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Smokeless Tobacco and Cigar and/or Pipe Are Risk Factors for Barrett Esophagus in Male Patients With Gastroesophageal Reflux Disease

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Abstract

Objective: To investigate the effect of smokeless tobacco (ST), cigar and/or pipe smoking (CP) on the development of Barrett esophagus (BE) in white male patients with gastroesophageal reflux disease (GERD).

Patients and Methods: A total of 1015 records of white male adults with BE (cases; n=508) or GERD (controls, n=507) were reviewed for lifestyle factors. Logistic regression analyses were performed after adjusting for lifestyle factors to assess the effects of ST and CP on the risk of developing BE. Differences between patients with BE and those with GERD were compared using chi-square and *t* tests.

Results: Patients with BE were significantly older than patients with GERD (mean age, 66±12 years for patients with BE and 55±15 years for patients with GERD; $P<.001$). The odds of developing BE in patients who used CS were 1.7 times higher than that in patients who never smoked cigarettes (odds ratio [OR], 1.7; 95% CI, 1.3-2.2). It was observed that when CS use was combined with either ST or CP use, the odds of having BE significantly increased (OR, 2.5; 95% CI, 1.2-5.2; $P=.01$ and OR, 1.9; 95% CI, 1.03-3.58; $P=.04$) in comparison to CS alone. There were no significant differences in body mass index and alcohol consumption between BE and GERD groups.

Conclusion: This study suggests that there is indeed an association between CS and BE. We believe that this is the first time that ST and CP were associated with an even higher odds of developing BE. Further studies are needed to investigate whether the use of ST and CP is also associated with an increased risk of developing BE-associated adenocarcinoma.

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In Barrett esophagus (BE), the squamous epithelial lining of the distal esophagus is replaced by a specialized columnar type of epithelium as a result of long-standing gastroesophageal reflux disease (GERD).[1,2] Barrett esophagus predisposes for esophageal adenocarcinoma (EAC) with an annual risk of less than 1%.[3,4] Barrett esophagus and EAC are most prevalent in white males.[5-7] Esophageal adenocarcinoma has a poor prognosis with a 5-year survival of less than 50% despite surgical treatment combined with chemotherapy and radiation therapy.[8] However, 5-year survival can be improved to more than 80% with early detection of EAC, as is the case in BE surveillance programs.[9,10] Therefore, identifying risk factors (particularly those that are modifiable) associated with the development of BE is of high importance.

The development of BE appears multifactorial in nature with a polygenetic component as well as a role for lifestyle factors such as abdominal obesity, cigarette smoking (CS), dietary factors, and possibly alcohol consumption.[11-18]

Although the prevalence of CS is decreasing steadily, the use of smokeless tobacco (ST; ie, chewing or spitting of tobacco-containing products) has not changed, or in some countries even increased. In third world

countries, chewing or spitting of tobacco products is considered harmless and observed even in children and women.[19] In Western countries, ST has been promoted as a less harmful alternative to smoking ("harm reduction theory"),[20] which resulted in a significant increase in the use of ST, predominantly in young male adults.[21,22]

Other types of tobacco products such as cigar and/or pipe (CP) smoking as well as the use of e-cigarettes (vaping) have also seen an increase in their use,[23-25] partly because of the same harm reduction theory, but also because of glamorization of these products by mass media.[24,26] Cigar and/or pipe, similar to ST, fall in the category of noninhaled tobacco products, because they are not to be (deeply) inhaled and kept in the mouth. As a consequence, most studies looking at possible carcinogenic effects of CP have investigated its relation to oral, and in some cases, upper (squamous-type) esophageal cancer.[27,28] A relation between CP specifically and BE or EAC has not been studied yet.

Tobacco products, besides containing nicotine, contain nitrite and nitrosamines, the latter being regarded as carcinogens and associated with an increased risk of several types of cancer.[29] Users of noninhaled tobacco products ingest high(er) amounts of nitrosamines through tobacco extract that accumulates in the saliva.[30,31] There are numerous studies implicating ST and CP as risk factors for oral cancers as well as for esophageal squamous carcinoma.[27,32,33] A study by Aro et al[34] has reported that the use of ST is associated with microscopic changes in the esophagus, resembling a chronic type of esophagitis. Clemons et al[35] found that nitrous oxide (a metabolite of nitrosamines) may contribute to the progression of BE to EAC by causing double-stranded DNA breaks. To our knowledge, there are no studies relating the use of ST or CP to the development of BE.

PATIENTS AND METHODS

Patients

The study was approved by the Mayo Clinic Institutional Review Board. Participants signed research authorization for the use of their patient information. An internal endoscopy database search was performed using the following search terms: *male patients*, *esophagitis*, or *Barrett esophagus*; this search resulted in a total of 7000 medical records of patients who underwent endoscopy between January 1, 2002, and December 31, 2010, at Mayo Clinic in Rochester, Minnesota, being reviewed. The 7000 patients whose charts were reviewed constituted both patients who were in primary care at Mayo Clinic and tertiary referrals. The 1043 included patients were white male adults who were diagnosed with either BE (cases; n=517) or GERD (controls; n=532). All BE cases were confirmed by histology, and all pathology reports, endoscopy reports, and clinical notes were reviewed. There was no information on the length of the BE segment because most endoscopies were performed before the implementation of the Prague criteria. All patients with GERD had both clinical and endoscopic signs of reflux disease (classified using the Los Angeles grade classification). For all patients with GERD, follow-up endoscopy, if performed, and all available pathology reports were reviewed to exclude later development of BE. Demographic and clinical data as well as lifestyle factors were both extracted from patient questionnaires taken at the initial visit to Mayo Clinic and confirmed using medical records, including age, ethnic origin, body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared), alcohol consumption, and tobacco use (self-reported both via the questionnaire and to the doctor at the initial appointment). A total of 34 patients were excluded from the analysis (see the Supplemental Appendix, available online at http://www.mayoclinicproceedings.org).

Statistical Analyses

Categorical variables were expressed as counts with corresponding percentages, and continuous normally distributed data were expressed as mean ± SD. Demographic and lifestyle factors were compared using the *t* test for continuous variables and the Pearson chi-square test for categorical variables between patients with BE (all), patients with BE-associated EAC, and patients with GERD.

To evaluate the combined effect of different types of tobacco use, we created 2 new variables: 1 variable for combined CS