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CASE REPORT

Alcohol and tobacco misuse: Reducing aerodigestive cancer risk

Gavin Wright, Marsha Y Morgan

Gavin Wright, Marsha Y Morgan, UCL Institute for Liver and Digestive Health, Royal Free Campus, University College London Medical School, University College, London NW3 2PF, United Kingdom
Gavin Wright, Department of Gastroenterology, Basildon and Thurock University Hospitals, Essex SS16 5NL, United Kingdom
Author contributions: Both authors contributed equally to the concept, data collection and manuscript development.
Correspondence to: Dr. Marsha Y Morgan, UCL Institute for Liver and Digestive Health, Royal Free Campus, University College London Medical School, University College, Rowland Hill Street, Hampstead, London NW3 2PF, United Kingdom. marsha.morgan@ucl.ac.uk
Telephone: +44-207-4332873
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Abstract

Significant concerns over the health, social and economic burdens of the two most common, and frequently co-misused drugs of abuse, alcohol and tobacco, has encouraged focused but separate health promotion and disease prevention policies. However, this separation of focus means that while individuals who present with alcohol-related problems are increasingly supported to attain and maintain abstinence from alcohol they are not routinely assisted to refrain from smoking. This is tragically inopportune as alcohol and tobacco have an established "synergistic" effect on aerodigestive cancer risk. Moreover, even when patients successfully tackle their alcohol problems they remain at increased risk for developing these cancers, especially if they continue to smoke. A case series is presented together with a discussion on how service provision for co-misuse could be improved to obviate aerodigestive cancer risk. Given the prevalence of alcohol and tobacco use in the United Kingdom, these observations may have far reaching implications for the individual, health provider(s) and wider society.

Key words: Tobacco; Alcohol; Substance misuse; Co-dependence; Behavioural control; Early intervention; Preventive therapy; Aerodigestive cancer; Mortality

Core tip: What is already known? Most people who drink heavily also smoke; alcohol and smoking synergistically increase aerodigestive cancer risk; people with alcohol problems and/or liver injury, are supported to attain and maintain abstinence, from alcohol but much less effort is employed to help them achieve smoking cessation. What is the key message? Patients who maintain abstinence from alcohol remain at risk for aerodigestive cancers for several years, especially if they continue to smoke. How might it impact on future clinical practice? Smoking behaviour should be addressed in co-dependent individuals if the health benefits of long-term abstinence from alcohol are to be maximized.

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INTRODUCTION

Alcohol consumption and tobacco usage are associated with major health issues and are principle causes of preventable deaths in developed countries. The risks to health they pose are also interrelated. Thus, cigarette smoking is independently related to the risk of developing alcohol-related cirrhosis, with smokers of a pack or more per day at three times the risk compared with lifelong non-smokers[1]. Both behaviours also have a significant effect on cancer risk, particularly the development of aerodigestive tract cancers (*e.g.*, squamous

cell cancers (SCCs) of the oropharynx, larynx, and oesophagus), with the risks correlating to the levels of both alcohol consumption and tobacco usage[2,3]. Moreover, the risk associated with alcohol and tobacco co-misuse is multiplicative or at least greater than additive[4]. Also of significant importance is the fact that the risk of cancer development persists even when behaviours are moderated although with temporal differences. Thus, a favourable effect of smoking cessation is evident within a few years[5], whereas the risk may remain persistently high for several years following abstinence from alcohol[6,7]. This is of particular concern in patient who undergo orthotopic liver transplantation in whom the risk of *de novo* aerodigestive cancers is increased, independently of immunosuppressant use, particularly in those with alcohol-related cirrhosis, a long history of cigarette smoking and continuation of smoking post-transplantation[8-11].

Intervening in addictive behaviours may provide the most effective was of limiting both the health and economic burden of upper aerodigestive cancers. However, despite the fact that some 80% of individuals seeking treatment for alcohol problems also smoke the opportunity to simultaneously address smoking issues is rarely effectively taken. Examples of the consequences of these missed opportunities are presented.

CASE REPORT

Case 1

A 42-year-old Caucasian woman presented in 1993 with a long history of alcohol misuse; her liver biopsy showed cirrhosis. Subsequently she attained and maintained abstinence from alcohol apart from one brief relapse in 1996; her liver disease was well-compensated. She was a long-standing, heavy smoker but declined referral for smoking cessation, only briefly engaging with these services in 2000. In 2001, aged 50 and still smoking, she presented with hoarseness and throat swelling; a diagnosis of SCC of the uvula and soft-palate was made. She underwent curative radical surgery and radiotherapy but was left with significant nasal regurgitation of food. Post-surgery, despite self-reported periods of smoking cessation, she never successfully quit. In 2009, aged 58, she developed anaemia and reflux symptoms secondary to a new mid-oesophageal SCC (T3N1M0). She was not a candidate for surgery due to advanced emphysema, large gastric varices and upper aerodigestive radiation damage that would have made oesophageal resection and anastomosis hazardous. She underwent her first cycle of palliative chemoradiotherapy but died 9-wk from cancer diagnosis with aspiration pneumonia and neutropaenic sepsis complicating endoscopic gastrostomy placement (Table 1).

Case 2

A 50-year-old Anglo-Indian man presented in 2001 with a history of ongoing mental health issues, previous intravenous drug misuse, current marijuana use and alcohol dependence. He had evidence of decompensated cirrhosis secondary to alcohol and newly diagnosis hepatitis C virus (HCV) infection, complicated by the development of subacute bacterial peritonitis (SBP). Following an initial stormy inpatient stay he eventually achieved stable disease with maintained abstinence from alcohol. However, despite efforts to encourage engagement with smoking cessation services he continued to smoke and to use marijuana occasionally. He initially declined antiviral therapy, but in 2007 was eventually and successfully treated for HCV with pegylated (PEG)-interferon and ribavirin. In 2010, aged 59, while still abstinent from alcohol, he presented with hoarseness, peri-tonsillar swelling and cervical lymphadenopathy due to a posterior hypopharyngeal SCC (T4M0N0). This was successfully treated with chemoradiotherapy; he independently quit smoking and remains well with no evidence of recurrence on positron emission tomography (PET)-scanning.

Case 3

A 55-year-old Caucasian man presented in 2000 with alcohol dependence and decompensated alcohol-related cirrhosis complicated by SBP. He was a lifelong heavy smoker and user of marijuana and although he subsequently maintained abstinence from alcohol and moderated his use of marijuana he repeatedly refused to consider smoking cessation. In 2007, aged 62 years, he presented with a cough and worsening shortness of breath; a diagnosis of early small-cell lung carcinoma was made and successfully treated with chemoradiotherapy with no evidence of recurrence to date. In 2011, a solitary small hepatocellular carcinoma was diagnosed on surveillance ultrasound and treated with radiofrequency ablation with no evidence of recurrence to date. Although he remains abstinent from alcohol he continues to smoke.

Case 4

A 46-year-old Caucasian woman presented in 1997 with a history of alcohol misuse, jaundice and ascites; she had cirrhosis on liver biopsy. Her initial hospitalisation was complicated by torrential haemorrhaging from a posterior, penetrating duodenal ulcer requiring gastroduodenal artery embolisation. Following discharge she maintained abstinence from alcohol and her liver disease stabilized with normalization of her liver function tests. However, she remained a heavy smoker despite medical advice to quit. In 2008, aged 57, she presented to her general practitioner with a history of painful neck swelling, otalgia and hoarseness. This failed to resolve with repeated courses of antibiotics but she was not referred for specialist review until she attended for her routine hepatology surveillance some 7 mo later. A diagnosis of laryngeal SCC (T1M0N0) was made and she underwent 2 mo of local radiotherapy. She independently quit smoking at cancer diagnosis but a year later was found, on surveillance imaging, to have a bronchogenic cancer (T1N0M0) and underwent further radiotherapy. In 2010 she developed faecal peritonitis secondary to a perforated sigmoid diverticulum and required a right hemicolectomy

Table 1 Details of the drinking and smoking behaviours of six patients with alcohol-related cirrhosis who developed aerodigestive cancers

Case	DoB	Sex	Alcohol misuse		Tobacco use		Age at diagnosis		Cancer	Misuse intervention					Cancer
											Smoking		Alcohol		
			Years	Units/wk	Pack years	cpd	Cirrhosis	Cancer		Provided yes/no	Quit (yr)	Relapsed (yr)	Abstinent (yr)	Recidivism	
1	1951	F	25	120	40	20	42	50	Uvula/soft palate SCC	Yes	0.3	Yes	7	No	Died
								58	Oesophageal SCC						
2	1951	M	30	100	18	10	50	59	Hypopharyngeal SCC	No	No	NA	8	No	Remission
3	1945	M	35	250	65	35	55	62	Small-cell lung cancer	No	No	NA	7	No	Remission
								65	HCC						Remission
4	1951	F	29	100	19	30	46	57	Laryngeal SCC	No	No	NA	12	No	Remission
								58	Bronchial carcinoma						Remission
5	1947	M	37	70	15	10	57	60	Posterior triangle neck SCC (unknown primary)	Yes	6	2	1	No	Remission
6	1947	F	22	200	63	40	52	64	Oesophageal SCC	Yes	No	NA	14	No	Remission

DoB: Date of birth; cpd: Cigarettes per day; HCC: Hepatocellular carcinoma; SCC: Squamous cell carcinoma; NA: Not applicable; F: Female; M: Male.

with colostomy. She is now well with no evidence of persistent or recurrent laryngeal or bronchial malignancy at follow-up. Of interest, her older sister, who had also been a heavy smoker and drinker, died from bronchial carcinoma five years after a successful liver transplant for alcohol-related cirrhosis.

Case 5

A 57-year-old Caucasian man initially presented in 2004 with a long history of alcohol and tobacco misuse, severe lethargy and abnormal liver function tests. He was found to have HCV infection secondary to prior drug misuse; his liver biopsy was consistent with cirrhosis secondary to both alcohol and HCV. In 2006 he was admitted for medically assisted withdrawal from alcohol and after 6 mo abstinence from alcohol was started on treatment for his HCV with PEG-interferon and ribavirin. He achieved an early viral response but at 3 mo he developed tender, rubbery lymph glands in his right neck diagnosed as a SCC of unknown origin (TxM0N3); the primary was never discovered despite extensive investigations including MRI and PET scanning and bronchoscopy. The antiviral therapy was stopped; he underwent radical block dissection of his right neck, a bilateral tonsillectomy and local radiotherapy. He stopped smoking at cancer diagnosis, although he admitted to occasional marijuana use. In 2008, despite support, he became depressed and returned to drinking, albeit at a lower level than previously. There are no sign of cancer reoccurrence, to date.

Case 6

A 50-year-old Caucasian woman of Polish origin was referred to our dermatology service in 1997 with spider naevi; on enquiry she admitted to a 22-year history of heavy drinking although she had stopped some 8 mo prior to presentation. Her initial liver biopsy showed severe hepatic fibrosis but by 1999 this had evolved to cirrhosis despite continued abstinence from alcohol. She smoked 40 cigarettes per day and did not wish to stop. In July 2011, having been abstinent from alcohol for 14 years, she presented with a 2.5 mo history of increasing dysphagia and a diagnosis of a mid-oesophageal carcinoma was made. Her cirrhosis was well-compensated with no clinical, radiological or endoscopic evidence of portal hypertension. Nevertheless she was not felt to be a candidate for surgery as she had limiting smoking-related emphysema. She underwent 3 mo of chemoradiotherapy and, when last reviewed, was in remission. She stopped smoking after cancer diagnosis.

DISCUSSION

Over the last 40 years the incidence of upper aerodigestive cancers has increased while mortality rates have shown little improvement despite earlier intervention with chemoradiotherapy and/or surgery[12]. Alcohol consumption and tobacco usage are the two most important risk factors for the development of these cancers and they are frequently co-misused.

Tobacco smoking is by far the most important risk factor for cancer in the United Kingdom and in 2010, was responsible for 61000 cases, equivalent to 19.4% of all new cancer diagnoses. This included 4500 oropharyngeal, 5600 oesophageal and 1700 laryngeal cancers, in addition to 34600 lung cancers[13,14]. The risk of developing upper aerodigestive cancers increases in relation to the amount and duration of tobacco use[2,4,7]. Thus, the RR of developing oral cancers increases threefold from 5.3 to 18.0 when usage increases from < 15 to 40 cigarettes per day.

Alcohol consumption is the fourth most important cause of cancer in the United Kingdom and in 2010 was responsible for 12500 cases of cancer equivalent to 4.0% of all new cancer diagnoses, including around 2100 oropharyngeal, 1760 oesophageal and 540 laryngeal cancers[13,14]. The risk of developing aerodigestive cancers, as with tobacco, increases with the amount and duration of exposure; thus increasing daily consumption from 25 to 100 g trebles the RR from 1.7 to 6.0[15]. Significantly, the risk of developing upper aerodigestive cancers with co-dependent tobacco and alcohol use is multiplicative and may increase by as much as 300-fold[16].

Currently, in the United Kingdom, 22% of men and 21% of women are smokers[14], while 33% of men and 16% of women regularly drink in excess of recommended guidelines in excess of recommended guidelines[17]. Thus, a substantial number of individuals are at risk for these essentially preventable cancers. Although the risks decrease with abstinence from alcohol and smoking cessation these patients remain at risk for several years and, as illustrated in the present cases, the multiplicative risk may not decrease substantially if one of the behaviours is retained.

Co-misuse and carcinogenesis

Alcohol itself is not a carcinogen, but its first endogenous metabolite, acetaldehyde, is genotoxic and causes DNA damage due to N^2-ethyl-2'-deoxyguanosidyne stable adduct formation[18,19]. Many microbes in the oral flora possess alcohol dehydrogenase (ADH) activity and are able to oxidize ethanol to acetaldehyde. However, their ability to remove it is limited, thus potentiating its local carcinogenic activity. Furthermore, human oral and oesophageal mucosa has been shown to possess high Km ADH activity but to lack low Km aldehyde dehydrogenase activity favouring the accumulation of acetaldehyde in the saliva and upper digestive tract in the presence of alcohol. Tobacco smoke is a direct source of acetaldehyde; its concentration is more than 1000 times greater than that of the other well known constituent carcinogens, *e.g.*, polycyclic aromatic hydrocarbons (PAH) or tobacco-specific nitrosamines. Chronic smoking modifies the oral flora favouring greater production of acetaldehyde from ethanol. Thus, upper digestive tract exposure to acetaldehyde increases further with concomitant alcohol and tobacco usage.

Alcohol, when taken habitually in high amounts, activates the cytochrome P450 enzymes system. As many of the pro-carcinogens in tobacco smoke require enzymatic activation to exert their carcinogenic activity alcohol may change the carcinogen activation pathway related to these substances. In addition, the solvent properties of ethanol can also facilitate the contact of substances dispersed in smoke with the mucosa.

Locally, alcohol can also affects cellular membrane permeability and acts as a liquid phase into which carcinogens diffuse, thereby facilitating their penetration into the intracellular domain of mucosal epithelial cells in the mouth. The increased membrane permeability causes changes in the diffusion/uptake patterns of other substances for which ethanol can also act as solvent.

Three of the six patients in this series (cases 2, 3 and 5) were also heavy marijuana users. Inhaled marijuana smoke contains various carcinogens some, including PAH and acetaldehyde, in concentrations up to 50% higher than in tobacco smoke[20]. Thus, the use of marijuana has been implicated in cancer development by direct DNA damage. Conversely, marijuana smoke also contains cannabinoids which have been shown to have anti-neoplastic properties[21]. Little is known about the effects of these competing factors. However, in a recent case-control study[22], marijuana smokers with consumption histories of between 10 and 20 years of continuous use demonstrated a significantly reduced risk for the development of head and neck SCC, compared to nonusers. Drinkers and tobacco users who also smoked marijuana retained a high but attenuated risk for the development of these neoplasms. Little is known, however, about the cellular and molecular pathways affected by these complex associations[20].

Intervening in co-misuse

Multiple environmental pressures act on genetic factors to alter addictive behaviour. In twin studies there is an approximately 60% likelihood of alcohol or tobacco misuse in those with a family history of dependence[23]. Both substances modify the activity of the mesolimbic dopamine system and this may explain features such as mutual cravings, cross-tolerance[24], and the reinforcement and reward effects. The frequency of co-dependence attests also to a degree of interdependence[25].

It has been shown that smoking cessation improves alcohol-related outcomes, with a possible 25% increase in the likelihood of long-term abstinence, most likely due to more intensive clinical contact, reduced triggers for misuse, behavioural skills practice, and a healthier lifestyle[26]. Nevertheless, smoking behaviour is frequently ignored

in individuals presenting with alcohol-related problems for a variety of reasons including: a lack of resources, professional apathy, poor training, a perception that this approach is ineffectual or simply that quitting alcohol and tobacco simultaneously is too difficult.

However, despite the acknowledged difficulties, smoking behaviour should be address in co-dependent individuals if the health benefits of long-term abstinence from alcohol are to be maximized.

Sequential vs simultaneous smoking cessation programs

Ellingstad *et al*[27], reported that over three quarters of alcohol abusers who also smoked would be willing to consider smoking cessation during or after treatment for their alcohol problems.

The merits of simultaneous tobacco treatment *vs* sequential treatment for alcohol-dependent patients are unclear. Seidner *et al*[28], found that those who accepted, or would consider concurrent treatment for smoking and substance use were more confident in their ability to stop smoking, had more smoking quit attempts, were more likely to believe that quitting smoking would benefit the resolution of their substance abuse problem, and were more likely to believe that the best time to quit smoking was during treatment or in the following 6 mo. However, some argue that concurrent treatment may be of limited impact, or even detrimental to achieving abstinence from alcohol[29-31]. Thus, Joseph *et al*[30], randomized 499 patients undergoing intensive treatment for alcohol abuse/dependence to smoking intervention in the form of individual behavioural counselling and nicotine replacement, delivered either concurrently or else delayed for 6 mo. Participants in the concurrent treatment group were significantly more likely to participate in smoking treatment than the delayed group (79% *vs* 65%). However, abstinence rates in the concurrent group were significantly lower at both 1 mo (51% *vs* 64%) and 6 mo (41% *vs* 56%). Nonetheless, there were no significant differences in smoking cessation rates (approximately 12%-14%) or in abstinence rates (41% *vs* 48%) between the two groups at 18 mo[30].

The concern that smoking cessation interventions might compromise sobriety were not confirmed in a systematic review and meta-analysis of 19 randomised controlled trials which showed that combined intervention was associated with a 25% increased likelihood of long-term abstinence from alcohol; this effect was observed independently of long-term smoking cessation[26]. Smoking cessation interventions were successful in the short term whether provided simultaneously or sequentially. Nevertheless, at 6 mo there was no significant treatment effect irrespective of when they were delivered. However, the strikingly low overall quit rate (3%) among smokers assigned to control groups suggests that few participants will likely attempt cessation on their own[26]. Also noticeable was the fact that treatment success rates were noticeably higher in programmes providing nicotine replacement therapy[26]. Overall these finding support the provision of smoking cessation interventions without fear that sobriety will be detrimentally affected.

Management of nicotine addiction in patients with alcohol misuse

It is estimated that 80% to 90% of individuals with alcohol problems smoke cigarettes[25,27]. Current evidence suggests that public health interventions that discourage both smoking and drinking are likely to be more beneficial than addressing the problems individually[7]. Failure to address smoking issues when dealing with patients with alcohol-related problems might convey the message that smoking cessation is not a priority for recovery or health. It is, however, particularly difficult for individuals with a history of alcohol misuse to maintain smoking cessation in the longer term[32]. Standard treatment with 8 to 12 wk of counselling and nicotine replacement therapy is better than no treatment. However, the success rates in this population are low and more sustained and intensive regimens are likely to be needed. Pharmacotherapy, particularly with the newer agents such as bupropion and varenicline needs to be used with caution particularly in patients who may have sustained alcohol-related liver or brain damage[33]. There is, therefore, still a need to identify: (1) the optimal timing and method for engaging alcohol misusers into smoking treatments; (2) effective treatment strategies for this population, including motivational, cognitive and behavioural, and pharmacological interventions; (3) methods for integrating smoking cessation interventions within treatments for alcohol misuse/dependence; and (4) the feasibility of staff providing alcohol treatment services also providing smoking cessation interventions.

In conclusion, alcohol consumption and smoking act synergistically to increase the risk of upper aerodigestive cancers. This risk could be significantly reduced with timely intervention and treatment for both addictions. There is a need to raise awareness amongst healthcare professionals of the impact of not addressing the issues of multiple drug addictions and the need to create more focused treatment and prevention strategies.

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