

The frequency of histologically confirmed Barrett's esophagus varies by the combination of ethnicity and gender

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Background: Barrett's esophagus (BE) is the primary risk factor for esophageal adenocarcinoma (EAC). Limited data exists regarding the frequency of histologically confirmed BE by both gender and ethnicity in the United States. The study aim was to determine whether the frequency of histologically confirmed BE varies by ethnicity and gender.

Methods: The University of Florida-Jacksonville endoscopy database was reviewed for all cases of salmon colored esophageal mucosa from September 2002 to August 2007. Histologic BE was diagnosed only if salmon colored esophageal mucosa was seen endoscopically and biopsy confirmed intestinal metaplasia with goblet cells. Data collected included: age at diagnosis, self-reported ethnicity [non-Hispanic white (nHw) or African American (AA)], gender, procedure indication, gastroesophageal reflux disease (GERD) history, atypical manifestations, cigarette smoking, alcohol use, proton pump inhibitor (PPI) use, BE endoscopic length, absence/presence of hiatal hernia, stricture or ulcer, and absence/presence/grade of dysplasia.

Results: Salmon colored esophageal mucosa was identified in 391/7,308 patients, distributed ethnically as 306 nHw and 85 AA. Histologic BE was confirmed in 111/391 patients with ethnic distribution of: 95 nHw and 16 AA. Histologically confirmed BE frequency varied both by gender and ethnicity with nHw males having the highest (42.3%) and AA females the lowest (12.3%). Histologically confirmed BE frequency differed significantly between nHw males and nHw/AA females only ($P < 0.005$).

Conclusions: Histologically confirmed BE frequency varies by ethnicity and gender with nHw males having the highest frequency/risk and AA females the lowest. Investigation to improve understanding of the impact of race and gender in BE formation should be performed.

Keywords: Barrett's esophagus (BE); gender; ethnicity; histology; frequency

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Introduction

The incidence of esophageal adenocarcinoma (EAC) has dramatically increased over the last several decades in the United States, primarily in males (1,2). Barrett's esophagus (BE), the accepted metaplastic precursor of EAC, has an

incidence rate highest in the non-Hispanic white (nHw) population (3). In addition, BE predominately affects men compared to women (3-6). Other risk factors for development of BE and EAC are gastroesophageal reflux disease (GERD), obesity, and tobacco smoking while *H. pylori* colonization and regular aspirin or non-steroidal anti-

inflammatory drugs reduce risk (7-15).

The mechanisms for the disparity seen in BE and EAC incidence across ethnic and gender groups remain unclear. A common hypothesis regarding BE formation suggests that years of unrecognized GERD results in damage to the squamous esophageal mucosa secondary to acidic gastric contents resulting in a metaplastic change. Females with reflux symptoms have less esophageal acid exposure than males on average (16). However, females and males with BE had similar reflux severity (16). Conversely, data indicate that not all with BE have a history of reflux symptoms, nor do the majority of GERD patients develop BE (17). Interestingly, evaluations similar to the above between nHw and African American (AA) patients with reflux or BE has not occurred to date.

In addition, minimal information exists evaluating BE using the combination of race and gender specifically. Only a single study to date has assessed the impact of ethnicity and gender in combination as risk factors for BE (18). Unfortunately, one ethnic group studied by Ford and colleagues was a composite group called "Afro-Caribbean" rather than individuals of only African descent. We therefore decided to retrospectively assess the frequency of histologically confirmed BE to determine if the combination of ethnicity and gender impacts this outcome at an urban United States tertiary care facility that cares for a significant number of female and AA patients.

Methods

A single center retrospective study was performed by reviewing all upper endoscopies performed at the University of Florida College of Medicine-Jacksonville (UFCOM-Jacksonville) between September 2002 and August 2007. The study was approved by the UFCOM-Jacksonville Institutional Review Board. All patients, at least of 18 years of age with self-reported nHw or AA ethnicity, who underwent upper endoscopy (EGD) and found to have salmon colored esophageal mucosa endoscopically during the study period were eligible for inclusion. The appearance of the esophagogastric junction (EGJ), defined as the junction of the proximal gastric folds with the tubular esophagus was carefully noted to assess for the presence of an irregular z-line or salmon colored mucosa arising from the EGJ. Then, biopsies were performed on any tongues measuring at least 1 cm of salmon-colored mucosa arising from the EGJ suspicious for BE. In addition, four-quadrant biopsies were taken from all areas of suspected intestinal

metaplasia every 1 cm of the length of the salmon colored mucosa. All EGDs were performed by six board-certified faculty attending gastroenterologists or gastroenterology fellows under direct supervision of faculty in the Division of Gastroenterology.

Exclusion criteria included patients who did not have specialized intestinal metaplasia on biopsy as well as insufficient or inconclusive biopsies. Histologic BE was diagnosed only if endoscopy revealed salmon colored mucosa at least 1 cm above the top of the gastric folds and intestinal metaplasia with goblet cells identified by hematoxylin-eosin and confirmed by Alcian blue on biopsy. Long-segment BE (LSBE) was defined as ≥ 3 cm of salmon colored mucosa on endoscopy and histologic confirmation as described above. Short-segment BE (SSBE) was defined as 1–3 cm of salmon colored mucosa on endoscopy and histologic confirmation as described above. If salmon colored mucosa was observed measuring at least 1 cm but an overall length not recorded with histologic confirmation described above, those individuals were classified as SSBE.

Data collected for all patients with histologic BE included age at diagnosis, gender, ethnicity, previous history of gastroesophageal reflux, atypical symptoms (chronic cough, aspiration, chest pain), cigarette smoking (by patient report), alcohol use (by patient report), body mass index (BMI), proton pump inhibitor (PPI) use, endoscopic length of BE, presence or absence of hiatal hernia, stricture or ulcer, presence or absence of dysplasia, and if present the grade of dysplasia.

Statistical analysis

Continuous data were compared using two sided Student *t* tests or ANOVA for normally distributed continuous data. Categorical data were analyzed using appropriate chi-square testing. Prevalence was recorded as a percent of the total group and for each ethnicity. Logistic regression modeling was also performed using male sex and nHw race as the basis of comparison to derive odds ratios of histologic BE. Differences between groups were considered significant if $P < 0.05$. Data analysis was performed using the IBM SPSS statistics statistical analysis program (version 22, IBM Corporation, Armonk, NY, USA).

Results

During the 5-year period between September 1, 2002 and August 31, 2007, a total of 11,163 EGDs were performed

Table 1 Demographics of all patients undergoing endoscopy during the study period

Demographic	Overall (n=6,835)	nHw (n=4,138)	AA (n=2,697)
Mean age (years)	57.3	57.6	57.3
Percent of male (%)	36.4	39.4	31.8*

*, compared to nHw, P<0.001. nHw, non-Hispanic white; AA, African American.

Table 2 Demographics in those with histologic Barrett's esophagus (BE) overall and by ethnicity

Ethnicity	Overall	nHw	AA	P value
No. of patients (%)	111	95 [86]	16 [14]	–
Age, mean ± SD [range] (years)	62±12 [39–84]	62±12 [39–84]	63±11 [40–74]	0.756
Percent of male (%)	67	69	56	0.079

nHw, non-Hispanic white; AA; African American.

Table 3 Histologic BE confirmation frequency by ethnicity and gender

Ethnicity/gender	Histologic BE	Salmon colored esophageal mucosa	Percent of confirmed (%)	Odds ratio (95% CI)
nHw males	66	156	42.3	1.000 (reference)
AA males	9	28	32.1	0.646 (0.275 to 1.518)
nHw females	29	150	19.3*	0.327 (0.195 to 0.547)*
AA females	7	57	12.3*	0.191 (0.081 to 0.448)*

*, compared to nHw males, P<0.005. BE, Barrett's esophagus; nHw, non-Hispanic white; AA, African American.

on 7,308 total patients. Of this amount, 6,835 patients were self-identified as either nHw [4,138] or AA [2,697] ethnicity and eligible for the investigation. Demographic information of the overall population as well as nHw and AA groups are listed in *Table 1*. Mean patient age of those undergoing endoscopy was 57.3 years and 36% of the overall patient population were male. No difference was seen in mean age between the overall population and either ethnic group studied. AA had fewer males undergoing EGD compared to nHw during the study interval (P<0.001, *Table 1*).

A total of 456 EGDs with salmon colored esophageal mucosa were retrieved from the endoscopic database, corresponding to 391 patients with findings suggestive of BE on EGD (5.4% of the population undergoing EGD during the study period). The ethnic distribution of patients with salmon colored esophageal mucosa was as follows: 306 (76%) nHw and 85 (21%), AA. Histologically confirmed BE was present in 111 patients (1.5% of the population undergoing EGD during the study interval, 28.4% of

patients with salmon colored esophageal mucosa); 95 (83%) were nHw while 16 (14%) were AA. A summary of the demographic and clinical information of the histologic BE group overall as well as by ethnicity is seen in *Table 2*. Mean age was similar between both groups with histologically confirmed BE. A higher proportion of nHw and AA males than females had histologically confirmed BE (*Table 2*). However the gender variation observed between the two ethnic groups did not reach significance.

The frequency of histologic confirmation of BE varied by the combination of gender and ethnicity (*Table 3*). The difference observed in the frequency of histologic BE was significant between nHw men compared to either nHw or AA females, P<0.005. Although AA men had a reduced frequency of histologic confirmation compared to nHw men, this variation did not achieve significance. Odds ratios for histologic confirmation based on ethnicity and gender are also indicated in *Table 3*. Compared to nHw males (reference), all combinations of ethnicity and gender were

Table 4 Presence of risk factors, length and dysplasia in histologically confirmed BE by combination of ethnicity and gender

Variable	nHw males (n=66)	AA males (n=9)	nHw females (n=29)	AA females (n=7)	P value
Hiatal hernia [%]	36 [55]	6 [66]	15 [52]	2 [28]	0.487
BMI, mean \pm SD	28.5 \pm 5.8	32.6 \pm 5.4	29.7 \pm 7.9	29.9 \pm 7.0	0.326
PPI use [%]	35 [53]	6 [66]	14 [48]	1 [14]	0.103
Cigarette use [%]	22 [33]	4 [44]	7 [24]	2 [28]	0.365
Alcohol use [%]	14 [21]	2 [22]	2 [7]	0	0.198
LSBE [%]	18 [27]	1 [11]	7 [24]	1 [14]	0.671
Dysplasia	5 (8%): 2 LGD, 3 HGD	0	2 (7%): both LGD	0	0.735

BE, Barrett's esophagus; nHw, non-Hispanic white; AA, African American; BMI, body mass index; PPI, proton pump inhibitor; LSBE, long-segment BE; LGD, low grade dysplasia; HGD, high grade dysplasia.

less likely to have histologic confirmation of BE with odds ratios for both nHw and AA females reaching significance [nHw females 0.327 (95% CI, 0.195 to 0.547); AA females 0.191 (95% CI, 0.081 to 0.448)].

Comparison of risk factors and dysplasia presence by the combination of ethnicity and gender are indicated in *Table 4*. Interestingly, in spite of the histologic confirmation frequency differences seen above, no variation was observed in the presence of common risk factors for BE between ethnic and gender combinations. This also occurred assessing dysplasia presence by the same parameters.

Discussion

Minimal data exists on the prevalence of BE when considering the combination of gender and ethnicity in the United States. The aim of this investigation was to determine whether the frequency of histologically confirmed BE varies by both ethnicity and gender at an urban United States tertiary care facility caring for a significant number of female and AA patients. In this retrospective study of BE at such a center, the frequency of histologically confirmed BE varies by the combination of gender and ethnicity. nHw males had the highest frequency of histologically confirmed BE while AA females had the lowest.

Several groups have evaluated histologically confirmed BE by gender in multiethnic populations (3,6,17-23). However, only three of the investigations report prevalence in detail using ethnicity and gender as measurable variables (6,17,23). AA and nHw were the only groups evaluated or the two largest ethnic populations assessed in these studies (6,17,23). Khoury and associates indicated that

AA and females had a lower prevalence than nHw and males, respectively, of histologically confirmed BE (6). Fan and Snyder reported that the rate of histologically confirmed BE in males was significantly higher than females irrespective of GERD symptoms (17). Interestingly, Fan and Snyder did not discover a significant difference in confirmed BE prevalence between nHw, AA, and Hispanic Americans (17). In a recent assessment of BE risk factors between AA and nHw at a large Veterans Affairs Medical Center, AA prevalence was lower than nHw and not accounted for by risk factor differences between groups (23). Males comprised more than 90% of individuals as expected from investigations from the Veterans Affairs system while our AA group was comprised of 44% females allowing for assessment by gender. In our cohort, no difference was seen in the presence of hiatal hernia, BMI, as well as PPI, cigarette and alcohol use across ethnic/gender combinations confirming the previous results while adding assessment of a female component, missing previously, to the BE literature.

Sex hormones, in combination with obesity, may be responsible for the disparities seen in BE and EAC by gender and ethnicity (3,8,9,24-27). Theories regarding the impact of these hormones consist of either estrogen protection, androgen carcinogenic effect and/or consequences of alterations in the ratio of androgen to estrogen. At present, two studies have assessed circulating sex hormones in either BE or EAC (28,29). Awan and colleagues performed a small case control investigation assessing serum testosterone in male EAC patients compared to age matched benign surgical controls (28). Preoperative serum testosterone was significantly higher in the EAC group compared with those having benign

surgery. Cook *et al.* evaluated, in case control fashion, circulating sex hormones in men with BE versus matched endoscopic controls (29). Elevated free testosterone and dihydrotestosterone were positively associated with BE risk while elevated estrone sulfate was associated with reduced risk. Regrettably, both investigations did not evaluate women or report on ethnic differences in serum sex hormone levels among men. Assessment of sex hormones by the combination of ethnicity and gender in those suspected to have BE endoscopically as well as those with histologic confirmation of BE may provide further evidence explaining the findings of the present investigation.

There are limitations to the present study that should be mentioned. Rates of *H. pylori* colonization were not included as such data was not available for all cases. *H. pylori* colonization is associated with a decreased risk of BE (30). The prevalence of *H. pylori* is higher among AA compared to nHw and this factor may contribute to the observed differences in BE seen among ethnic groups (31). In addition, males are known to have higher rates of *H. pylori* colonization than females after controlling for the influence of race/ethnicity (32). The number of males in the AA group undergoing endoscopy was significantly less than observed in the nHw group in the present investigation. It is well known that males, especially AA males, have decreased health seeking behavior as well as significant medical mistrust, which can contribute to the diminished frequency observed (33). Individual statin and aspirin use was not recorded for all subjects. Both statin and aspirin use have been associated with reduced risk of BE formation (34). Recent data indicate that AA men and all races/ethnicities of women are less likely to report use of these drugs (35). This finding suggests that the decreased rate of histologically confirmed BE observed presently in AA men as well as AA/nHw females could be even further reduced if use of those agents was recorded and found to be equal between groups. The present study was a single center retrospective evaluation, which could reduce the generalizability of our findings in other patient populations. Finally, the small number of AA with biopsy proven BE in our investigation limits the impact of any observations noted and warrants confirmation in larger studies.

To conclude, histologically confirmed BE frequency varies by ethnicity and gender with nHw males having the highest frequency/risk and AA females the lowest. Investigation to improve understanding of the impact of ethnicity and gender in BE formation should be performed including assessment of sex hormones, wound healing and *H. pylori* infection on

those at risk or currently with the disease.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This research was approved by the University of Florida College of Medicine-Jacksonville Institutional Review Board (No. UFJ 2007-150).

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