Published in final edited form as:
J Clin Gastroenterol. 2012 March ; 46(3): 251–252. doi:10.1097/MCG.0b013e318238353e.

Expression of Androgen Receptors in Barrett Esophagus

Helena Nordenstedt, MD, PhD[*,†], **Mamoun Younes, MD**[‡], and **Hashem B. El-Serag, MD, MPH**[*]

[*]Michael E. DeBakey Veterans Administration Medical Center and Baylor College of Medicine, Houston Center for Quality of Care and Utilization Studies Houston, TX

[†]Upper Gastrointestinal Research Department of Molecular Medicine and Surgery, Karolinska Institutet Stockholm, Sweden

[‡]Department of Pathology, Baylor College of Medicine, Houston, TX

To The Editor

The overwhelming male predominance in esophageal adenocarcinoma (EA), with an overall male-to-female incidence rate ratio as high as 7 to 10:1, remains unexplained.[1] The male-tofemale ratio seems to be age dependent with the highest ratio in those below 50 years of age and the lowest in those above 80 years of age.[2]

Barrett esophagus (BE), a metaplastic change of the squamous epithelium of the esophagus to a columnar epithelium is the only known precursor lesion to EA.[3] In BE the male predominance is less than that in EA, with a male-to-female ratio of 2 to 4:1.[4]

As a result of these observed sex differences, it has been hypothesized that sex hormones are involved in the development of BE and EA.[5] Estrogen receptors have been detected in BE mucosa,[6] but the existence of androgen receptors (ARs) in the esophagus have not been adequately examined.[7]

Taking into account the fact that testosterone levels gradually decrease in men with age[8] and that the sex ratio in EA becomes less pronounced with age,[2] testosterone exposure might provide a biological basis to the male predominance of EA. We therefore set out with the aim to demonstrate the existence of ARs in BE mucosa.

Esophageal biopsies were taken in the Endoscopy clinic at the Veterans' Administration Medical Center in Houston, Texas, from 10 cases (all men) with endoscopically and histologically confirmed BE and 20 controls (10 men and 10 women) with no BE on endoscopy or histology. These 30 individuals were randomly selected from a large ongoing cohort study enrolling patients referred for nonurgent upper endoscopy and randomly selected veterans eligible for colonoscopy belonging to the Endoscopy clinic at the Veterans' Administration Medical Center. Cases were found to have suspected BE on upper

The authors declare that they have nothing to disclose.

endoscopy and the diagnosis was confirmed by the finding of intestinal metaplasia with goblet cells on pathology.

After deparaffinization in xylene and rehydration in decreasing concentrations of ethanol ending in phosphate-buffered saline, sections were subjected to steam heat antigen retrieval in Dako High-pH Target Retrieval Solution (Dako, Carpinteria, CA). The sections were then incubated with 1:40 dilution of a monoclonal anti-AR antibody (Clone AR441, Dako) for 30 minutes at room temperature using a Dako autostainer. The bound antibody was detected using Envision plus mouse peroxidase kit (Dako) with diaminobenzidine as chromogen. The sections were counterstained in hematoxylin, dehydrated, mounted, and coverslipped. Sections of normal human prostate and human tonsil were used as positive and negative controls, respectively. Sections stained as above but without the AR antibody were also used as negative controls.

The study was approved by the Institutional Review Board at Baylor College of Medicine and by Research and Development at the Michael E. DeBakey Veterans Affairs Medical Center, both in Houston, Texas.

A total of 30 individuals were evaluated. Cases were slightly older and somewhat more likely to be white than controls. All samples with BE tissue were negative for ARs on staining in BE epithelium, stroma, and squamous epithelium. Only 1 male control was found to have ARs in the squamous esophageal mucosa.

In this study, we have shown that ARs are not present in either BE mucosal tissue or to any substantial degree in normal esophageal mucosa. In, to our knowledge, the only previous attempt to detect ARs in BE mucosa, immunohistochemical staining for ARs was performed on sections of 20 paraffin blocks from patients with BE and associated adenocarcinoma (10 male and 10 female). The investigators found very weak AR staining in adenocarcinoma from 1 male and in BE (called “intestinal metaplasia”) in 1 female with all other sections reported as negative.[7] The investigators concluded that ARs are not implicated in BE or adenocarcinoma. The study lacked several methodological details including the number of sections with BE or cancer that were examined from each patient, how BE was defined, what negative controls were used, and what staining procedure was followed. It is well known that there is quite a variation in biomarker expression with malignant progression; therefore, examination of AR expression in patients with BE early in the disease and before malignant progression was important to determine whether AR plays a role early in the disease. Our study had several advantages including the wellcharacterized cases and controls, the clear endoscopic and histologic definitions, and the purposefully selected and balanced controls.

In conclusion, the fact that ARs are not found in BE warrants further research to find alternative explanations for the high male-to-female ratio in BE and in EA.

Acknowledgments

This work was supported by NCI R01 116845 and NIDDK K24-04-107.

References

1. Vizcaino AP, Moreno V, Lambert R, et al. Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973 to 1995. Int J Cancer. 2002; 99:860–868. [PubMed: 12115489]
2. Rutegard M, Shore R, Lu Y, et al. Sex differences in the incidence of gastrointestinal adenocarcinoma in Sweden 1970 to 2006. Eur J Cancer. 2010; 46:1093–1100. [PubMed: 20188539]
3. Yousef F, Cardwell C, Cantwell MM, et al. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. Am J Epidemiol. 2008; 168:237–249. [PubMed: 18550563]
4. Corley DA, Kubo A, Levin TR, et al. Race, ethnicity, sex and temporal differences in Barrett's oesophagus diagnosis: a large community-based study, 1994 to 2006. Gut. 2009; 58:182–188. [PubMed: 18978173]
5. Lagergren J, Nyren O. Do sex hormones play a role in the etiology of esophageal adenocarcinoma? A new hypothesis tested in a population-based cohort of prostate cancer patients. Cancer Epidemiol Biomarkers Prev. 1998; 7:913–915. [PubMed: 9796637]
6. Akgun H, Lechago J, Younes M. Estrogen receptor-beta is expressed in Barrett's metaplasia and associated adenocarcinoma of the esophagus. Anticancer Res. 2002; 22:1459–1461. [PubMed: 12168823]
7. Tiffin N, Suvarna SK, Trudgill NJ, et al. Sex hormone receptor immunohistochemistry staining in Barrett's oesophagus and adenocarcinoma. Histopathology. 2003; 42:95–96. [PubMed: 12493034]
8. Veldhuis JD. Aging and hormones of the hypothalamo-pituitary axis: gonadotropic axis in men and somatotropic axes in men and women. Ageing Res Rev. 2008; 7:189–208. [PubMed: 18343203]