# Risk Indicators for Esophageal Cancer: Some Medical Conditions and Tobacco-related Indicators

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Because of little progress in the prognosis and survival of esophageal cancer patients, the early diagnosis and prevention have been prioritized. Alcohol consumption and tobacco smoking are the main risk factors of squamous cell carcinoma, and high body mass index and gastroesophageal reflux are strongly linked to adenocarcinoma of the esophagus. However underlying mechanisms for the observed associations between these risk factors and esophageal cancer are not fully understood. This thesis was aimed to shed further light on the etiology of this cancer through a series of epidemiological studies. An inverse relation between H. pylori infection and the risk of esophageal adenocarcinoma, and a positive link with the risk of squamous cell carcinoma is suggested. We identified retrospective cohorts of patients hospitalized for gastric and duodenal ulcers both strongly linked to H. pylori infection between 1965 and 2003 through the Swedish Inpatient Register. We found a 70% excess risk of esophageal adenocarcinoma in duodenal ulcer patients (SIR=1.7 95% CI 1.1-2.5) compared to the general Swedish population. This finding was plausible because duodenal ulcer is associated with hyperacidity and gastroesophageal reflux, a strong risk factor for esophageal adenocarcinoma. However, it was not consistent with the reported inverse relationship between H. pylori and adenocarcinoma of the esophagus. On the other hand, gastric ulcer patients exhibited 80% higher risk of squamous cell carcinoma (SIR=1.8 95% CI 1.4-2.3), supporting the postulated hypothesis in which bacterial overgrowth in an atrophic stomach may lead to the generation of Nnitroso compounds, a suspected risk factor for esophageal squamous cell carcinoma. In a large cohort study among achalasia patients, we found a strong association between achalasia and risk of esophageal cancer (SIR=10.5 95% CI 7.0-15.9). The excess risk was evident for both adenocarcinoma and squamous cell carcinoma, particularly among men. We also found that the risk of esophageal cancer was high among both operated and unoperated achalasia patients. However, there was some indication that the risk of squamous cell carcinoma may decrease among patients undergoing esophagogastric myotomy. This study showed that achalasia surgery does not increase the risk of esophageal adenocarcinoma. Scandinavian moist snuff (snus) is increasing in Sweden. There are strong forces from tobacco lobbies to encourage snus use as a safer alternative to smoking and to lift the ban put on snus use in most Euopean countries. Using information from 336,381 male Swedish construction workers, we studied the associations between snus use and tobacco smoking and the risk of esophageal cancer. In an analysis among smokers, we found no convincing evidence to support that additional snus use among smokers may decrease the risk of esophageal adenocarcinoma and squamous cell carcinoma compared to those who were only smoking. Moreover, the risk of esophageal squamous cell carcinoma was 3.5-fold higher among never-smoking snus users compared to never-users of any tobacco (95% CI 1.6-7.6). The latter analysis was restricted to never smokers to discard the confounding by smoking appropriately. We therefore concluded that snus cannot be considered an entirely safe alternative to smoking and should not be marketed as a means for harm reduction until strong evidence is able to refute its carcinogenicity. Strong associations between tobacco smoking and the risks of esophageal adenocarcinoma (RR=2.3 95%CI 1.4-3.7) and squamous cell carcinoma (RR=5.2, 95% CI 3.1-8.6) were also noted. Finally, in a population based case-control study we studied the association between polymorphisms of some tobacco-metabolizing genes (GSTP, GSTT1 and GSTM1) and the risk of esophageal cancer. Although there were no associations between these polymorphisms and the risk of adenocarcinoma, the variant GSTP1 Val105 was associated with an increased risk of squamous cell carcinoma (OR=1.7, 95% CI 1.0-2.9). The association tended to be stronger among smokers and homozygotes with the variant allele. Together with the combined literature, we concluded that carriage of the variant GSTP1 Val105 allele may be associated with the risk of both histological types of esophageal cancer among Caucasian populations.