Oral cancer and tobacco: developments in harm reduction

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Key points

- Informs readers of the development of nicotine containing products.
- Informs readers of the carcinogenic potential of these nicotine containing products.
- Allows dentists to have informed discussion of these products with their patients who smoke.

Oral squamous cell carcinoma is associated with the use of tobacco products. The predominant addictive substance in tobacco is nicotine, however, the major carcinogenic substances are in the other components of the tobacco leaf. The highest risk from tobacco use arises from combustion in the form of cigarettes. While cigarette consumption remains prevalent in the developing world, in the UK the rates of smoking are falling. In Sweden, modified smokeless tobacco in the form of snus has been available for many years and has contributed to reduced levels of smoking. In high income countries, new forms of tobacco consumption and nicotine delivery products have been developed over the last few years. These include heat-not-burn cigarettes and electronic cigarettes, and these products are now being actively marketed by many companies, including the tobacco industry. This paper reviews this changing pattern of tobacco and nicotine consumption and the current evidence regarding the risk of these products causing oral cancer.

Introduction

The consumption of tobacco has been recognised as increasing the risk of head and neck cancer for many years, alongside other risk factors including alcohol.[1,2] Tobacco smoking is also strongly linked with cancer of the lung, chronic obstructive airways disease and cardiovascular disease. Tobacco has traditionally been consumed in several forms. It has frequently been used in products where it is burnt and smoked, including factory-made cigarettes and cigars, as well as loose tobacco in pipes or hand-rolled cigarettes. Tobacco has also been used in other ways. Smokeless tobacco has been popular in the developing world where it is placed in contact with mucous membranes usually in nasal snuff or placed in the oral vestibule, either loose or in a packet. The use of smokeless tobacco in this way is common to many parts of the world and is associated with increased risk of squamous cell carcinoma.[3] In developing countries in south-east Asia, the tobacco is frequently mixed with other ingredients, especially in the form of betel quids. These are prepared from areca nut and slaked lime, wrapped in a Piper betel vine leaf, with tobacco a frequent component of the mixture as well. In these betel quids both the tobacco and the areca nut have carcinogenic potential and their use increases the incidence of oral squamous cell carcinoma.[4] In all forms of tobacco use the addiction formed is predominantly to the nicotine component.

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Tobacco, nicotine and carcinogenesis

In tobacco smoke, over 300 carcinogens have been identified which will dissolve in saliva.[1] These include the aromatic hydrocarbon benzpyrine and the tobacco specific N-nitrosamines including four (metylnitrosamino)-1-3-(3-pyridyl)-1-butanon (NNK) and N-nitrosonornicotine (NNN).[5] Such carcinogens are generated when tobacco is burnt but also to a limited extent from some smokeless tobacco. They act on the oral mucosa and are absorbed and cause damage in many body systems. There is damage to all replicating cells.

The primary component of tobacco responsible for addiction is nicotine. Nicotine is readily absorbed across the epithelium of the oral mucosa, the nose, the lungs and the skin. Its half-life in plasma is approximately two hours.[6] The majority of nicotine absorbed is metabolised in the liver before elimination via renal excretion. Nicotine binds to nicotinic acetycholine receptors (nAChR's) in the brain.[7] This binding is involved in the rewarding effects of nicotine. Receptor adaption occurs in response to chronic exposure with release of dopamine which gives rise to dependence and to withdrawal responses.[8] While nicotine is the primary addictive substance in tobacco, its role as a potential carcinogen is unclear. It is clearly not a major carcinogen in comparison to other tobacco products such as NNN or NNK, although there is on-going debate based on theoretical and animal studies as to its exact cancer inducing potential, if any.[9]

Over the last 70 years since the link between smoking and lung cancer was identified, the UK has been slowly regulating the promotion

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Table 1 Tobacco risk identification and regulation in the UK	
Year	**Risk and identifcation**
1954	Doll and Bradford Hill publish paper identifying link between smoking and lung cancer
1965	Television advertising of cigarettes banned in the UK
1971	Health warnings on cigarette packets introduced
1986	Cinema advertising of cigarettes banned in the UK
1997	Ban on tobacco advertising in all media
2007	Ban on smoking in enclosed public places in England
2017	Standardised logo-free cigarette packaging introduced

Fig. 1 Snuff-dippers lesion in the maxillary sulcus.

of tobacco in an attempt to reduce consumption (Table 1). Alongside this approach it has been recognised that nicotine is the ingredient that causes the addiction. Several attempts have been made to produce products that satisfy the nicotine addiction while minimising the harmful effects associated with tobacco. Since the 1980s, pharmacological grade nicotine replacement products have been developed and promoted as aids to patients in quitting smoking. These are available as chewing gum, oral and nasal sprays, sub-lingual lozenges, inhalators and transdermal patches and are available both on prescription and as over the counter purchases.[10] They are widely advocated by smoking cessation clinics as they improve quit rates compared to relying on willpower alone.[10] They are generally regarded as safe to use long-term when nicotine addiction cannot be fully overcome.

Snus

In Sweden, a modified form of smokeless tobacco called snus has been used for many years. Newer manufacturing methods for snus were developed in the 1970s by the then government owned tobacco monopoly. The aim was to produce a smokeless tobacco with much lower levels of toxicants including nitrosamines, than traditional tobacco products. In addition, the Swedish government, while making no health claims, initially allowed snus to be taxed at a lower rate than cigarettes. As such, it was advocated that use of snus would be a less dangerous alternative to smoking in those addicted to nicotine.

The use of snus over such a long period has given us data on the effects of long-term use of one form of a modified tobacco product used to deliver nicotine to the user. The balance of the evidence is that snus use is significantly less harmful than smoking. An association with a poorer outcome from cardiovascular disease has been identified although whether this is a direct effect of snus use or a result of confounding by other factors is unclear.[11,12] The risk of oral cancer developing from the use of snus appears to be low. Epidemiological studies do not show an increase in oro-pharyngeal cancer with, for example, a long-term follow-up study of 1115 individuals with snuff-dippers lesions (Figure 1) not found to show development of cancer at the site of the lesions observed.[11,13] However, in 2012 a paper described 16 male patients seen in Swedish hospitals, all with oral squamous cell carcinomas reported to have developed at the exact anatomical location of snus placement in the buccal vestibule in the mouth.[14] The mean duration of snus use before cancer diagnosis was 42.9 years. Six patients also had a history of smoking. While the reported cases raises concern there is difficulty in interpreting this case series in the light of the epidemiological evidence, and the consensus remains that any increased risk is small.[11]

There have been public health concerns regarding the use of snus, however, including questions such as does it increase the total prevalence of tobacco use, does it serve as a gateway to cigarette smoking and does it reduce smoking cessation? A recent epidemiological study has looked at these issues.[15] By 1996 the use of snus in men exceeded cigarette use, although its use in women remained uncommon.[15] Rates of smoking have reduced to 11% among women and 10% among men.[15] These rates of daily smoking are the lowest in Europe, with a European average of 28%.[16] In England, adult smoking prevalence in 2016 was 15.5%.[17] The Swedish pattern of declining smoking and increasing snus use has also occurred in Norway where snus is available.[18]

People who commenced daily tobacco use with snus have been found to be much less likely to take up smoking that those who had not.[15] Furthermore, among smokers who started using snus over 70% stopped smoking completely including over one third who quit all forms of tobacco use.[15] These data indicate that snus has contributed to decreased initiation of smoking rather than serving as a gateway to smoking.

Tobacco and nicotine use: worldwide trends

In the developing world cigarette usage is increasing. The near monopoly China National Tobacco Corporation is now the world's largest manufacturer of cigarettes and its products

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contribute 7–10% of total government revenues.[19] China's tobacco industry now has more than 30 factories abroad, including Africa and Asia where markets are still developing.

In high income countries, including the UK, the use of tobacco and nicotine addiction is changing. The use of tobacco in products where it is burnt to release its nicotine, such as cigarettes, is reducing as other forms of tobacco usage and nicotine delivery products are becoming more popular. Two of these developments are the growing popularity of electronic cigarettes (e-cigarettes) and the development of heat-not-burn tobacco products.

New developments and regulatory control

In most parts of the UK, tobacco products and e-cigarettes have a minimum age of sale of 18 years and they cannot be purchased on behalf of someone under the age of 18. In the UK, the Tobacco and Related Products Regulations 2016 transposed the European Union Tobacco Products Directive into law. This legislation also covers e-cigarettes that do not contain nicotine when sold (including disposable e-cigarettes and 0% nicotine e-liquids) and products that do not have a medicinal licence. These regulations include minimum standards for safety and quality of e-cigarette products, standards for information provision (such as a warning notice if containing nicotine) and advertising restrictions including the banning of advertisements for e-cigarettes in print, broadcast and online media. In May 2017, further restrictions from this legislation came into force with respect to e-cigarettes. These include: restricting e-cigarette tanks to a capacity of no more than 2 ml; requiring nicotine containing products to be child resistant and tamper evident; banning certain ingredients including colourings and caffeine; and requiring all e-cigarettes and e-liquids to be notified to the Medicines & Healthcare products Regulatory Agency before they can be sold.

Heat-not-burn cigarettes

Heat-not-burn (HNB) cigarette products are a recent addition to the tobacco market, being developed and marketed by tobacco companies. They heat tobacco to a lower temperature compared to conventional cigarettes where tobacco is burnt.[20] The aim is to produce a tobacco aerosol product that matches the sensation and behavioural aspects of tobacco smoking while reducing the intake of carcinogenic products found in burnt tobacco.

The first commercial HNB cigarette was the RJ Reynolds Premier, launched in 1998 which was withdrawn from the market a year later after a poor reception by smokers and regulatory authorities. Over the subsequent years the tobacco companies have developed new HNB products that are now becoming available. Most are designed to be similar in style to a traditional combustible cigarette. Some are designed to be a tobacco stick along with a heating element, whereas others use loose-leaf tobacco that is placed in a chamber and electrically heated using an element. Some of the most prominent products are Glo and iFuse made by British American Tobacco (BAT) and iQOS (I-quit-ordinary-smoking) made by Philip Morris International (PMI). Glo uses a product that looks like a short and thin traditional cigarette that comes with an electronic heater about the size of an iPod. The cigarette is placed in the heater while being inhaled. iFuse is the size of a large pen with the battery incorporated into the body of the product which heats a liquid into vapour which is then passed through the tobacco before being inhaled. iQOS is designed so that a tobacco heatstick is heated in a holder the size of a large pen while being inhaled. The holder is recharged by a charger. In these products the tobacco is warmed to less than 350 Celsius, significantly lower than when a cigarette is burnt but warm enough to generate smoke vapour.[20] Both iFuse and iQOS products are the only HNB products currently available in the UK.

Both BAT and PMI have been using Japan as a test centre for these products over the last few years.[21] iQOS and Glo now account for over half of BAT and PMI sales in the test city of Sendai where they are being heavily marketed. Japan is still a major market for tobacco as over 30% of men smoke.[22] Regulation of tobacco products is light and Japanese customers are open to new hi-tech products and electronic cigarettes have not yet made a significant impact. The big tobacco firms appear to see HNB cigarettes as the future of tobacco consumption in developed markets. They expect steadily increasing sales and PMI have already declared that they are aiming to phase out their traditional cigarettes from some markets.[23] Tobacco companies hope that profit margins may be greater than for traditional cigarettes as they expect buyers will need to replace their microheaters every few years and will wish to purchase accessories to personalise their equipment.[22]

The health risks of heat-not-burn cigarettes are unclear. Much of the research has been undertaken by the tobacco companies, and are laboratory based as the products have not been available long enough for us to fully understand their effect on health. They are, however, being marketed by their manufacturers as a less harmful alternative to conventional cigarettes. Nicotine levels are thought to be lower.[24] The HNB tobacco aerosol does include carcinogens although these have been found to be at a lower level than the smoke from ordinary cigarettes.[25] Concern has also been raised regarding evidence of pyrolysis and release of a toxicant from the polymer-film filter.[26] There are currently no data on the risk of HNB cigarettes with respect to oral cancer. The aerosol from HNB tobacco products has been found to have a lower impact on the pathophysiology of various oral epithelial cultures compared to cigarette smoke.[27–29]

In the UK, the Committee on Toxicology, which offers independent scientific advice to the UK government, reported its comprehensive toxicological assessment of HNB products in December 2017.[20] It reported that the HNB products investigated showed a decrease in the harmful and potentially harmful compounds (HPHCs), including carcinogens, to which the user would be exposed compared to the HPHCs from a conventional cigarette. The reduction was judged to be between 50% and 90% of HPHCs. It further reported that while some of the measured HPHCs increased environmental exposure to bystanders, the exposure levels were much less than from conventional cigarettes.

Electronic cigarettes

E-cigarettes were originally developed in a commercial form in China around 2003.[30] They were designed to be an aid to smoking cessation as a new form of nicotine replacement therapy. The aim was for the nicotine aerosol to replace the nicotine in the tobacco smoke while also recreating the sensation and behavioural aspects of addiction in smoking cigarettes. Since then there has been a rapid development in their design and use. There is a lack of standard nomenclature surrounding their composition and usage. The terms electronic cigarette and e-cigarette are interchangeable. They are characterised by a device with a heating element that produces an aerosol from a liquid that users can inhale. Even though originally designed to deliver nicotine, the liquids used in e-cigarettes can also be nicotine

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free. The 'e-liquid' or 'e-juice' is stored in disposable or refillable storage reservoirs. The e-liquid usually comprises of propylene glycol and/or glycerol, with or with-out nicotine, and with or without flavourings. E-cigarette usage can be described as 'vaping'.

The first generation of e-cigarettes are frequently called 'mini e-cigarettes' or 'cigalikes'. They were purposefully designed to look and feel like a conventional cigarette. Initially, multiple manufacturers started making e-cigarettes with variable quality of product and aerosol produced, and many delivered only small amounts of nicotine in comparison to conventional cigarettes. Smokers who used them to try and quit smoking frequently found the nicotine substitution to be inadequate. More recently, the technology involved has generally improved with better delivery of nicotine on vapour inhalation. In addition, the large tobacco companies have started to invest in e-cigarettes; for example, BAT vaping products now include Vuse, the most popular brand in the USA, and Vype, the most popular brand sold in pharmacies in the UK.

The second generation of e-cigarettes developed are called 'vape pens' or 'tanks'. These look like larger mini e-cigarettes but come with a stronger battery and a re-fillable e-liquid reservoir instead of a pre-filled cartridge. This means that more flavour options are available and a denser vapour cloud can be produced on exhalation. The third generation of e-cigarettes are frequently called 'vape mods'. These are increasingly popular. They have a larger battery and can store more e-liquid. They allow flexibility in power usage thus producing a range of density of aerosol volume according to vapour preference. Due to the volume of aerosol produced, the e-liquids used are usually low in nicotine concentration and this type of e-cigarette is particularly popular with users of non-nicotine e-liquid.

Over the past few years, e-cigarette usage has plateaued at around 6% of the adult UK population.[17] The most common reason for e-cigarette usage is as an aid to reducing smoking conventional cigarettes and smokers who use them generally have more motivation to quit than other smokers.[17]

Table 2 Comparison of conventional cigarettes, heat-not-burn (HNB) cigarettes and e-cigarettes

Conventional cigarettes	HNB cigarettes	e-cigarettes
Tobacco containing	Tobacco containing	Tobacco extract, or non-tobacco, containing
Nicotine containing	Nicotine containing	Nicotine or non-nicotine containing
Burning of tobacco (>800°c)	Heating of tobacco (<350°c)	Heating of e-liquid
Smoke generated	Predominantly aerosol generated	Aerosol generated
Smoke contains significant levels of carcinogens	Aerosol contains some carcinogens	Aerosol contains low or insignificant levels of carcinogens

E-cigarettes and smoking cessation

The relatively recent invention of e-cigarettes has limited our knowledge about how helpful they are for quitting smoking and what their long-term health effects will be. A Cochrane review of randomised controlled trials of e-cigarettes for smoking cessation published in 2016, found that e-cigarettes with nicotine might help people stop smoking compared to placebo e-cigarettes without nicotine (9% abstinence versus 4% abstinence).[31] The conclusions, however, were hampered by the small number of trials and the first generation cigarettes used which are no longer available because of poor nicotine delivery.[32,33] Uncontrolled studies have shown higher quit rates.[31] In 2017, quit rates in England were at their highest rates so far observed and for the first time, parity across different socio-economic groups was observed.[17] It has been postulated that e-cigarettes have contributed to this.[17] In its recent guidance on smoking cessation interventions, NICE cautiously supported the use of e-cigarettes for this purpose (Box 1).[34]

Box 1 NICE: advice on e-cigarettes for health workers in primary care settings[34]

For people who smoke and who are using, or are interested in using, a nicotine-containing e-cigarette on general sale to quit smoking, explain that:

- Although these products are not licenced medicines, they are regulated by the Tobacco and Related Products Regulations 2016.
- Many people have found them helpful to quit smoking cigarettes
- People using e-cigarettes should stop smoking tobacco completely, because any smoking is harmful
- The evidence suggests that e-cigarettes are substantially less harmful to health than smoking but are not risk free
- The evidence in this area is still developing, including evidence on the long-term health impact

General health concerns associated with e-cigarettes

The true long-term effects of e-cigarettes remain unclear. Over the recent past, different reports of experts on e-cigarette usage and their effects show some uncertainty. Two thirds of deaths associated with smoking are from heart disease and non-cancerous lung conditions. The predicted effect of e-cigarette usage on these diseases is generally less clear than the expected benefits with respect to cancer. In the UK, a 2016 Royal College of Physicians report, based on comparisons of carcinogens and toxicants in tobacco smoke and e-vapour, estimated that the harm arising from long-term e-cigarette vapour inhalation is unlikely to exceed 5% of the harm from smoking cigarettes.[35] A recent Public Health England publication on this subject has echoed this viewpoint.[17] However, the opinion of a recent US Academy report is more cautious.[36] In addition, this report expresses concern about e-cigarettes acting as a gateway for introducing new generations to nicotine addiction. All reports, however, conclude that except for nicotine, under typical conditions of use, exposure to potentially toxic substances from e-cigarettes is significantly lower compared with combustible tobacco cigarettes. In addition, there appears to be minimal risks from second-hand vapour to the health of bystanders.

E-cigarettes and oral cancer

Given the relatively recent introduction of e-cigarettes, there is a paucity of evidence on the long-term effects of e-cigarettes on all smoking related cancer outcomes, including oral cancer. The evidence base at present relies predominantly on *in-vitro* studies and theoretical modelling. The main carcinogens in tobacco smoke, such as NNK and NNN, are not found in e-cigarette vapour. Other chemical

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constituents of e-cigarette aerosols such as reactive aldehydes can react with DNA and can be carcinogenic. However, the relatively low exposure of these chemicals, combined with their relatively low carcinogenic potential suggest that the cancer risk from long-term use of e-cigarettes is likely to be low.

A paper published in the journal *Oral Oncology* in 2016 by Yu *et al.*[37] raised concerns that e-cigarette vapour had significant carcinogenic potential and this paper received widespread attention in the medical and wider press. The paper has since undergone critical review and while it is agreed that the evidence shows that e-cigarette vapour is not inert and can lead to damaging effects, the effects of cigarette smoke are significantly more damaging.[38] A comparison of conventional cigarettes, HNB cigarettes and e-cigarettes is given in Table 2.

Conclusion

In high income countries the use of conventional cigarettes is in decline and this is likely to continue. The decline is likely to be a response to multiple factors including taxation, regulation and public health messages, and in due course this should lead to a reduction in the incidence of tobacco-related oral cancer. New alternative forms of nicotine consumption are being developed including heat-not-burn cigarettes and e-cigarettes. Our knowledge of the long-term health risks involved in these new products is still developing, however, from our current understanding, electronic cigarettes represent a significantly safer form of nicotine consumption with markedly reduced carcinogenic potential. Electronic cigarettes are now starting to be recommended as part of smoking cessation strategies.

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