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# Reviews

# Alcohol in the Aetiology of Upper Aerodigestive Tract Cancer

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## INTRODUCTION

THE INCIDENCE rates of upper aerodigestive tract cancer are much higher in males than in females and show marked geographical variations [1]. They are generally high in France, Brazil, India and U.S. blacks, and low in China, Japan, the Middle East and several eastern and northern European countries [1]. However, these variations are not consistent across subsites of the upper aerodigestive tract. For example, high incidence rates for oesophageal cancer are observed in China and Japan [1].

Early epidemiological studies on upper aerodigestive tract cancer identified several possible aetiological factors. In studies conducted in high-risk areas of developing countries, an increased risk was associated with deficiencies in dietary vitamins and minerals [2–4], insufficient intake of animal products [2, 3], nitrosamine intake from pickled vegetables [4] and salted fish [5] and consumption of hot beverages [2]. Case–control studies in western countries have generally supported the protective effects of vegetables, fruit and certain vitamins [6–8]. Both case–control and cohort studies have shown a strong association between tobacco consumption and this cancer [9].

Excessive use of alcoholic beverages has also been considered an important risk factor for upper aerodigestive tract cancer [10]. Several lines of epidemiological evidence have supported this association. In this review on alcohol and upper aerodigestive tract cancer, emphasis is placed on epidemiological studies (first cohort and second case-control studies), but experimental studies are also briefly covered.

## STUDIES OF CANCER RATES IN RELIGIOUS GROUPS

Certain religious sects, such as Seventh-Day Adventists and Mormons, usually abstain from alcohol by church proscription and have therefore provided researchers with opportunities to study the effect of alcohol drinking on cancer incidence and mortality, as summarised in Table 1. Wynder *et al.* found that the frequency of cancer of the mouth, larynx and oesophagus among Seventh-Day Adventists in eight U.S.A. hospitals was only 13% of that seen among non-Adventists [11]. Lemon *et al.* [12] and Phillips *et al.* [13] confirmed that there was a decreased risk of oral, pharyngeal and oesophageal cancers among Californian Seventh-Day Adventists, based on mortality data. Cancer incidence and mortality among Mormons have also been studied. In Utah, where detailed cancer incidence rates are available, the incidence of cancer of the oral cavity, pharynx, oesophagus and larynx was 20–40% among Mormons compared with non-Mormons [14]. In California, mortality rates among Mormon men were 53% for oral–pharyngeal, 45% for oesophageal and 30% for laryngeal cancer, compared with the general population of the U.S.A. [15]. Even lower risks for these cancer sites were observed among active Mormons abstaining almost completely from the use of alcohol [15].

## COHORT STUDIES OF PRESUMED EXCESSIVE DRINKERS

Alcoholics, by definition, are addicted to the excessive use of alcohol. Their cancer mortality and incidence rates have been studied in several countries and compared with the prevailing rates in the general population. These studies included alcoholics in Norway, Finland, Sweden, Canada and Massachusetts and among U.S. veterans, as summarised in Table 2 [10, 16]. A 3–6-fold increased risk of upper aerodigestive tract cancer was reported for these alcoholics, with a lower risk observed in the cohort of U.S. veterans. The risk tended to be higher for oral and pharyngeal cancers than for laryngeal cancer.

Brewery workers are also presumed to drink a larger amount of beer than the general population. There have been cohort studies of brewery workers in Dublin , Denmark and Sweden (Table 3). The mortality rates were studied only for major causes of deaths in Dublin [17], but there was no increase in risk of oesophageal cancer. Cancer incidence rates were statistically significantly increased for oesophageal cancer at the Danish and Swedish breweries [18, 19] and for pharyngeal and laryngeal cancers at the Danish brewery [18]. In contrast to the studies in alcoholics, the increase in risk of oral cancer was relatively small among brewery workers and not statistically significant. This may be due to the difference in types of

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*Table 1. Ratios of observed (O) and expected (E) numbers of cases in studies of cultural subgroups*

| Reference | Population/measurement | Cancer site | O/E ratio | | |
|---|---|---|---|---|---|
| | | | Male | Female | Total |
| 11 | SDA/hospital records | Mouth–larynx–oesophagus | 0.12 | 0.16 | 0.13 |
| 12 | SDA/morality | Mouth–pharynx | — | — | 0.19 |
| | | Oesophagus | — | — | 0.38 |
| 13 | SDA/mortality | Oesophagus | 0.36 | 0.30 | 0.34 |
| 14 | Mormon/incidence | Lip | 0.86 | 0.69 | — |
| | | Tongue | 0.32 | 0.24 | — |
| | | Salivary gland | 0.68 | 0.55 | — |
| | | Gum and mouth | 0.30 | 0.23 | — |
| | | Nasopharynx | 1.55 | 0.69 | — |
| | | Other pharynx | 0.39 | 0.33 | — |
| | | Oesophagus | 0.37 | 0.22 | — |
| | | Larynx | 0.34 | 0.27 | — |
| 15 | Mormon/mortality | Mouth–pharynx | 0.53 | 1.18 | 0.72 |
| | | Oesophagus | 0.45 | 0.69 | 0.51 |
| | | Larynx | 0.30 | 0.88 | 0.37 |
| | Active Mormon/mortality | Mouth–pharynx | 0.13 | — | — |
| | | Oesophagus | 0.00 | — | — |
| | | Larynx | 0.14 | — | — |

SDA = Seventh-Day Adventists.

*Table 2. Observed (O) and expected (E) numbers of cases in studies of alcoholics*

| Study population (No.) | Measurement | Cancer site | O | E | O/E |
|---|---|---|---|---|---|
| Norway (1722) | Mortality | Mouth | 13 | 2.60 | 5.0 |
| | | Pharynx | 9 | 2.05 | 4.4 |
| | | Larynx | 5 | 1.61 | 3.1 |
| | | Oesophagus | 40 | 9.76 | 4.1 |
| Finland (4370) | Indicence | Pharynx | 3 | 0.53 | 5.7 |
| | | Larynx | 3 | 2.16 | 1.4 |
| | | Oesophagus | 4 | 0.98 | 4.1 |
| Massachusetts (1382) | Mortality | Mouth–pharynx | 13 | 3.93 | 3.3 |
| | | Larynx | 6 | 1.58 | 3.8 |
| | | Oesophagus | 5 | 2.63 | 1.9 |
| US veterans (4401) | Mortality | Mouth–pharynx | 14 | 6.36 | 2.2 |
| | | Larynx | 11 | 6.47 | 1.7 |
| | | Oesophagus | 13 | 6.40 | 2.0 |
| Canada (9543) | Mortality | Mouth–pharynx | 24 | 5.71 | 4.2 |
| | | Larynx | 12 | 2.79 | 4.3 |
| | | Oesophagus | 16 | 5.00 | 3.2 |
| Sweden (9353) | Incidence | Mouth–pharynx | 36 | 8.80 | 4.1 |
| | | Larynx | 11 | 3.34 | 3.3 |
| | | Oesophagus | 27 | 4.00 | 6.8 |

alcoholic beverages predominantly consumed or to other differences between brewery workers and alcoholics.

## COHORT STUDIES OF OTHER POPULATIONS

There are some limitations to the cohort studies described in the previous sections. An important shortcoming is that alcohol intake was not estimated for individuals in each of the cohorts, all the subjects in a particular cohort being assumed to have a similarly low or high consumption. Consequently, it was not possible to look for a dose–response relationship. In addition, religious groups and alcoholics are very different from the general population with respect not only to alcohol intake, but also to cigarette smoking habits, diet and other life style factors, which are likely to modify considerably the risk of upper aerodigestive tract cancer.

There have been several large cohort studies in more representative study populations. A total of 122 261 men from the general population in Japan was surveyed in 1965 and followed until the end of 1982 [20]. There were 59, 28 and 438 deaths from oral, pharyngeal and oesophageal cancers, respectively. As shown in Table 4, daily drinkers had relative risks of 2.3–2.4 for the three cancer sites compared with non-drinkers. No increase in risk was observed among occasional drinkers. In another study in Japan, a cohort of 5135 male physicians was followed for 19 years [21]. The mortality from upper aerodigestive tract cancer was significantly increased among daily drinkers who consumed 54 ml or more of alcohol

*Table 3. Observed (O) and expected (E) numbers of cases in studies of brewery workers*

| Study population (No.) | Measurement | Cancer site | O | E | O/E |
|---|---|---|---|---|---|
| Dublin (no data) | Mortality | Oesophagus | 10 | 15.8 | 0.6 |
| Denmark (14227) | Incidence | Oral cavity–tongue | 14 | 10.0 | 1.4 |
| | | Pharynx | 11 | 5.3 | 2.1 |
| | | Oropharynx–tonsils | 4 | 2.2 | 1.8 |
| | | Hypopharynx | 7 | 2.9 | 2.4 |
| | | Oesophagus | 36 | 16.0 | 2.3 |
| | | Nose–sinuses | 4 | 2.7 | 1.5 |
| | | Vocal cords | 15 | 8.2 | 1.8 |
| | | Other larynx | 24 | 9.4 | 2.6 |
| Sweden (6230) | Incidence | Mouth–pharynx | 22 | 18.4 | 1.2 |
| | | Larynx | 13 | 7.7 | 1.7 |
| | | Oesophagus | 20 | 8.1 | 2.5 |

*Table 4. Relative risks (RR) associated with alcohol intake in other types of cohort studies*

| Reference | Characteristics of cohort/endpoint | Cancer cases (No.) | Exposure categories | RR |
|---|---|---|---|---|
| 20 | General population 122 261 men/deaths | Mouth (59) | Non-drinker | 1.0 |
| | | | Occasional | 0.7 |
| | | | Daily | 2.3 |
| | | Pharynx (28) | Non-drinker | 1.0 |
| | | | Occasional | 0.9 |
| | | | Daily | 2.4 |
| | | Oesophagus (438) | Non-drinker | 1.0 |
| | | | Occasional | 1.0 |
| | | | Daily | 2.3 |
| 21 | Physicians 5135 men/deaths | All subsites combined* (18) | Occasional | 1.0 |
| | | | $<54$ ml/day | 1.5 |
| | | | $\geqslant 54$ ml/day | 8.6 |
| 22 | General population 8006 men/incidence | All subsites combined* (75) | Non-drinker | 1.0 |
| | | | $<30$ ml/day | 1.2 |
| | | | $\geqslant 30$ ml/day | 5.4 |
| 23 | Participants in multiphasic health check-up programme 8060 men and women/deaths | Mouth–pharynx–oesophagus (15) | Non-drinker | 1.0 |
| | | | 1–2 drinks/day | 0.0 |
| | | | 3–5 drinks/day | 2.5 |
| | | | $\geqslant 6$ drinks/day | 4.0 |

*Cancer of the mouth, pharynx, larynx and oesophagus combined.

per day. Adjustment for cigarette smoking did not affect the results.

In Hawaii, 8006 Japanese–American men were followed for more than 20 years in a prospective study [22]. Subjects who subsequently developed cancer of the mouth, pharynx, oesophagus or larynx had consumed more than three times as much alcohol per day compared with cancer-free subjects. The risk of cancer of the upper aerodigestive tract increased progressively with increasing amount of alcohol consumed, even after adjustment for cigarette smoking. In a multiphasic health programme in the U.S.A., 8060 participants were followed for 10 years [23]. The risk of death from oral, pharyngeal and oesophageal cancers combined among alcohol drinkers who consumed six or more drinks per day was 4.0 times higher than among non-drinkers, after adjustment for cigarette smoking.

## CASE–CONTROL STUDIES

Although the results from cohort studies have been consistent, information about detailed drinking habits and other confounding factors is generally limited in cohort studies. In addition, it is often difficult to study the effects of alcohol at individual sites of the upper aerodigestive tract because of the relatively small numbers of cases in cohort studies. As a result, most detailed data about alcohol intake and cancers at individual sites have come from case–control studies. A number of case–control studies have been conducted for each site of cancer. Table 5 summarises the results of several case–control studies involving more than 1000 cases or three or more subsites of the upper aerodigestive tract.

Franceschi *et al.* [24] studied 157 cases of oral cancer, 134 of pharyngeal cancer, 162 of laryngeal cancer and 288 of oesophageal cancer along with 1272 hospital controls in Italy. For each site of cancer, there was a strong dose–response effect, based on the number of drinks consumed per week. The association was strongest for oesophageal cancer, followed by pharyngeal and oral cancer.

In Korea, Choi and Kahyo [25] studied 113 male cases of oral cancer, 133 of pharyngeal cancer, 94 of laryngeal cancer and 1020 hospital controls. They found that both the

*Table 5. Relative risks (RR) associated with alcohol intake from the selected case–control studies*

| Country | Type of control (No.) | Exposure category | Cancer site (No.) Relative risk | | | |
|---|---|---|---|---|---|---|
| Italy | Hospital (1272) | | Mouth | Pharynx | Larynx | Oesophagus |
| | | Drink† | (157) | (134) | (162) | (288) |
| | | ⩽19/wk | 1.0 | 1.0 | 1.0 | 1.0 |
| | | 20–34 | 1.1 | 0.9 | 0.8 | 1.0 |
| | | 35–59 | 3.2 | 1.5 | 1.3 | 3.1 |
| | | ⩾60 | 3.4 | 3.6 | 2.1 | 6.0 |
| Korea* | Hospital (1020) | ml | (113) | (133) | (94) | — |
| | | None/day | 1.0 | 1.0 | 1.0 | — |
| | | <5.5 | 0.6 | 1.2 | 0.3 | — |
| | | 5.5–11.1 | 3.6 | 2.2 | 1.2 | — |
| | | 11.1–22.2 | 4.2 | 4.1 | 2.4 | — |
| | | >22.2 | 14.8 | 11.2 | 11.1 | — |
| Puerto Rico* | Hospital and | Unit‡ | (108) | (39) | | (111) |
| | neighbourhood | 0/day | 1.0 | 1.0 | — | 1.0 |
| | tobacco-matched | ⩽1 | 0.5 | 4.1 | — | 0.6 |
| | (258) | 2–4 | 1.7 | 1.4 | — | 2.1 |
| | | ⩾5 | 2.8 | 14.7 | — | 7.7 |
| U.S.A. | Hospital (2280) | | Floor of the mouth | Oral tongue | Soft palate | ANT TP‖ |
| | | WE§ | (153) | (50) | (44) | (49) |
| | | ⩽1/day | 1.0 | 1.0 | 1.0 | 1.0 |
| | | 2–5 | 5.2 | 2.5 | 1.2 | 5.0 |
| | | 6–10 | 9.6 | 7.6 | 4.3 | 20.3 |
| | | 11–21 | 12.1 | 10.9 | 4.0 | 17.7 |
| | | ⩾22 | 10.2 | 8.1 | 3.7 | 16.6 |
| France/ Italy/ Spain/ Switzerland | Population (3057) | | Supra glottic | Other glottic | Epilarynx | Hypolarynx |
| | | Gram | (426) | (270) | (118) | (281) |
| | | ⩽20/day | 1.0 | 1.0 | 1.0 | 1.0 |
| | | 21–40 | 0.9 | 0.8 | 0.9 | 1.6 |
| | | 41–80 | 1.1 | 1.1 | 1.5 | 3.2 |
| | | 81–120 | 1.7 | 1.7 | 5.1 | 5.6 |
| | | ⩾121 | 2.0 | 3.4 | 10.6 | 12.5 |

*Results are presented only for males.
†1 drink corresponds to around 15 ml of ethanol.
‡1 unit is nearly equal to 20 ml of ethanol.
§Whisky-equivalent: 10.24 g of ethanol.
‖Anterior tonsillar pillar.

frequency and the amount of alcohol were strongly related to the risk of cancer at each site in men, although the amount gave a clearer dose–response relationship. Oral cancer showed the strongest association with alcohol intake.

Martinez studied 153 cases of oral cancer, 68 of pharyngeal cancer and 179 of oesophageal cancer and 1200 controls in Puerto Rico [26]. Among them, 346 pairs of cases and controls were matched for tobacco use. Although no association was found in the small group of women, men who consumed more than 5 units (around 20 g of ethanol) of alcoholic beverages showed a statistically significantly increased risk for cancer at each site in tobacco-matched pairs. The risk was highest for pharyngeal, followed by oesophageal cancer.

Some researchers have separated cancers of the oral cavity into specific subsites and studied their association with alcohol intake. In a study at a U.S.A. Veterans Medical Center, the association between alcohol intake and oral cancer was analysed in relation to the following subsites of oral cavity: floor of the mouth, oral tongue, soft palate, anterior tonsillar pillar [27]. A dose–response effect of amount of alcohol consumed per day was observed for each site. The association was strongest for cancer of the anterior tonsillar pillar, followed by cancer of the floor of the mouth and oral tongue. In two other studies, cancer of the oral cavity was divided into cancer of the tongue and cancer of other oral sites [28, 29]. The strength of the association was similar for the two sites, and a dose–reponse relationship was seen in both studies.

An international case–control study was conducted in four European countries involving 281 cases of cancer of the hypopharynx, 118 of cancer of the epilarynx, 426 of cancer of the supraglottis, 270 of cancer of the glottis and subglottis and 3057 population controls. A striking dose–response relationship was observed for cancers of the hypopharynx and epilarynx. Men who consumed 121 g or more alcohol per day had more than 10 times the risk for cancer at these sites, compared with those who consumed 20 g or less of alcohol per day. The association with cancer of the endolarynx (glottis and supra- and subglottis) was much weaker but still statistically

*Table 6. A summary of relative risks (RR) for joint exposure to alcohol and smoking*

| Reference | Cancer site (No.) | RR for combination | | |
|---|---|---|---|---|
| | | AH/SL | AL/SH | AH/SH |
| 28 | Mouth (232) | 23.1 | 15.2 | 141.6 |
| 37 | Mouth-pharynx (598) | 2.3 | 2.4 | 15.5 |
| 35* | Pharynx (762) | 5.8 | 7.4 | 37.7 |
| 24 | Mouth-pharynx (291) | 2.3 | 17.6 | 79.6 |
| | Oesophagus (288) | 7.9 | 6.4 | 17.5 |
| 38 | Oesophagus (226) | 17.0 | 5.9 | 43.1 |
| 36 | Larynx (63) | 2.4 | 3.4 | 7.7 |
| 39 | Glottis (197) | 5.1 | 19.2 | 289.4 |
| | Supraglottis (214) | 50.6 | 46.8 | 1094.2 |
| 30 | Endolarynx (727) | 3.8 | 11.5 | 43.2 |
| | Hypopharynx-epilarynx (399) | 14.7 | 4.9 | 135.5 |
| 22 | All subsites combined (75)† | 8.6 | 3.3 | 17.3 |

AH = Highest exposure category for alcohol intake in each study.
AL = Lowest exposure category for alcohol intake in each study.
SH = Highest exposure category for smoking in each study.
SL = Lowest exposure category for smoking in each study.
*The results are presented only for males.
†Mouth, pharynx, larynx and oesophagus combined.

significant [30]. These results suggest that subsites of the larynx that are more likely to be directly exposed to alcohol are at a greater risk of developing cancer.

## THE RISK ASSOCIATED WITH TYPES OF ALCOHOLIC BEVERAGE

Alcoholic beverages contain numerous chemicals besides ethanol that vary with the type of beverage. The relationship between specific types of alcoholic beverage and certain types of cancer has been of considerable interest among epidemiologists. Three cohort studies (two among brewery workers and a cohort study in Hawaii) have suggested that the risk of cancer of the upper aerodigestive tract may be associated more strongly with beer consumption [18, 19, 22], whereas a cohort study in Japan showed that daily drinkers of shochu (a type of hard liquor) had the highest mortality rate from oesophageal cancer [31]. In Brazil, 'cachaca' (a local type of spirit) was specifically related to the risk of oral [28] and oesophageal cancer [3]. In Italy, only wine showed a strong association with the risk of upper aerodigestive tract cancer [24, 29]. The risk of oesophageal cancer was strongly associated with wine consumption in a case–control study in Los Angeles [32]. In the other studies conducted in the U.S.A., beer or hard liquor yielded the highest risk of cancers of oral, pharyngeal, laryngeal and oesophageal cancers [33–35].

The predominant type of alcohol consumed in different areas of the world differs, so that the results available for types of alcoholic beverage tend to vary with the study area. It is often difficult to separate the effect of individual type of alcoholic beverage from that of total alcohol. In addition, the risk associated with each type of alcoholic beverage is not always comparable because the ethanol content is not always taken into account. Nevertheless, the association with total alcohol has been consistent, suggesting that total alcohol consumption may be more important than the type of beverage in determining risk.

## JOINT EXPOSURE TO ALCOHOL AND TOBACCO

Tobacco smoking is causally related to cancer of the upper aerodigestive tract [9]. Because the consumption of alcohol and tobacco are usually strongly correlated, it is difficult to separate the effect of alcohol from that of smoking. However, some cohort and case–control studies have found an increased risk of upper aerodigestive tract cancer associated with alcohol drinking in non-smokers [22, 24, 28, 35, 36]. Several studies have shown a synergistic effect of joint exposure to alcohol and smoking [22, 24, 28, 30, 35–39]. The definition of the highest exposure combination of alcohol and smoking varied from study to study, but the risk of each site of cancer among persons who drank heavily and smoked heavily increased more than 7 times compared with the reference group (Table 6). The results also suggest that the risk increases multiplicatively rather than additively. These epidemiological observations are supported by a recent experimental study that showed that the overexpression of the p53 gene is more likely to be induced among persons who both drink and smoke heavily [40].

## POSSIBLE MECHANISMS FOR ALCOHOL-RELATED CARCINOGENESIS

Although ethanol has been administered to laboratory animals using various method and protocols, there is no evidence that ethanol itself is carcinogenic [10]. Results from tests for mutagenicity have also shown that ethanol is not mutagenic unless it is metabolised to acetaldehyde and superoxide. These ethanol metabolites have been found to be mutagenic and cytotoxic, and acetaldehyde has been found to be carcinogenic [10]. Besides ethanol, alcoholic beverages also contain nitrosamines and other contaminants that have carcinogenic properties [10].

Ethanol alters intracellular metabolism in the liver and other sites, resulting in increased activation of certain carcinogens [41]. Liver damage caused by alcohol abuse decreases the metabolic clearance rates of some carcinogenic substances [41]. Ethanol may act as a co-carcinogen by solubilising a true

carcinogen [41], or may act as a promoter by stimulating cell proliferation [42]. It has been postulated that alcohol intake may alter hormonal balance in women in relation to hormone-related cancers [43]. An indirect effect of alcohol abuse, i.e. nutrient deficiencies, could be more important. Certain vitamins and minerals have been shown to be anti-carcinogenic and deficiencies of these nutrients are frquently observed among alcoholics [41]. In our cohort in Hawaii, men who subsequently developed oral-pharyngeal cancer had decreased levels of serum cholesterol [44] and haematocrit [45], suggesting a suboptimal nutritional state, although these might also be signs of subclinical disease. The importance of each mechanism is not likely to be the same for every site. In the case of the upper digestive tract, local effects should be emphasised. However, other possible mechanisms also remain to be clarified.

## CONCLUSION

In spite of inadequate evidence for the carcinogenicity of ethanol and of alcoholic beverages in experimental studies, there is sufficient evidence for the carcinogenicity of alcoholic beverages at the oral cavity, pharynx, larynx and oesophagus in humans. The results from retrospective and prospective cohort studies and a number of case–control studies are consistent. A dose–response relationship is observed clearly in most of the studies and the association is much stronger than those observed for other sites, such as the stomach, colorectum, pancreas and female breast [10]. It is biologically reasonable that the association should be stronger for subsites directly exposed to alcohol. It is therefore concluded that the development of cancer of the upper aerodigestive tract is most likely causally related to the consumption of alcoholic beverages. The impact of alcohol consumption on the aetiology of this cancer depends on the prevalence of alcohol drinking in a population, and it should be greatest in western countries where the consumption of alcoholic beverages is high. Considering the synergistic effect of alcohol and cigarette smoking, moderation in alcohol consumption together with quitting smoking should be effective preventive measures for upper aerodigestive cancer in western societies.


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