Alcohol and oral cancer

Graham R. Ogden*

Unit of Oral Surgery & Medicine, University of Dundee Dental School and Hospital, Park Place, Dundee DD1 4HN, United Kingdom

Abstract

Alcohol, particularly when associated with tobacco use, has been recognized as an important risk factor for mouth cancer for almost 50 years. Together, they are associated with approximately 75% of upper aerodigestive tract cancers. However, intake of alcohol remains high in many countries. The rising incidence of oral cancer has prompted a revaluation of the role of alcohol (both alone and in partnership with other etiologic agents). In this article, the potential role of alcohol in the development of oral cancer is reviewed. In particular, the effect of alcohol on cellular structure and function is considered by reference to histologic and exfoliative cytologic studies of the oral epithelia. Alcohol may influence the proliferative cells by both intracellular (e.g., endocytosis) and intercellular (permeability) pathways. The carcinogenic exposure of the proliferating stem cells in the basal layer may be regulated through these pathways. Individual variation might help explain why oral cancer arises in some, but not in most, people who smoke and consume excess alcohol. Despite this finding, alcohol is strongly associated with the development of oral cancer and other upper aerodigestive tract cancers. Efforts to reduce this burden on the individual and society must be directed toward patient and professional education and research regarding (genetic) susceptibility. © 2005 Elsevier Inc. All rights reserved.

Keywords: Alcohol; Oral mucosa; Oral cancer; Exfoliative cytology; Epidemiology; Etiology

1. Trends in alcohol use

Alcohol, particularly in association with tobacco, has been recognized as an important risk factor for mouth cancer for almost half a century (Wynder & Bross, 1957). Approximately 75% of all oral cancers arise in association with alcohol and tobacco use (La Vecchia et al., 2004; Llewellyn et al., 2003). Despite this knowledge, there is little evidence that people have modified their alcohol intake (Erens, 2000). In the United Kingdom, oral cancer rates have more than doubled during the past 20 years and have increased elsewhere in Europe and the United States (La Vecchia et al., 2004; Schantz & Yu, 2002).

The toll alcohol takes on society is readily apparent from the United Kingdom statistics that 1.7 billion pounds is spent each year tackling alcohol-related conditions within the National Health Services in the United Kingdom (Prime Minister's Strategy Unit, 2004). Indeed, during the past 50 years, the number of liters of pure ethanol consumed per capita each year within the United Kingdom has doubled, from 4 to 8 liters (The Academy of Medical Sciences, 2004; Partanen & Simpura, 2001). It is estimated that 2.9 million individuals (7% of the adult population in the United Kingdom) are dependent on alcohol.

The role of ethanol in alcoholic beverages can be considered to be rather similar to that of nicotine in tobacco, when it comes to causing cancer. Although there is a lack of clear experimental evidence for pure ethanol to be considered a carcinogen (Wight & Ogden, 1998), alcoholic beverages are important in the etiology of oral cancer (Kabat & Wynder, 1989; Tuyns & Griciute, 1980).

When one assesses the role of alcohol, it is difficult to compare study findings, owing to the differing methods of classification quite apart from inaccuracies within alcohol histories (Wight & Ogden, 1998). For example, in the United Kingdom the term *units* of alcohol is used, which approximates to 8 g of alcohol (Ogden & Wight, 1998). This roughly equates to half a pint of beer, a glass of wine, or a pub measure of spirits. However, beers and wines vary greatly in strength. Other authors use the term *drink*. However, this is also imprecise, as some authors equate this to 14 g of alcohol (e.g., a 330-ml bottle of beer, 150 ml of wine, or 36 ml of spirits) (Castellsagué et al., 2004), whilst others equate this to 12 g of alcohol (Dal Maso et al., 2002). In the United States, *ounces* of alcohol is often used, with

* Corresponding author. Tel.: ++44 1382 635989; fax: ++44 1382 425783.

E-mail address: g.r.ogden@dundee.ac.uk (G.R. Ogden).

Accepting Editor: T.R. Jerrells

one drink being the equivalent of 12 oz of beer, 4 oz of wine, and 1.5 oz of spirits (Day et al., 1993). In the United Kingdom, safe levels for drinking of alcohol equate to no more than 21 units per week for men and 14 units per week for women (*Alcohol and the Heart in Perspective: Sensible Limits Reaffirmed*, 1995), whilst high risk is associated with weekly intake greater than 50 units for men or 35 units for women. In the United States, high risk has been defined as 7 or more ounces of alcohol per day (Kabat & Wynder, 1989).

These differences in what defines a drink are yet another factor to consider when one compares study findings and assesses the role of alcohol in the development of oral cancer. That a not insignificant number of oral cancers arise in people who do not smoke, nor drink, has prompted consideration of other sources of alcohol (e.g., mouthwashes). Using the pollen tube growth test, Friedrich and Kristen (2003) found that many mouthwashes were cytotoxic. However, they noted that because mouthwashes are classified as cosmetic, rather than as medicinal, there was no legal obligation on the part of the manufacturers to list all the contents. A review by Gagari and Kabani (1995) revealed alcohol concentrations up to 26%. They found it difficult to establish the exact role of mouthwashes in patients with oral cancer owing to the presence of other confounders (e.g., tobacco) or their use in masking daytime intake of alcohol.

Although most oral cancers arise in individuals who smoke and drink alcohol [with evidence that alcohol alone does not increase the risk for oral premalignant lesions (Jaber et al., 1998)], the increasing incidence of mouth cancer, at a time when smoking is declining (Hindle et al., 2000; Tarvainen et al., 2004), has shifted attention back to alcohol, as an important factor.

Whilst alcohol intake has increased (or remained high) in those countries in which oral cancer rates have risen, the mechanisms by which alcohol exerts a propensity to malignant change are less clear. The following discussion outlines the influence of alcohol on morphologic and mucosal transport mechanisms.

2. Possible mechanisms of action of alcohol on the oral mucosa

2.1. Quantitative exfoliative cytology

The influence of alcohol in patients at risk of oral cancer has been assessed by using quantitative exfoliative cytology (Ogden et al., 1997, 1999a, 1999b; Ogden & Wight, 1998). Smears taken from normal buccal mucosa of alcohol-dependant patients were compared with those obtained for age- and sex-matched control subjects (who were not anemic). A statistically significantly reduction ($P < .001$) in mean cytoplasmic area for high alcohol intake was found irrespective of age (Ogden & Wight, 1998). With the use of exfoliative cytology, malignant disease is associated with a reduction in cytoplasmic area and abnormal DNA profiles (Cowpe et al., 1988). However, when DNA profiles of buccal cells obtained from alcohol-dependent patients were analyzed by using Feulgan-stained cells, a diploid (i.e., normal) profile was always found (Ogden et al., 1999a). Polyploid profiles within clinically normal cells of patients without cancer would have been significant. However, further studies are warranted to assess those oral sites more commonly associated with oral cancer in the United Kingdom (i.e., lateral/ventral tongue, rather than buccal mucosa). Further, because polyploid DNA profiles were seen only in results from established oral cancers, more subtle changes in DNA and nuclear morphologic characteristics may be observed in clinically normal mucosa. These may be just as important for detecting future cancer in the susceptible patient as polyploidy is for detecting cancer. One technique that may detect subtle changes is the micronuclear assay.

The micronucleus (MN) test [measurement of small extranuclear material formed by the exclusion of chromosomal fragments (or whole chromosomes lagging at mitosis)] has been used for many years as an indicator of genotoxic exposure. The assay has been applied to smears obtained from alcohol users in the case in which MN frequency was increased in buccal cells obtained from individuals with a history of smoking and alcohol consumption (Stich & Rosin, 1983). However, when Bloching et al. (2000) assessed patients with oral cancer, they did not find any relation between daily alcohol intake and MN rates. However, they did not state how many of their subjects in the experimental group (and, indeed, in the control group) were nonsmoking alcohol users. Because tobacco use was associated with increased MN (and most patients with oral cancer smoke and drink), it seems likely that any subtle changes in alcohol-induced MNs would have been overshadowed by confounding influences. Findings of a more recent study (Ramirez & Saldanha, 2002) also failed to tease out the nonsmoking alcohol misusers from the smoking alcohol misusers (because these data are not given). Other factors that require investigation include the influence of type, quantity, and years of exposure to alcohol, as well as whether nutritional or hematologic deficiencies influence such results. These areas need to be addressed to ascertain the reliability of the MN assay for detecting oral cancer risk.

2.2. Mucosal transport: intercellular passage

Several papers on the permeability of the oral mucosa have been published by Squier, either alone (Squier, 1991) or in collaboration with his colleagues (Du et al., 2000; Howie et al., 2001; Squier et al., 1986). They have suggested that ethanol may increase the penetration of carcinogens across the oral mucosa (Squier et al., 1986). This may be through intercellular passage of carcinogens