1. INTRODUCTION

The vast majority of patients with head and neck squamous cell carcinoma (HNSCC) report a history of tobacco and alcohol use. The risk of oral cancer increases as a function of both intensity and duration of each exposure, indicating that alcohol and tobacco act synergistically to promote cancer development (1–3).

In the absence of tobacco exposure, alcohol remains an important cause of HNSCC. Several case-control studies have evaluated the risk for HNSCC associated with alcohol use among nonsmokers (NS); only high levels of alcohol use (more than 5 drinks per day) were associated with increased risk of oral cancer (OR = 3.7–8.0) (1–6). NS who drink less than 21 drinks per week do not have increased HNSCC risk compared with NS nondrinkers (ND) (OR = 0.7–1.5) (1–6). Acetaldehyde, a metabolite of alcohol, may be responsible for the tumor-promoting effect of ethanol via free radical production and DNA damage (7). Metabolism of ethanol to acetaldehyde is performed by alcohol dehydrogenases (ADHs) and oral microflora. ADH alleles that increase ethanol metabolism to acetaldehyde increase the risk of HNSCC (8–11). In contrast to NS, studies consistently reported that smokers who have 1–14 drinks per week have increased HNSCC risk (OR = 1.6–3.7) compared with nondrinking smokers (2,3,6,12–14). The effect of alcohol may be more pronounced in smokers because of an interaction between tobacco and alcohol. Smokers have higher salivary acetaldehyde concentrations than NS after exposure to the same amount of alcohol (15), suggesting that the synergy between alcohol and tobacco may in part be attributed to increased exposure to carcinogenic salivary acetaldehyde. Therefore, although moderate alcohol use does not appear to be an important cause of HNSCC in NS, it may interact with tobacco to increase HNSCC risk in smokers.

1.1. Current Problems in the Definition of the “Nonsmoker–Nondrinker”

Despite the preponderance of HNSCC cases in individuals who smoke and or drink, cases do occur in individuals without either of these major risk factors. Estimates of the proportions of head and neck cancers that arise in the “nonsmoker and nondrinker” (NSND) depend on how this category is defined. Ideally, the definition would be based on a biologically or epidemiologically defined cutoff of exposure known not to be associated with elevated risk.
for HNSCC. Currently, however, there is no consensus on the minimal duration or intensity of tobacco exposure associated with a significant increase in risk for head and neck cancer. Further complicating this issue is the considerable variability in measures of tobacco exposure (e.g., pack-years, cigarettes per day, years smoked, grams of tar per day, and so on) used in epidemiologic studies, as well as the variety of tobacco products available (6), and the fact that associations may differ by anatomic site (16,17). Significantly elevated risk for oral (1,6,14,18–21), pharyngeal (1,6,14,18–20), laryngeal (18,22), and esophageal (18,23) cancers has been reported among individuals who smoke 1–15 cigarettes per day compared with never smokers. However, it is unclear whether exposures as low as 1, 5, or 10 cigarettes per day elevate risk. Those studies that estimate risk based on pack-years of exposure similarly group together individuals with less than 20 pack-years of exposure. A limited number of studies have explored risk associated with other sources of tobacco, including bidi, pan, and cigars, and have demonstrated elevated odds of oral cancer with exposures of less than 20 bidi per day, less than 5 pan per day (13,20,24), and less than 4 cigars per day compared with never smokers (14).

There are several common working definitions of the nonsmoker, including individuals who have a cumulative lifetime exposure of less than 100 cigarettes, or individuals who have smoked daily for less than a year, and the never smoker (an individual who has never used any form of tobacco). A strict definition of NSND as those who have never used alcohol or tobacco may underestimate the proportion of cases that could be attributed to non-traditional risk factors. Further complicating data interpretation are issues of data quality, including retrospective determination of tobacco and alcohol use by means of medical record review (25–34), a method with limited accuracy that can differentially misclassify exposure and attenuate real differences between the NSND and the smoker-drinker. Even studies that use patient interviews (35–40), can still have problems of differential recall bias among cases and controls that may accentuate differences.

To illustrate the effect of the definition of NSND on estimates of the proportion of HNSCC among NSND, results from several case series are presented in Table 1. In a case-series defining NSND stringently as no history of ever using tobacco or alcohol and excluding individuals with a history of immunosuppressive disease or medication, only 40 (2.4%) of 1648 HNSCC cases were NSND (39) (Table 1). This study probably underestimates the true proportion of individuals without alcohol- and tobacco-related risk by misclassifying individuals with very low tobacco and alcohol use as “users”; inferences are further limited by extraction of exposure data from medical records. The exclusion of individuals with immunosuppression may underestimate the proportion of cases among NSND because risk of infectious causes of HNSCC is greater among immunosuppressed individuals (e.g., HIV-infected individuals) (41). In a case series of 48 oral cavity cases, the nonsmoker was defined as individuals with less than 1 pack-year of exposure and the nondrinker as an individual who took less than 0.1 shots per day. Use of these definitions, by comparison with the previous study, resulted in higher proportions of non-smoking patients (19%) and nonsmoking-nondrinking patients (8.3%) (40). In a third case series of 129 patients with HNSCC, the researchers collected data from hospital charts and also interviewed patients and physicians as necessary to collect more complete exposure information. They defined NSND more loosely as those who never used, rarely used, or had stopped using tobacco and alcohol more than 20 yr ago and they found that a higher proportion (18.6%) were NSND (36).