HGD/EAC (21,22). In concordance with prior observations, our study found that BE patients in PR 75 years and older have more than double the risk of EAC than those younger than 55 years old (AOR: 2.38, 95% CI = 1.14 – 4.94), and men had more than two-fold the odds (AOR = 2.23, 95% CI: 1.23 – 4.06) of having EAC than women. Moreover, there was a trend of increased risk of having HGD and LGD in males 65 years and older than those younger than 55 diagnosed with BE, as evidenced by a higher odds ratio; however, this risk excess was not statistically significant (P > 0.05).

In 2008, the American College of Gastroenterology (2) updated their guidelines for the diagnosis, surveillance and therapy of BE. The new guidelines recommend a systematic endoscopic biopsy protocol with four quadrant biopsies every 1 cm for surveillance of dysplasia in HGD patients, and confirmation of all dysplasias by expert/experienced pathologists. Theoretically, these changes in guidelines could have affected the prevalence of BE in PR during the 2009-2010 period when the total number of BE biopsies declined about 40%. However, changes in practice guidelines do not usually result in abrupt changes as the one observed during the 2009-2010 period, and the rapid recovery in the number of biopsies in the following years, make this an unlikely explanation. Perhaps, unmeasured socio-economic changes which occurred in PR during this period may have resulted in an increase of uninsured patients, with a concomitant decreased in referrals to healthcare specialists precluding access to endoscopic interventions.

Surveillance of dysplasia in BE is the most important strategy in the prevention and early detection of EAC. Current clinical guidelines by major professional organizations in the US (Table 5) recommend endoscopic surveillance of dysplasia at least every 3 years, with shorter intervals if BE-associated dysplasia is present (2,23,24). In our cohort of 1,232 BE patients, only 16% of patients (186 non-dysplastic BE, 8 LGD and 5 HGD) had multiple biopsies reported during the study period. Five patients with initial non-dysplastic BE progressed to LGD, one to HGD and one EAC. Only five out of 14 patients with initial HGD had multiple biopsies reported, and one of them progressed to

Table 5. Endoscopic surveillance guidelines for Barrett's esophagus by Major Professional Societies (2, 23, 24)

Grade of dysplasia	ACG	AGA	ASGE
NDBE	2 EGD within 1st year, then every 3 years if still NDBE	2 EGD within 1st year, then every 3-5 years if still NDBE	2 EGD within 1st year, then every 3 years if still NDBE
LGD^	Repeat EGD within 6 months; if no higher-grade dysplasia, then every 1 year	Repeat EGD within 6 months; if no higher-grade dysplasia, then every 6-12 months	Repeat EGD in 6 months; if no higher-grade dysplasia, then every 1 year
HGD^	Repeat EGD within 3 months to rule out EAC, then every 3 months	Repeat EGD within 3 months to rule out EAC, then every 3 months	Repeat EGD within 3 months to rule out EAC, then every 3 months

ACG = American College of Gastroenterology, AGA = American Gastroenterological Association, ASGE = American Society of Gastrointestinal Endoscopy, NDBE = Nondysplastic BE, LGD = Low Grade Dysplasia, HGD = High Grade Dysplasia, ^Biopsies with dysplasia should be confirmed by an expert or experienced GI pathologist.

EAC. These findings emphasize the importance of compliance with surveillance biopsy protocols since the degree of dysplasia found in endoscopic esophageal biopsy specimens is the sole predictor of cancer risk.

The current study has several limitations. This clinic-based study of histopathology reports relies completely on biopsy specimens examined only in three anatomic pathology laboratories thus the estimated prevalence is not entirely representative of the PR population. In addition, the pathological findings were not correlated with clinical information regarding patients' symptoms or endoscopic findings suggestive of BE such as description of "salmon-colored" or "BE-like mucosa" in distal esophagus or proximal displacement of the squamous-columnar junction. Without this endoscopic correlation, it is uncertain if esophageal biopsies were correctly taken from "BE-like mucosa" located above the squamous-columnar junction and not from gastric cardia where intestinal metaplasia can also developed (25). As a result, BE prevalence in this study could have been overestimated due to misclassification of cardiac intestinal metaplasia as BE. Also, methodological differences in biopsy protocols of BE mucosa possibly existed among gastroenterologists; endoscopic reports were not available for analysis. The sensitivity of detecting intestinal metaplasia in columnar-lined epithelium as required for tissue diagnosis of BE, is around 35%-73% (26,27), and some investigators have suggested the need of at least eight random biopsy samples for detecting intestinal metaplasia in columnar-lined epithelium (26). For the detection of dysplasia and/or EAC, major professional organizations recommend systematic four quadrant biopsies every 2 cm of BE mucosa (2,23,24). Hence, it is uncertain if an adequate number of systematic endoscopic biopsies were performed during endoscopy producing a possible underestimated prevalence of BE and BE-associated dysplasia. Another limitation of the study is the lack of a standardized pathology review given the known high inter-observer variability that exist among pathologists examining BE dysplasia (28). For example, the distinction between high-grade dysplasia and the earliest intramucosal carcinoma remains difficult, and the inter-observer variation is poor (29,30). Last, the study did not include data from patients who underwent endoscopy without biopsy due to the difficulty of collecting information from gastroenterologists across PR, which could possibly had an impact on our estimated of BE prevalence. Despite these limitations, this study provides knowledge for the first time about the prevalence of BE associated dysplasia in PR.

In conclusion, the prevalence of BE in PR seems to be similar to NHW and Hispanics, but higher than NHB with GERD symptoms in the US. The lower occurrence of BE-associated dysplasia detected in this study compared to other racial/ethnic groups in the US could explain the lower risk of EAC in our population. Efforts should be made to increase the compliance with established guidelines, mainly by increasing public health awareness about BE as the strongest risk factor EAC, both general population and in the medical community. Further prospective studies in BE are needed to determine the risk of developing EAC in PR.

Resumen

Objetivo: El esófago de Barrett (EB) es el factor de riesgo más importante en el desarrollo de adenocarcinoma de esófago (ACE). Un estudio previo encontró diferencias en la incidencia de ACE entre los puertorriqueños y otros grupos étnicos/raciales en los Estados Unidos (EE.UU.). No obstante, la epidemiología de EB en Puerto Rico (PR) es desconocida. El estudio tiene como objetivo: i) determinar la prevalencia de EB en individuos con informes de patología gastroenterológica realizados en tres laboratorios de patología anatómica en PR y (ii) describir la asociación entre la displasia de EB con la edad y el género. Métodos: En este estudio clínico se examinó datos recopilados de tres laboratorios de patología anatómica que abarcan la mayoría de las prácticas de gastroenterología en PR. Individuos con reporte histológico de EB desde enero 2007 hasta diciembre 2011 fueron analizados (n = 1232). Se estimó la prevalencia de EB con diferentes grados de displasia y la proporción de probabilidades ajustadas (AOR) para evaluar la magnitud de la asociación entre la displasia de EB con la edad y el género mediante modelos de regresión logística. Resultados: En general, la prevalencia de EB fue 4.4% (IC 95% = 4.1 a 4.6). La mayoría de los pacientes eran varones (relación hombre-mujer = 2.3:1) con una media de edad de 64 $\pm$ 13 años. Noventa y uno por ciento de las biopsias de EB no mostraron displasia mientras que 6.2% tenían ACE. Pacientes con EB mayores de 74 años tienen un mayor riesgo de ACE (AOR: 2.38, IC 95% = 1.14-4.94) que los pacientes menores de 55 años de edad. Los hombres tenían mayor riesgo de desarrollar ACE (AOR: 2.23, IC 95% =1.123- 4.6) que las mujeres. Conclusiones: La prevalencia de EB en PR es similar a las reportadas para los blancos no-hispanos y los hispanos en EE.UU. Una menor incidencia de EB con displasia en los puertorriqueños podría explicar las diferencias en la incidencia de ACE entre los puertorriqueños y otros grupos étnicos/raciales en los EE.UU.

Acknowledgments

This work was supported by grants from the National Institutes of Health (NCRR Award Number U54-RR 026139-01A1 & NIMHD Award Number 8U54-MD 007587-03) to the Puerto Rico Clinical and Translational Research Consortium (PRCTRC), and the Hispanic Clinical and Translational Research Education and Career Development Program (HCTRECD Award Number R25MD007607) to the Post-Doctoral Master of Science in Clinical and Translational Research Program at the University of Puerto Rico, Medical

Sciences Campus. Its contents are solely the responsibility of authors and do not necessarily represent the official view of the National Institutes of Health. We greatly appreciate the collaboration of Dr. Manuel Rivero from Puerto Rico Pathology, Dr. Adalberto Mendoza from Southern Pathology Services and Dr. Guillermo Villarmarzo and Mrs. Eva Parente from Hato Rey Pathology.

References

1. Spechler SJ. Clinical practice. Barrett's esophagus. N Engl J Med 2002;346:836-842.
2. Wang KK, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol 2008;103:788-797.
3. Abrams JA, Fields S, Lightdale CJ, Neugut AL. Racial and ethnic disparities in the prevalence of Barrett's esophagus among patient who undergo upper endoscopy. Clin Gastroenterol Hepatol 2008;6:30-34.
4. Cameron AJ, Lomboy CT. Barrett's esophagus: age, prevalence, and extent of columnar epithelium. Gastroenterology 1992;103:1241-1245.
5. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005;97:142-146.
6. Blot WJ, Devesa SS, Kneller RW, Fraumani JF Jr. Rising incidence of adenocarcinoma of the esophagus and cardia. JAMA 1991;265:1287-1289.
7. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998;83:2049-2053.
8. van Soest EM, Dieleman JP, Siersema PD, Sturkenboom MC, Kuipers EJ. Increasing incidence of Barrett's oesophagus in the general population. Gut 2005;54:1062-1066.
9. Fan X, Snyder N. Prevalence of Barrett's esophagus in patients with or without GERD symptoms: Role of race, age, and gender. Dig Dis Sci 2009;54:572-577.
10. Rex DK, Cummings OW, Shaw M, et al. Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. Gastroenterology 2003;125:1670-1677.
11. Sharma P. Clinical practice. Barrett's esophagus. N Engl J Med 2009;361:2548-2556.
12. Abrams JA, Fields S, Lightdale CJ, Neugut AI. Racial and ethnic disparities in the prevalence of Barrett's esophagus among patient who undergo upper endoscopy. Clin Gastroenterol Hepatol 2008;6:30-34.
13. Gonzalez L, Magno P, Ortiz AP, Ortiz-Ortiz K, Noguera G, Suarez E. Esophageal cancer incidence rates by histological type and overall: Puerto Rico versus the United States SEER population, 1992-2005. Cancer Epidemiol 2013;37:5-10.
14. Kleinbaum DG, Kupper LL, Nizam A, Muller KE. Applied regression analysis and other multivariable methods. 4th ed. Belmont, CA: Thompson Brooks/Cole; 2008.
15. Wani S, Falk G, Hall M, et al. Patient with nondysplastic Barrett's esophagus have low risks for developing dysplasia or esophageal carcinoma. Clin Gastroenterol Hepatol 2011;9:220-227.
16. Gaddam S, Singh M, Balasubramanian G, et al. Persistence of nondysplastic Barrett's esophagus and risk of high-grade dysplasia or adenocarcinoma in patients without dysplasia. Gastroenterology 2013;145:548-553.
17. Falk GW, Buttar NS, Foster NR, et al. A combination of esomeprazole and aspirin reduces tissue concentrations of prostaglandin E (2) in patients with Barrett's esophagus. Gastroenterology 2012;143:917-926.
18. Omer ZB, Ananthakrishnan AN, Nattinger KJ, et al. Aspirin protects against Barrett's esophagus in multivariate logistic regression analysis. Clin Gastroenterol Hepatol 2012;10:722-727.
19. Beales IL, Vardi I, Dearman L. Regular statin and aspirin use in patients with Barrett's esophagus is associated with a reduced incidence of oesophageal adenocarcinoma. Eur J Gastroenterol Hepatol 2012;24:917-923.
20. Nguyen DM, Richardson P, El-Seraq HB. Medications (NSAIDS, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. Gastroenterology 2010;138:2260-2266.
21. de Jonge PFJ, van Blankenstein M, Looman CWN, Casparie MK, Meijer GA, Kuipers EJ. Risk of Malignant Progression in Patients with Barrett's Esophagus; a Dutch Nationwide Cohort Study. Gut 2010;59:1030-1036.
22. Pohl H, Wrobel K, Bojarski C, et al. Risk factors in the development of esophageal carcinoma. Am J Gastroenterol 2013;108:200-207.
23. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology 2011;140:1084-1091.
24. American Association of Gastrointestinal Endoscopy Standards of Practice Committee. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. Gastrointest Endosc 2012;76:1087-1094.
25. White N, Gabril M, Ejeckam G, et al. Barrett's esophagus and cardiac intestinal metaplasia: two conditions within the same spectrum. Can J Gastroenterol 2008;4:369-375.
26. Harrison R, Perri I, Haddadin W, et al. Detection of intestinal metaplasia in BE: an observational comparator study suggests the need for a minimum of eight biopsies. Am J Gastroenterol 2007;102:1154-1161.
27. Lieberman DA, Oehlke M, Helfand M. Risk factors for Barrett's esophagus in community-based case control study. GORGE consortium. Gastroenterology Outcomes Research Group in Endoscopy. Am J Gastroenterol 2011;106:1604-1611.
28. Montgomery E, Goldblum JR, Greenson JK, et al. Dyplasia as a predictive marker for invasive carcinoma in Barrett's esophagus: a follow-up study based on 138 cases from a diagnositic variability study. Hum Pathol 2001;32:379-388.
29. Montgomery E, Bronner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. Hum Pathol 2001;32:368-378.
30. Downs-Kelly E, Mendelin JE, Bennett AE, et al. Poor interobserver agreement in the distinction of high-grade dysplasia and adenocarcinoma in pretreatment Barrett's esophagus biopsies. Am J Gastroenterol 2008;103:2333-2340.