

Oral health risks of tobacco use and effects of cessation

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The purpose of this paper is to review the epidemiologic evidence for the effects of tobacco use and tobacco use cessation on a variety of oral diseases and conditions. Exposures considered include cigarette and bidi smoking, pipe and cigar smoking, and smokeless tobacco use. Oral diseases and disorders considered include oral cancer and precancer, periodontal disease, caries and tooth loss, gingival recession and other benign mucosal disorders as well as implant failure. Particular attention is given to the impact of tobacco use cessation on oral health outcomes. We conclude that robust epidemiologic evidence exists for adverse oral health effects of tobacco smoking and other types of tobacco use. In addition, there is compelling evidence to support significant benefits of tobacco use cessation with regard to various oral health outcomes. Substantial oral health benefits can be expected from abstention and successful smoking cessation in a variety of populations across all ages.

Key words: Smoking, smokeless tobacco, oral cancer, pre cancer, periodontal disease, tooth loss, implants, dental caries, smoking cessation

Tobacco is used in a variety of ways, mostly as smoked, but many populations use smokeless tobacco, which comes in two main forms; snuff (finely ground or cut tobacco leaves that can be dry or moist, loose or portion packed in sachets) and chewing tobacco (loose leaf, in pouches of tobacco leaves, plug or twist form). This review examines the oral health risks of both smoked and smokeless tobacco.

This literature review aims to present published evidence regarding our current understanding of the epidemiology, aetiology and pathogenesis of tobacco use-related disorders. In addition we also review significant improvements in oral health following cessation. The focus of the review is on the adverse effects of tobacco on several oral disorders including oral cancer, other oral mucosal disorders, periodontal disease and tooth loss, and how tobacco affects clinical management

such as implantology, and to discuss the oral health benefits of tobacco cessation.

Smoking

Oral cancer

Among sites that have been considered to be at highest relative risk for cancer due to smoking is the lung. Following lung cancer the highest relative risks are observed for the larynx and oral cavity¹. The risk of oral cancer has increased in recent decades in many countries in the world². In those countries in which epidemiological studies have been conducted, it is clear that oral cancer risk is high among smokers. A recent meta-analysis reported 12 studies that estimated oral cancer risk in the USA, Uruguay, Italy, Sweden, India, China, Taiwan

and Korea³. The reported pooled cancer risk estimate was 3.43 times higher in smokers compared with non-smokers (95% CI 2.37, 4.94) (*Figure 1*). The results for risks associated with tobacco smoking were generally consistent across countries entered into the meta-analysis except in the study conducted among females in Sweden⁴. In a study reported from Northern Italy, the single factor with the highest attributable risk was smoking, which accounted for 81-87% of oral cancers in males and for 42-47% in females⁵. It is evident that oral cancer risk is related to both intensity and duration of tobacco smoking. The differential risk between non-smokers and heavy smokers, and the steady progression of risk with increasing amount smoked both provide sufficient evidence for tobacco as a major risk factor for oral cancer. Furthermore most studies show an inverse relation with age when starting to smoke. Among young people in southern England, a significant risk among males (alcohol adjusted OR: 19.5, 95%CI 1.3,286.8) was associated with starting to smoke under the age of 16

years⁶. These risks are also increased synergistically with alcohol consumption. However, among never drinkers, cigarette smoking was associated with an increased risk of 2.13 (95% CI 1.52,2.98) confirming an independent association with tobacco use⁷. This had also been demonstrated in an earlier study among 19 cases and 213 controls who described themselves as non-drinkers; the ORs were 3.8 (95%CI 0.2, 58.2) and 12.9 (95%CI 2.3,106.3) for smokers of <15 and \geq 15 cigarettes per day, with a strong trend⁸.

In many European and US studies the risks for oral and oropharyngeal cancers are similar for cigarette and cigar smokers⁹. Smoking bidi (hand-rolled Indian cigarette consisting of flaked tobacco rolled in temburni leaf) is a common practice in India and this may be relevant for Indian ethnic migrants to Europe. A meta-analysis has shown that the risk of oral cancer associated with bidi smoking is about three times higher compared with cigarettes¹⁰.

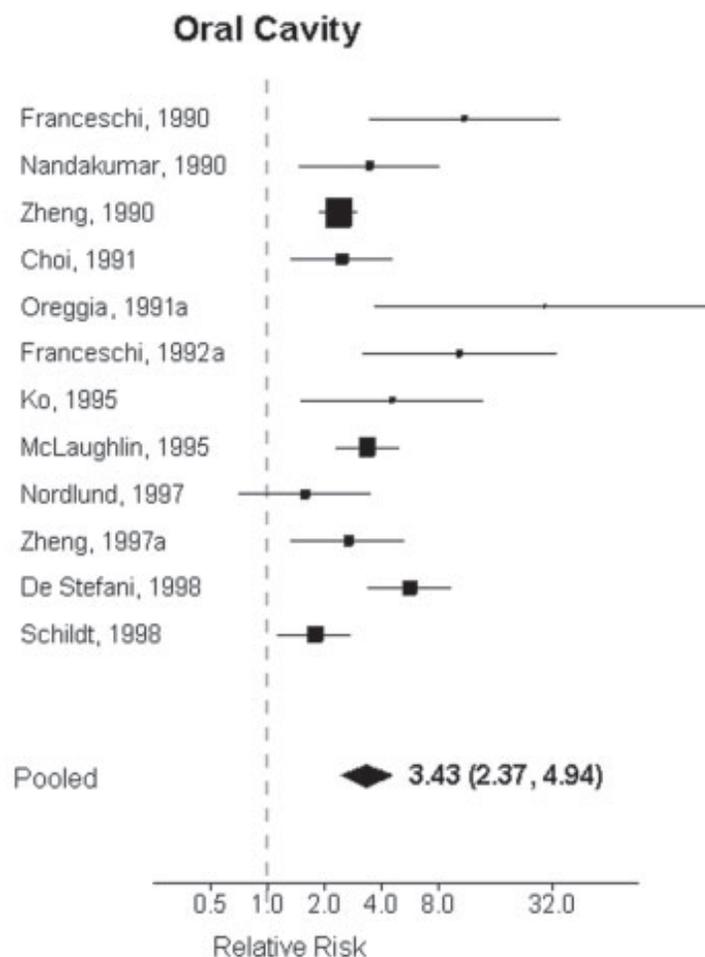


Figure 1. Forest plot for current smokers and oral cavity cancers. Pooled RR indicates a significant association between tobacco smoking and oral cavity cancers³. Reprinted with permission of John Wiley & Sons, Inc.

Pathogenesis

Several lines of evidence indicate that oral cancers arise as a result of mutagenic events (arising mainly from tobacco and alcohol) causing multiple molecular genetic events in many chromosomes and genes. The consequence of this chromosomal (genetic) damage is the impairment of cell regulatory processes leading to acquired capabilities within cells such as self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis and tissue invasion and metastasis¹¹. As shown by epidemiological data, exposure to tobacco is unquestionably the major risk factor for oral cancers, however, only a minority of those exposed develops a malignancy. The balance between how enzyme systems metabolise and deactivate tobacco carcinogens varies among individuals and is likely to contribute to cancer risk. An individual's susceptibility to cancer may therefore be explained by genetic polymorphisms in a number of enzymes involved in the metabolism of tobacco carcinogens.

Two main carcinogens present in tobacco smoke are benzo(a) pyrene and tobacco smoke derived nitrosamines (*TSNA*). These are primarily metabolised to their activated molecules by cytochrome P450 and these intermediates are detoxified by glutathione S-transferase (GST) to hydrophilic and non-toxic GST conjugated substances¹². Genetic polymorphisms in these metabolising enzyme systems (Cytochrome P450 and GST) and resulting variants are relatively common in populations and may partly explain susceptibility to cancer in various organs¹³⁻¹⁵. If detoxification does not take place, then the metabolically activated tobacco products would adduct to DNA. In studies of DNA obtained from clinically normal oral mucosa in patients with oral cancer, a significantly higher level of a variety of aromatic adducts was noted in smokers than from non or former smokers^{16,17}. DNA adducts associated with tobacco smoking could provide a marker of the biologically effective dose of tobacco carcinogens and improve individual cancer risk prediction¹⁸.

Precancer

Several potentially malignant disorders (particularly oral leukoplakia and erythroplakia) are known¹⁹ and a proportion of these transforms to cancer over a period of time²⁰. Presence of epithelial dysplasia in precancers is a hallmark for cancer development²¹ and several studies from the US and the UK have demonstrated significant associations with smoking in relation to oral epithelial dysplasia^{22,23}. Exclusive tobacco consumption appears to be more likely to contribute to epithelial dysplasia than exclusive alcohol use suggesting that tobacco has an independent role in the aetiology of oral epithelial dysplasia²⁴.

Oral leukoplakia is the most common precancer associated with tobacco use. The clinical appearance of leukoplakias varies considerably. The lesion may appear smooth, fissured, nodular or corrugated and the colour is predominantly white. Leukoplakias also vary with regard to size and distribution in the oral cavity. They may be barely discernible clinically, or may cover entire mucosal surfaces²⁵. Two different clinical types of oral leukoplakia exist: homogeneous and non-homogeneous. The distinction between these two entities is primarily based on their clinical appearance (surface colour and morphological characteristics), and has some bearing on the prognosis and risk for malignant transformation of the lesion²⁰. Homogeneous lesions are uniformly flat, thin, and exhibit shallow cracks on their surface. Non-homogeneous lesions include *speckled* leukoplakias (white and red lesions with a predominantly white appearance, also termed 'erythroleukoplakia'), nodular and verrucous lesions, as well as the widespread and multifocal rarer entity known as *proliferative verrucous* leukoplakia²⁶.

Periodontal disease

Clinical evidence

In a recent systematic review on periodontal disease and smoking, it was concluded that the evidence in support of a negative impact of smoking on periodontal health is strong²⁷. The review was based on an appraisal of 70 cross-sectional studies and 14 case-control studies, all of which indicated an association between smoking and periodontal disease, and a further 21 cohort studies of which 20 indicated the same.

In the last few years following this review, additional articles on the topic have appeared in the scientific literature²⁸⁻⁴⁵. A summary of these new articles is presented in *Table 1*. Fourteen of the studies used a cross-sectional study design, whereas five were cohort studies. Scrutiny of the articles reveals that all the cross-sectional studies except one, and four of the five cohort studies conclude that there is an association between smoking and periodontal disease. In addition, some studies have evaluated the periodontal condition in former smokers. Six out of eight of these studies report inferior periodontal status also in former smokers. Thus, the observations reported in most of the new studies confirm the above contention that smoking has a major negative impact on periodontal health.

As can be seen from *Table 1*, the majority of the newly published studies, interestingly, have been carried out in countries outside the USA and Europe, which is in contrast to the findings of the previous review²⁷. The concordance of observations (i.e. that smoking is a major risk factor for periodontal disease) made in different parts of the world reflecting different living, environmental and cultural conditions greatly increases the generalisability of the findings.

Table 1 Summary of recent studies that have investigated the relationship between smoking and periodontal disease. CS = current smoker, FS = former smoker, NS = non-smoker. Effect = presence of positive relationship (1) or not (0). n = number of participants.

First author	Pub. year	Nation	Study type	Study size (n)	Age range	CS (n)	FS (n)	NS (n)	Endpoint	Effect CS	Effect FS
Baharin ²⁹	2006	England	Cross	88	46-60	39		49	PD, BH	1	
Borges-Yanez ³⁰	2006	Mexico	Cross	315	60-80+	31	226	58	AL	0	
Buduneli ³¹	2006	Turkey	Cross	40	25-58	23		17	PD, GB, TEETH	1	
Levin ³⁴	2006	Israel	Cross	642	18-30	256		385	PD, BH	1	
Ojima ³⁷	2006	Japan	Cross	4828	20-93	1207	572	3049	CPI	1	1
Okamoto ³⁸	2006	Japan	Cohort	1332	30-59	625	384	323	TEETH, CPI	1	0
Shimazaki ⁴⁰	2006	Japan	Cross	958	40-79	174	144	640	AL, PD, GB	1	1
Van d Velden ⁴²	2006	Indonesia	Cohort	128	15-25	53		75	AL, PD	0	
Kibayashi ³³	2007	Japan	Cohort	219	18-63	108		111	PD	1	
Linden ⁴⁷	2007	N Ireland	Cross	1362	60-70	233	593	544	AL, PD	1	1
Nicolau ³⁶	2007	Brazil	Cross	251		46	45	160	AL	1	1
Thomson ⁴¹	2007	N Zealand	Cohort	810	32-32	255	141	414	AL	1	0
Wang ⁴⁴	2007	China	Cross	1590	25-69	430	90	1032	AL, PD	1	1
Al-Bayaty ²⁸	2008	Yemen	Cross	2506	15-64	548		1958	TEETH	1	
Do ³²	2008	Australia	Cross	3161	15-65	500	842	2206	AL, PD	1	1
Rosa ³⁹	2008	Argentina	Cohort	81	17-26	42		39	AL, BH, GR	1	
Vered ⁴³	2008	Israel	Cross	7056	20-21	2487		4503	CPI	1	
Ylostalo ⁴⁵	2008	Finland	Cross	2841	30-49	833	681	1325	PD	1	

PD Pocket Depth
 AL Attachment Loss
 BH Bone Height
 CPI Community Periodontal Index

Table 2 Summary of recent studies that have estimated the relative risk for periodontal disease associated with smoking. LS = light smoker, MS = moderate smoker, HS = heavy smoker. Risk = odds ratio or prevalence ratio. n = number of participants.

First author	Study size (n)	Disease definition	Severe disease definition	Disease risk	Severe disease risk	Risk LS	Risk MS	Risk HS
Borges-Yanez ³⁰	315	2+ sites with AL 4+mm	1+ site(s) with AL 6+mm	1.8				
Ojima ³⁷	4828	CPI = 3 or 4	CPI = 4	1.4	1.4			
Okamoto ³⁸	1332	CPI = 3 or 4	CPI = 3 or 4	1.7		1.3	1.7	3.9
Shimazaki ⁴⁰	958	>20% teeth with PD 4+mm	>10% teeth with CAL 5+mm	2.4	2.8	1.2		2.3
Kibayashi ³³	219	3+ sites with 2+mm increase	3+ sites with 2+mm increase	2.3				
Linden ⁴⁷	1362	AL 6+mm	15% sites with AL 6+mm	3.3	3.5	2.6		4.8
Nicolau ³⁶	251	low AL	high AL	2.2	2.6			
Thomson ⁴¹	810	1+ site(s) with AL 4+mm	1+ site(s) with AL 4+mm	5	7.1			
Wang ⁴⁴	1590			1.5				
Do ³²	3161	2+ sites with AL 4+mm or PD 5+mm				1.2	1.6	1.6
Do ³²	500*		2+ site(s) with AL 6+mm and PD 5+ mm		3.3	1.8	4.7	3.3
Vered ⁴³	7056	CPI = 3 or 4	CPI = 3 or 4	1.6				

* Subset with severe periodontitis

It can further be seen from *Table 1* that the sample size of the studies varies considerably from 40 participants in a clinical study of therapeutic outcomes to 7,056 individuals in a screening study of army personnel. On average, the number of participants per study was 1,567, similar to that reported in the previous review²⁷.

The authors of these studies assessed the periodontal condition by means of a variety of clinical and/or radiographic measures such as pocket depth, attachment level (loss), and bone height (loss). A few studies used the number of retained (or lost) teeth as the endpoint of choice. Most studies made use of more than one clinical measure for assessment of the periodontal condition and three studies used a compound measure, the Community Periodontal Index (CPI), which relies on pocket depth. The most commonly used clinical measures or endpoints are pocket depth and attachment level (loss). The outcome with regard to the influence of smoking, however, is independent of endpoint, which is in good agreement with the observations of the review referred²⁷. The fact that observations based on different criteria or measures used for disease assessment arrive at the same conclusion, again, increases the generalisability of the findings.

Pocket depth is a frequently used measure for the assessment of the periodontal clinical condition. Although common and accepted, pocket depth may be a problematic measure when studying periodontal disease in relation to smoking. Pocket depth measurements are influenced by the quantity and quality of the inflammatory tissue at the apical base of the pocket. The inflammatory tissue at the base of the pocket is commonly tighter and less extensive in the smoker compared with a corresponding non-smoker, which results in less 'probe penetration' in the smoker⁴⁶. This may be a problem in studies comparing pocket depth measures between smokers and non-smokers with a risk for underestimating the depth among smokers relative to non-smokers. In addition, gingival recession is commonly more extensive in smokers resulting in a reduced pocket depth when compared with the corresponding situation in a non-smoker. Both elements of the pocket depth measurement process could lead to underestimation of the severity of the clinical condition in a smoker.

Two of the more recent articles in this review have presented data that are inconclusive with respect to the influence of smoking on periodontal disease^{30,42}. Although the objective of the present review was not primarily to scrutinise in detail the quality of single studies, a closer look at these two might be relevant. One of the studies³⁰ concerns elderly persons and suffers severely from the fact that tooth loss was high in this population (23% were edentulous). Furthermore, only 36% out of 473 persons were found with complete dental records, and only 10% of these persons were smokers (17 persons). It seems unrealistic even to try to get reliable information from such data. Moreover, studies based

on elderly persons, in general, are problematic regarding the exploration of smoking effects, since premature mortality at older ages affects smokers more than non-smokers. Elderly smokers eligible to participate in such a study will most likely not be representative of the wider population, and the effect of smoking, therefore, could be underestimated.

The other study is a 15-year longitudinal follow-up of an Indonesian population cohort⁴². The main problem with this study is the immense (50%) loss to follow-up. In addition, a problem particularly related to smoking was encountered: whereas nearly all men were smokers, women were not. Under such extreme circumstances the effect of smoking will most likely be confounded by gender. An analysis restricted to males would have been instructive in such a situation. The shortcomings of these two studies illustrate some of the difficulties that may be met when estimating the influence of smoking on periodontal health.

Risk estimation

The relative risk for periodontal disease associated with smoking was assessed in 11 of the 18 new studies: seven cross-sectional^{30,32,36,37,40,43,44,47} and four cohort^{33,38,41,42} studies. A summary is presented in *Table 2*.

The magnitude of the relative risk estimates varied from 1.4 to 5.0 in the different studies. A considerable variation of the magnitude of the relative risk estimates was also observed in a previous review⁴⁸. There may be several explanations for such variation, the main ones probably being the definitions of periodontal disease as well as smoking. In all the studies that have estimated the smoking associated relative risk at more than one level of disease severity, the relative risk increases as the severity level increases (*Table 2*)^{30,32,33,36-38,40,41,43,44,47}. Thus, as the criteria become stricter, indicating more severe disease, the lower the prevalence and the greater the proportion of smokers⁴⁹. Hence, the smoking associated risk increases as the prevalence of periodontal disease decreases. Furthermore, data from studies that have estimated the smoking associated relative risk at more than one level of smoking exposure indicate that the relative risk for periodontal disease in light smokers, on average, is less than that for heavy smokers (*Table 2*). This suggests an exposure gradient or a 'dose-response' relationship. Similarly, most of the studies that have included former smokers^{32,37,38,40,41,47} suggest that former smokers have a better periodontal condition or less relative risk than comparable smokers who continue to smoke, which points in the same direction. Both circumstances, increasing risk with increasing disease severity and increasing risk with increasing exposure, favour a causal effect by smoking.

In two of the cohort studies, estimates of the incident risk were presented^{38,41}. Surprisingly little information is available about periodontal disease incidence, i.e., the occurrence of new cases of the disease among

previously unaffected persons. This lack of knowledge has now been remedied to some extent from these two studies. According to these observations the 4-year³⁸ and the 6-year⁴¹ cumulative incident risk for periodontal disease was 1.7-fold and 5.2-fold, respectively, higher in smokers. These two studies show that smokers, in addition to carrying a larger periodontal disease burden, also develop the disease earlier than non-smokers. This novel information is important and again favours a causal effect of smoking on periodontal disease.

Thus, it is clear that more recently published articles on the topic of smoking and periodontal disease truly confirm earlier evidence and expand our understanding that smoking exerts a strong untoward effect on periodontal health and is a major risk factor for periodontal disease.

Mechanisms of periodontal disease causation

The periodontal tissues are continuously exposed to nicotine and its metabolites due to deposition of nicotine on the root surface⁵⁰ and cotinine levels (a metabolite of nicotine) are elevated in saliva and gingival crevicular fluid⁵¹. The current knowledge on periodontal disease causation by smoking has been summarised in excellent reviews⁵²⁻⁵⁵ in which several aetiological effects of tobacco smoke are discussed. However, tobacco related periodontal pathogenesis is not well understood. Some potential mechanisms are briefly presented here.

The importance of oral micro-organisms for the development of periodontal inflammation was proven about 40 years ago⁵⁶. Cigarette smoking is likely to affect the composition of the oral microflora due to a decrease in oxygen tension in periodontal pockets and may lead to a selection of anaerobic bacteria⁵⁷. However, the literature is inconclusive concerning a specific smoking associated microbial profile^{58,59}. The oral bacteria are organised within biofilms. In addition, the oral microflora consists of more than 700 different types of bacteria and many of these are not classified and cannot be cultured⁶⁰. Periodontal diseases are likely to be associated with different microbial profiles, rather than to be associated with distinct pathogenic bacteria. The pathogenic subgingival biofilm has both direct and indirect effects on the periodontal tissues. In fact, damage to the periodontium results even without influence of bacterial invasion into the corresponding periodontal tissues because of the immune response of the host to bacterial stimulation⁶¹. Tobacco smoking affects the humoral mediated and the cell mediated immunity of the host and this may increase susceptibility to periodontal disease^{53,62-66}. However, available data are conflicting and precise mechanisms have yet to be confirmed.

The periodontal tissues are very well vascularised⁶⁷. Typical signs of an inflammation, such as changes in gingival colour, swelling of the marginal as well as papillary gingiva, an increase of gingival crevicular fluid

flow as well as bleeding on gentle periodontal probing (BOP) are caused by alterations of the vascular system. In smokers the clinical signs of inflammation and BOP are suppressed^{68,69}. The literature is inconclusive concerning a clear smoking associated pathohistological correlate⁷⁰⁻⁷³ but clearly, periodontal inflammatory responses are altered as a result of smoking.

There is evidence for an impact of smoking on bone metabolism such as an increased secretion of the bone resorbing factors PGE₂ and IL-1 β ⁷⁴ or a decreased intestinal uptake of calcium⁷⁵, and these factors may also increase susceptibility to periodontal disease in smokers. Periodontal disease is influenced by genetic factors⁷⁶. There is some evidence that tobacco smoking may affect the genetically determined susceptibility for periodontal diseases⁷⁷⁻⁷⁹, though again, precise mechanisms remain to be elucidated.

Smoking-induced periodontal destruction results from a wide range of effects of tobacco on the different functions of cells, tissues and organs. Some of these effects are opposed to each other due to the effects of different tobacco constituents. However, when summarising the characteristics of tobacco-induced alterations on periodontal tissues and humoral immunity, it is very likely that tobacco smoking disrupts the physiological turnover of tooth-supporting structures with the net effect being periodontal tissue breakdown^{53,64,80}.

Smoking and tooth loss

Cigarette smoking has been shown to be associated with fewer remaining teeth in a plethora of cross-sectional studies in various populations^{35,81-88}. Furthermore, increased rates of tooth loss among smokers have been observed in a number of longitudinal studies^{84,89-94}. Among 789 men followed for up to 35 years in the VA Dental Longitudinal Study (VA DLS), an ongoing closed panel longitudinal study of men in the Greater Boston area (USA), rates of tooth loss among current cigarette smokers were approximately twice those of never smokers (adjusted HR: 2.1, 95% CI 1.5, 3.1)⁹⁴. In another study conducted in Boston, the relative risk of tooth loss in current smokers compared to never smokers was 3.4 (95% CI 2.1, 5.7) among 248 dentate women followed over 2 to 7 years⁸⁴. Okamoto *et al.* followed a total of 1,332 adult Japanese men over four years and found that current smokers were approximately twice as likely to experience tooth loss as never smokers³⁸. In a study of 1,031 Swedish women followed over 12 years, women who smoked at baseline lost a mean number of 3.5 teeth compared to a mean of 2.1 teeth lost among never smokers⁸⁹. Results of the largest prospective cohort study on cigarette smoking and tooth loss were recently reported by Dietrich *et al.*⁹⁰. In this study, a total of 43,112 US male health professionals, including 26,284 dentists, were observed from 1986 to 2002, and data on smoking behaviour and tooth loss were updated

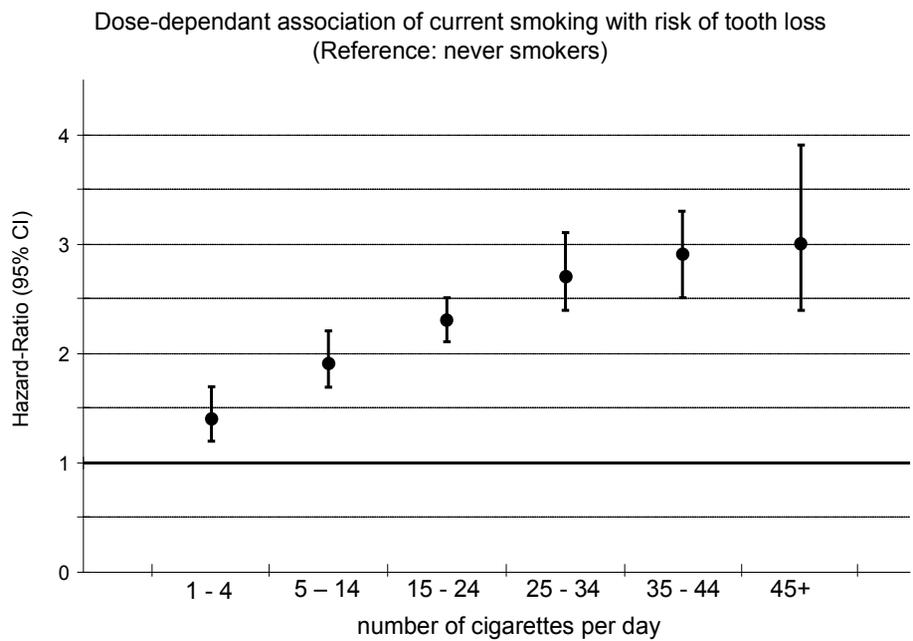


Figure 2. Hazard ratios and 95% confidence intervals (CI) for the dose-dependent association between current cigarette smoking and risk of tooth loss in the Health Professionals Follow-up Study, United States 1986-2002. (used with permission). HR adjusted for age, race, BMI, physical activity, diabetes, profession, routine medical examination, alcohol consumption, caloric intake, multivitamin use and vitamin C supplement use.

Table 3 Systematic reviews on implant failures in smokers versus non-smokers.

Author Year	Type of study	Groups	Outcome	Level of analysis	Results
Hinode <i>et al.</i> 2006 ⁹⁷	Systematic review (up to August 2005); 12 case-control and 7 cohort studies (retro-/prospective) Mean follow-up: NR	Smokers vs non-smokers	Removed implant	Implant level	OR 2.17 (95% CI 1.67-2.83) Significant effect of smoking only in the maxilla
Klokkevold & Han 2007 ⁹⁸	Systematic review (up to May 2005); 14 case-control studies (retro-/prospective) Mean follow-up: 4.7 years	Smokers vs non-smokers	Implant survival	Implant level	Smokers 89.7% (95%CI 87.0-92.4) Non-smokers 93.3% (95%CI 91.0-95.6) Pooled estimate of difference in implant survival 2.68% (95%CI 1.1-4.26)
Strietzel <i>et al.</i> 2007 ⁹⁹	Systematic review (up to December 2005); 29 case-control and cohort studies (retro-/prospective) Mean follow-up: NR	Smokers vs non-smokers	Removed implant, bone loss >50%, mobility, persistent pain or peri-implantitis	Implant level (19 studies) Subject level (10 studies)	OR 2.17 (95% CI 1.67-2.83) OR 2.64 (95% CI 1.70-4.09) No significant difference in OR for early (<1 year) and late (>1 year) failures

NR: not reported
OR: odds ratio

Table 4 Publications after the time period covered by the systematic reviews described in Table 3.

Author Year	Type of study	Number of patients/ implants Years of follow-up	Groups	Outcome	Level of analysis	Risk of failure / % failed	Comments
Moy <i>et al.</i> 2005 ¹⁰⁴	Retrospective	1140/4680 0.5-21 years	Smokers vs non-smokers	Removed im- plant, bone loss >50%, mobility, persistent pain or peri-implan- titis	Subject level	Risk ratio: 1.56 (95%CI 1.03-2.36)	Majority of failures within the first year
Mundt <i>et al.</i> 2006 ¹⁰⁵	Retrospective	157/663 Mean 7.3 years	Smokers, ex- smokers, never- smokers	Removed implant	Implant level Subject level	Smokers 15%, Ex-smoker 9.6% Never-smokers 3.6% (sign. difference be- tween all groups) Sign association between duration of smoking and implant failure	
Wagenberg & Froum 2006 ¹⁰⁷	Retrospective	891/1925 1-16 years; Mean 6 years	Smokers, non- smokers	Removed implant	Implant level	Smokers 5.6% Non-smokers 3.7% (p=0.34)	No significant dif- ference between rough- and smooth-surface implants.
Ellegard <i>et al.</i> 2006 ¹⁰⁰	Prospective cohort	68/262 0-12.6 years; Mean 5.4 years	Smokers, non- smokers	Removed implant	Implant level	Hazard rate 2.2 (95%CI 0.8-6.1)	Sinus membrane lift
Kinsel & Liss 2007 ¹⁰²	Retrospective	Smokers 12/95 Non-smokers 95/249 2-10 years	Smoker (≥ 20 cig/day), non- smokers	Removed implant	Subject level Implant level	Smokers 5/12; 42% Non-smokers 5/31; 16% (p=0.11) Smokers 7.4% Non-smokers 3.6%	Immediate loading protocol
Roos-Jansåker <i>et al.</i> 2006 ¹⁰⁶	Cross-sec- tional	218/999 9-14 years	Smokers, ex- smokers, never- smokers	Peri-implantitis (bone loss ≥ 3 threads after year 1 and pus/ bleeding on probing)	Subject level	Smokers OR 4.6 (95% CI 1.1-19) Ex-smokers OR 0.42 (95%CI 0.1-12.1)	No association between smoking habits and implant loss.
Fransson <i>et al.</i> 2008 ¹⁰¹	Cross-sec- tional	82/ 439 Mean 9.4 years	Smokers, non- smokers	History of progressive peri- implant bone loss (bone loss ≥ 3 threads after year 1)	Implant level	OR 2.2 (95%CI 1.5- 3.3)	No data on implant loss in smokers versus non- smokers
Mesa <i>et al.</i> 2008 ¹⁰³	Retrospective	316/1084 Up to 2 nd stage surgery (early failures)	Smoker (≥ 20 cig/day), non- smokers	Primary implant stability	Implant level	OR 1.36 (95%CI 0.87/2.12)	5.1% of the implants removed before 2 nd stage surgery. No data on implant loss in smokers versus non- smokers

OR: odds ratio

biannually. The study demonstrated a dose-dependent association between current smoking and incidence of tooth loss, with heavy smokers having three times higher rates of tooth loss than never smokers (Figure 2).

Cigar and pipe smoking are also likely to be related to tooth loss risk, but very few studies have investigated this hypothesis. A cross-sectional study of 705 individuals enrolled in the Baltimore Longitudinal Study of Aging reported a higher number of missing teeth among smokers of pipes and cigars compared to non-smokers⁹⁵. Two longitudinal studies in predominantly white US males have analysed pipe and cigar smoking as determinants of tooth loss risk^{90,96}. In the VA DLS, both cigar and pipe smoking were independently associated with increased tooth loss risk in a longitudinal study of 690 men⁹⁶. Among US health professionals, current pipe or cigar smoking was independently associated with tooth loss incidence compared to never or former smokers of pipes or cigars (HR: 1.20, 95% CI: 1.11, 1.30)⁹⁰. Because the reference category in this study included former smokers of pipe and cigars some of whom may have quit relatively recently, current pipe and cigar smoking may actually elevate the risk of tooth loss by more than 20%; however, the effect is likely to be small compared to the effect of cigarette smoking.

Implant failure

The influence of smoking on the short and long-term outcomes of implant therapy has been addressed in three recent systematic literature reviews (Table 3)⁹⁷⁻⁹⁹. The reviews cover the literature up to the year 2005. A literature search performed in PubMed covering the time period 2006 until June 2008 identified a further eight articles addressing the issue of outcomes of implant therapy in smokers (Table 4)¹⁰⁰⁻¹⁰⁷. Three of these articles did not have implant removal (or implant survival) as primary outcome variable, but described prevalence of peri-implantitis¹⁰⁶, progressive bone loss¹⁰¹ or primary implant stability¹⁰³.

The systematic review by Hinode *et al.*⁹⁷ used 'removed implant' (without specifying reasons for removal) as the outcome. The analysis included 19 studies and revealed that implants in smokers had a significantly higher risk to be lost (OR: 2.17, 95%CI 1.67,2.83), and also that the increased risk was significant only for implants placed in the maxilla. Klokkevold and Han⁹⁸ included 14 studies in their systematic review and found the implant survival rate to be lower in smokers than non-smokers; pooled estimate of risk 2.68 (95%CI 1.1,4.26) over a mean follow-up of 4.7 years. While the two systematic reviews referred to above described data at the implant level, Strietzel *et al.*⁹⁹ performed analyses at both the subject and implant levels. In this review, a broader definition of implant failure was used and included removed implant, bone loss >50%, mobility, persistent pain or peri-implantitis. Based on informa-

tion from 10 studies providing data at the subject level, smokers showed an overall OR of 2.64 (95% CI 1.70, 4.09) to experience implant failure. Five of the 10 included studies (50%) reported a statistically significantly increased risk for implant failure in smokers. The corresponding OR at the implant level (18 studies included) was 2.17 (95% CI 1.67, 2.83). No significant difference in OR for early (<1 year) and late failures was found for the pooled data for smokers and non-smokers.

Out of the eight additional retrieved studies on the effect of smoking on the outcome of implant therapy, five studies^{100,102,105-107} reported data on implant loss at the subject and/or implant levels. Four of these studies showed no significant difference between smokers and non-smokers. One study, which used the broader definition of implant failure (removed implant, bone loss >50%, mobility, persistent pain or peri-implantitis), demonstrated a higher risk of implant failure among smokers (HR: 1.56, 95% CI 1.03,2.36) and with the majority of the failures occurring within the first year of function¹⁰⁴. A study evaluating primary implant stability¹⁰³, however, revealed no significant difference between heavy smokers (≥ 20 cig./day) and non-smokers. Two cross-sectional studies focused on peri-implantitis⁹ or history of progressive peri-implant bone loss¹⁰¹ as the outcome variable and for each showed a significantly higher prevalence in smokers than in non-smokers, OR 4.6 (95% CI 1.1,19) and 2.2 (95% CI 1.5, 3.3), respectively.

The evaluation of the current literature indicates that implant failure is more common among smokers than non-smokers, although the scientific evidence must be considered limited. A general problem in the analysis of the literature regarding the influence of smoking on the short- and long-term outcome of implant therapy is the insufficient quality of the studies with regard to design and/or description. Since smoking is a subject related factor, analysis of the effect of smoking habits on the outcome of implant therapy should be performed at the subject level. However, a majority of the studies include evaluation only at the implant level. Further, in most studies the data have been collected retrospectively and usually analysed using bivariate statistical methods without considering potential confounding factors (e.g. severity of periodontal disease, standard of hygiene, maxillary/mandibular jaw, characteristics of implant surface). Hence, in order to be able to properly define the effect of smoking on the prognosis of implant therapy there is an obvious need for adequately designed prospective studies. Although the proven beneficial effects of smoking cessation in general are known, the effect of smoking cessation intervention on implant survival rates should be evaluated.

Dental caries

Few cross-sectional studies have explored the relationship between smoking and dental caries, and of these, many have not considered the confounding factors in sufficient detail. A study of military personnel from Illinois (mean age=25.9 years), found that smokers had a significantly higher number of untreated decayed teeth, missing surfaces and total DMFS than non-smokers (DMFS of 19.38 for non-smokers compared to 24.59 for current smokers)¹⁰⁸. No information was obtained regarding diet or oral hygiene.

In a sample of 1,156 elderly patients, Jette *et al.*¹⁰⁹ also found a relationship between smoking (current) and dental decay, ORs (compared with all smoking categories combined) being 1.47 for smokers (95% CI 1.00,2.17), 1.02 for ex-smokers (95% CI 0.78,1.34) and 0.67 for never smokers (95% CI 0.50,0.89).

In a longitudinal study which followed patients undergoing periodontal therapy by a specialist for a period of 12 years, Ravald *et al.*¹¹⁰ found that smokers developed significantly ($p < 0.05$) more root caries lesions (both active and inactive) than non-smokers. A significant difference in the median values of salivary lactobacillus counts between smokers and non-smokers, was also observed in this study.

A Swedish study evaluated a randomised sample of adults belonging to well defined age groups (35-, 50-, 65- and 75-year-old) and found that smokers had significantly fewer intact tooth surfaces than non-smokers in all age groups⁸¹ and more missing surfaces (50-, 65- and 75-year-old), even though these missing surfaces could be due to periodontal disease and not caries. No differences in plaque scores nor oral hygiene habits, or intake of sweets or sugars containing confectionary were observed between smokers and non-smokers, but soft drinks and snacks were consumed more often by smokers ($p = 0.000$ and $p = 0.003$, respectively). Other studies that have investigated compliance with oral hygiene regimens among cigarette smokers also reported conflicting findings¹¹¹⁻¹¹³.

Regarding a plausible aetiopathogenesis of caries related to smoking, it has been demonstrated that cigarette smoke impairs salivary function, which has an important protective role against dental caries¹¹⁴. Other authors have indicated that smokers and non-smokers may have different salivary buffering capacity, which may also affect susceptibility to caries.

Other effects of tobacco smoking

Smoking has been reported to cause brown/black discolouration of teeth¹¹⁵, dental restorations and dentures¹¹⁶, alteration of taste and smell¹¹⁷, to be associated with a coated tongue (black hairy tongue)¹¹⁸, and to impair and delay wound healing after dento-alveolar surgical procedures such as tooth extractions¹¹⁹. Furthermore, smokers are more susceptible to oral candi-

dosis¹²⁰. Pipe smoking¹²¹ has been associated with tooth abrasion in association with placement of the pipe stem.

An interesting (negative) correlation with tobacco smoking exists regarding recurrent aphthous ulceration. Rivera-Hidalgo and co-workers demonstrated a significantly increased predisposition to aphthous ulcers in non-smokers¹²². The phenomenon of a lower prevalence of aphthae in smokers reaching statistical significance was also observed in several other studies¹²³⁻¹²⁵. The reason for an apparent inhibitory effect of smoking on aphthae remains unknown¹²⁵.

Among extrinsic causes of halitosis, smoking is often quoted as an aetiological factor. This is generally referred to as smoker's breath¹²⁶. Correlations between self-reported halitosis and smoking can be found, especially in studies based on questionnaires^{127,128}. Cigarette smoke contains volatile sulphur compounds (VSCs) which can be detected using a halimeter^{126,129}, although the concentration of detectable VSCs in the breath is strongly influenced by the time since the last cigarette was smoked. However, in a recent study, cigarette smoking was inversely correlated with VSC readings and no correlation could be found between smoking and organoleptic oral malodour measurements in a population of 20 year old male subjects¹³⁰.

Smoker's melanosis presents as diffuse, irregular, brownish pigmentation of the oral mucosa with a preference for the keratinised mucosa but also can be seen on the buccal mucosa, floor of the mouth, and the soft palate^{131,132}. Tobacco smoking is known to stimulate oral melanocytes resulting in increased melanin production particularly in dark-skinned ethnic groups¹³³. A recent study in a Nigerian population showed that smokers had a significantly higher prevalence of pigmented oral mucosal sites than non-smokers, and the number of pigmented sites increased with the degree and duration of smoking¹³⁴. Smokers' melanosis is not classified as a precancerous or precursor lesion, and is reversible on tobacco cessation.

Smokers' palate (synonyms: nicotinic stomatitis, stomatitis nicotina, stomatitis palatini, leukokeratosis nicotina palati) is seen especially in heavy, long-term pipe smokers as well as in cigarette or cigar smokers. The so-called smokers' palate develops with its distinctive clinical features¹³⁵: a white, plaque-like change on the palatal mucosa due to hyperkeratosis combined with multiple red dots located centrally in small elevated nodules representing the dilated and inflamed duct openings of minor salivary glands in this region. Thermal more than chemical agents acting locally are responsible for the occurrence of this condition^{72,136}. Smokers' palate is not considered to be a precancerous condition. Regression of the lesion has been reported after smoking cessation¹³⁷. Necrotising sialometaplasia of the palate has been reported to represent the necrotising (ulcerative) or terminal stage of nicotinic stomatitis¹³⁸ and is known to heal spontaneously.

Smokeless tobacco (ST)

Oral cancer

Smokeless tobacco (ST) products available in south Asia include Gutkha, Khaini, Kiwam, Mawa, Mishri, Nass (naswar, niswar), Zarda and chewing tobacco; these are often mixed with areca nut as a mixture of betel quid. Carcinogenicity of many of these products has been reported especially associated with a substantial risk of oral cancers in India¹³⁹. Wasnik *et al.*¹⁴⁰ in a matched case-control study from India reported unadjusted odds ratios for chewing tobacco without betel quid on 33 oropharyngeal cancers (4.1; 95%CI 2.0, 8.7). A study from Pakistan on ever users of naswar was reported giving an odds ratio (adjusted for smoking and alcohol use) of 9.5 (95%CI 1.7, 52.5). Cancer of the gingivae has been reported in a descriptive study from Saudi Arabia¹⁴¹ and on the lower lip in users of Toombak from the Sudan¹⁴².

Two meta-analyses on the effects of ST and oral cancer in the US and northern European populations were published recently^{143,144}. The authors concluded a minor increased risk. Weitunkat *et al.*¹⁴³ in their meta-analysis included 32 studies of oral and pharyngeal cancer from the USA and northern Europe (excluding studies conducted in south Asia). The exposure was ST and outcome defined as oral cancer. For ST, based on the random-effects estimate the overall relative risk was 1.87 (95% CI 1.40-2.48) and based on 15 studies adjusted for smoking the fixed-effect estimate was 1.31 (95% CI 1.13,1.53). For these 15 studies the random effects estimate was 1.35 (95% CI 1.04,1.76), most appropriate given the heterogeneity of estimates across the studies. The authors concluded that available data suggest at most a minor increased risk of oral cancer associated with the use of western chewing tobacco and snuff. In the meta-analysis by Boffetta *et al.*¹⁴⁴ the pooled estimate for 13 studies of oral cancer was 1.8 (95% CI 1.1, 2.9). A brief description of studies from the USA and Europe is given below.

The best evidence on carcinogenicity of ST among users in north America comes from a case-control study conducted by Winn *et al.*¹⁴⁵. The relative risk for white women in south-eastern USA who exclusively used oral snuff (locally grown; dry snuff) and developed oral cancer was 4.2 (95% CI 2.6, 6.7). The risk was much higher in whites compared with black women (RR 1.5: 95% CI 0.5, 4.8) who used comparatively less snuff. A dose response was also reported as related to years of use. In a further population based study¹⁴⁶ OR for snuff use among non-smoking women presenting with oral cancer was 6.2 (95% CI 1.9,19.8).

In four Swedish studies, the evidence for an increased risk of oral cancer among moist snuff users was limited or lacking¹⁴⁶⁻¹⁵⁰. However, in one of these studies an increased risk of head and neck cancer was observed among a small group of never-smokers RR

4.7 (95% CI 1.6,13.8)¹⁴⁷. Moreover, in a recent cohort study of 9,976 men, a statistically significant elevated relative risk of combined oral and pharyngeal cancers among ever users of snuff compared to never daily use of snuff was demonstrated (HR:3.1; 95% CI 1.5,6.6)¹⁵¹. Overall, mortality was also slightly increased. Among never smokers, the relative risk of ever daily use was 2.3 (95% CI 0.7,8.3)¹⁵¹. In a long term follow up study of 1,115 snuff users the same authors also concluded that the incidence of new oral cancers in the group previously diagnosed with snuff-induced mucosal lesions was higher than expected¹⁵². Although earlier studies had shown limited or no association on risks of Scandinavian snuff these recent studies provide evidence for increased risk for oral cancer with the regular use of snuff. Thus the evidence from Sweden is contradictory. However, several expert reports indicate that smokeless tobacco increases risk for oral and pancreatic cancer^{153,154}.

Genotoxic effects of Indian chewing tobacco, some brands of American chewing tobacco and Swedish moist snuff were reported by *in vitro* studies using aqueous extracts of these products¹⁵⁵⁻¹⁵⁷. These experimental systems were detailed in a recent IARC monograph¹⁵⁴ (vol 89) and reviewed by Warnakulasuriya and Ralhan¹⁵⁸.

Precancer

Oral mucosal disorders arise at the site where smokeless tobacco is regularly placed. These are mostly white plaques with a wrinkled surface. The terms 'leukoplakia' or 'snuff induced lesions' are used to refer to these mucosal abnormalities. Clinical changes and pathological findings were discussed in a recent review¹⁵⁸. Smokeless tobacco use is a strong risk factor for both oral leukoplakia and snuff-induced lesions¹⁵⁴ and length of use is a predictor of the severity of the lesion.

Most studies from India reporting on oral precancer have been among betel quid or khini users in which tobacco is mixed with other ingredients^{159,160}. Multiple oral premalignant lesions were described in a cohort of tobacco chewers in Kerala, India¹⁶¹. Snuff-induced changes have been reported on the lower lip in Sudanese males where smokeless tobacco (toombak) is habitually placed¹⁶². Among English coal miners (280 tobacco chewers) prevalence of oral leukoplakia was reported at 3.6%¹⁶³.

Use of ST is prevalent among US baseball players. In two US studies the prevalence of leukoplakia was 28-39%^{164,165}. In a further study of over 1,000 professional baseball players, leukoplakia was significantly associated with smokeless tobacco use (OR: 60, 95% CI 40.5, 88.8)¹⁶⁶. In a US national survey among adolescents, the prevalence of white lesions was reported to be 2.9% in males and 0.1% in females. By multivariate analysis, the odds ratios for the presence of one or more smokeless tobacco lesions among white males (aged 12-17 years) for snuff use was 18.4 (95% CI 8.5, 39.8) and

for chewing tobacco was 2.5 (95% CI 1.3, 5.0)¹⁶⁷. Long term significance of ST associated oral white lesions or leukoplakia in these young US populations has not been reported.

Scandinavian reports on snuff/snus induced lesions (SILs) are mostly from Denmark and Sweden. These occur mostly on the inner side of lower lip in Danish snuff dippers¹⁶⁸ and on the upper lip or upper vestibular area among Swedes due to different traditional habits of quid placement¹⁶⁹. The most extensive study among 20,333 adults in middle Sweden was by Axell who reported a prevalence of SILs in 15.9% of men and of less than 1% in women¹⁷⁰. A later study reported a similar prevalence (14.5%) in men¹²⁴. Among regular snuff users presence of these mucosal lesions is quite common (80-94%)^{124,170}.

Gingival recession and periodontal disease

Studies on ST have focused on periodontal conditions among young athletes, baseball players and adolescent male teenagers. In 1990, a survey of 1,109 professional baseball players in the USA found that 39% were using ST and these players had significantly more gingival recession and attachment loss in the mandibular anterior quadrant than non-users¹⁶⁵.

Among 565 North American male schoolchildren (mean age 13.8 years: 13.3% using ST, 1.4% cigarette smoking), the odds of having gingival recession were nine times greater in the children using ST compared with non-users¹⁷¹. In contrast to these findings, in a study of Navajo Indian adolescents aged 14-19, of whom 64% used ST (75% of the males and 49% of the females), no consistent relationship could be identified between ST use and gingival recession or attachment loss¹⁷².

Many individuals in Sweden are users of ST. In Swedish schoolchildren aged 13-14 years (many of whom used snuff), snuff usage was strongly correlated with gingival inflammation after controlling for plaque^{173,174}. In another study of Swedish males aged 16-25 years, 17% of those using ST demonstrated evidence of gingival recession and attachment loss¹⁷⁵. Increased gingival recession was again reported in a study of 252 Swedish men of whom 23.5% of subjects using loose snuff demonstrated gingival recession¹⁷⁶. More recently, the increased prevalence of gingival recession among users of ST in Sweden has again been confirmed, and 42% of ST users had gingival recession compared to 17% of non-users¹⁷⁷.

Regarding an effect of ST on periodontal disease, epidemiological data from 12,932 adults who participated in the NHANES III survey identified that adult never smokers who currently used ST were twice as likely to have severe periodontal disease at any site compared to non-users (OR: 2.1 95% CI 1.2, 3.7)¹⁷⁸. In contrast, in a Swedish study, use of ST was not associated with increased interproximal alveolar bone loss¹⁷⁹.

The biological effects of ST on the periodontium have been investigated in a number of studies. In a cell culture system, co-culture of monocytes with ST and *P. gingivalis* LPS resulted in a 10-fold increase in the release of PGE₂ by the monocytes treated with ST compared to LPS alone¹⁸⁰. Furthermore, exposure of gingival keratinocytes to aqueous ST extracts resulted in increased production of PGE₂, IL-1 β and IL-1 α by the cells¹⁸¹. Use of ST clinically was shown to result in increased GCF PGE₂ concentrations and exacerbated gingival inflammation, and relocation of the ST to a new site in the mouth led to inflammatory reactions in the mucosa at the new site of placement after just seven days that ranged from erythema to ulceration¹⁸². In a later study in patients with periodontal disease the effect of nicotine and ST on stimulating PGE₂ production by peripheral blood mononuclear cells was confirmed¹⁸³.

ST extracts have also been shown to increase the production of TNF- α and IL-1 β in a macrophage cell line and to enhance lymphocyte proliferation in mice¹⁸⁴. In endothelial cells, ST extracts resulted in increased expression of the adhesion molecule E-selectin and chemokines such as IL-8 and monocyte chemoattractant protein-1, leading to enhanced migration of neutrophils across endothelial monolayers¹⁸⁵.

Laboratory research examining the association of ST with gingival recession leads to an understanding that exacerbated inflammatory responses induced by ST contribute to accelerated periodontal breakdown and gingival recession at the site of placement. Mechanical trauma resulting from the abrasive nature of the ST being held in close proximity to thin gingival tissues could also be contributory to recession.

Dental caries

In addition to increased gingival recession¹⁶⁵ ST use in professional baseball players has also been associated with cervical abrasion and root caries¹⁸⁶. The NHANES III data also confirmed that men who used ST had more decayed and filled tooth surfaces (including root surfaces) than users of other forms of tobacco or non-users¹⁸⁷. Increased susceptibility to root caries is presumed to result from the gingival recession caused by ST and the high sugar content of ST, which has been reported to be 34% on average in different preparations of chewing tobacco¹⁸⁸.

Effects of cessation

Table 5 summarises reported interventions and the potential benefits of smoking cessation for oral cancer, precancer, melanosis, periodontal disease, tooth loss and dental caries^{90,94,132,189-197}.

Table 5 Effects of smoking cessation.

Oral disease	Type of study & Ref	Outcome	Benefit for former smokers?	Benefit time dependent?	Time for risk to equate never smoker
Oral cancer	CC	Incidence	Yes	Yes	≥20yrs ^{189,190}
Periodontal disease	CS, PCS	Prevalence/Incidence	Yes	Yes	≈10yrs ¹⁹¹⁻¹⁹³
	Intervention	Severity of disease (PPD)	Yes	N/A	1 Year ¹⁹⁴
Tooth loss	PCS	Incidence	Yes	Yes	≈10/13yrs ^{90,94}
Caries	CS, PCS	Incidence/Severity	Yes	No data	No data
Precancer	CS	Prevalence	Yes	Yes	No data ^{195,196}
Melanosis	CS	Prevalence	Yes	Yes	≥6yrs ^{132,197}

Case control studies – CC, Cross sectional studies - CS

Prospective cohort studies – PCS

Periodontal Pocket Depth - PPD

Publications on precancer^{195,196} refer to interventions but not clinical evolution

Cancer and precancer

A significant reduction of risk for oral cancer has been shown among quitters and follow up studies indicate that the level of risk approaches that of never smokers approximately 10 years after cessation. In a meta-analysis, pooled risk estimates for ex-smokers (OR: 1.40, 95% CI 0.99,2.00) were significantly lower compared with current smokers (OR: 3.43, 95% CI 2.37,-4.94)³.

In a comprehensive study in an Italian population (961 cases with oral and pharyngeal cancer), stopping smoking has been shown to reduce the life time risk of developing oral and other cancers. For oral/oropharyngeal cancers, the cumulative risk by 75 years of age was 3.3% for men who continued to smoke any type of tobacco, but dropped to 1.4% and 0.5% for men who stopped smoking at around 50 and 30 years of age, respectively¹⁹⁸. The authors concluded that stopping smoking in or before middle age enabled an individual to avoid most of the eventual risk of developing cancer of the oral cavity. Among young people, a significant reduction in risk was also shown for ex-smokers (OR:0.2, 95% CI 0.5,0.8) compared with current smokers⁶. In a combined study from three countries (USA, Italy and China) the authors reported that having stopped for less than one year prior to diagnosis meant no change in risk, but thereafter the risk decreased with an increase in the time period for which a person had stopped smoking. Among those who had stopped between one and nine years ago, the relative risk was 0.7 (95% CI 0.5,1.1), for those that had stopped more than nine years ago the risk reduction was significant and the relative risk was half that of current smokers 0.5 (95% CI 0.3,0.7)¹⁹⁹. Cessation of smoking was associated with a markedly reduced risk for oral cancer in a combined study from Italy and Switzerland¹⁸⁹. This study demonstrated that after stopping smoking for over 10 years, the OR was no longer above unity. Among Brazilians, RRs for long term (>20 years) ex-smokers tended to be lower for mouth

(RR:1.61) than for laryngeal cancer (RR:3.63)¹⁹⁰. These data suggest that for ex-smokers, the relative risk for oral cancer declines with time since stopping smoking, to almost reach the levels observed for non smokers.

In a Swedish study, patients with oral leukoplakia who were smokers were asked to give up their smoking. It was found that leukoplakias present in persons with smoking habits were reversible when the smoking habit was reduced or given up¹⁹⁵. In a 10-year follow up study in India the cessation of tobacco use led to a substantial fall in the incidence of oral leukoplakia²⁰⁰.

Effects of smoking cessation on the periodontium

There are few articles in the periodontal literature which specifically address the impact of smoking cessation on the periodontium, presumably because of the inherent difficulties in motivating patients to quit smoking. Most investigations of the impact of smoking cessation on the periodontium have been either cross-sectional comparisons of periodontal status in current smokers, former smokers and never smokers, or have been prospective cohort studies. To date there has only been one intervention study to assess the effect of smoking cessation on periodontal treatment outcomes (described in more detail below)¹⁹⁴.

The periodontal literature that has focused on smoking cessation can therefore be divided depending on the type of study conducted. Cross-sectional and prospective cohort studies can be split into two categories: the effect of smoking cessation on periodontal status and the effect of smoking cessation on the outcome of periodontal therapy. Intervention studies of the impact of smoking cessation on the periodontium constitute their own category and include studies of the biological effects of quitting smoking. For more background, the reader is referred to excellent reviews by Tonetti²⁰¹, Ramseier²⁰², Heasman²⁰³ and Johnson⁸⁰.

The effect of smoking cessation on periodontal status

In broad terms, studies have indicated that periodontal status in former smokers is usually intermediate to that of current smokers and never smokers. Current smokers usually have significantly worse periodontal status (greater probing depths, attachment loss, and alveolar bone loss) than either former smokers or never smokers. Several studies have indicated that the periodontal status of former smokers, while intermediate to that of current smokers or never smokers, is usually closer to that of never smokers than current smokers. Such findings provide indirect evidence of the periodontal benefits of quitting smoking and permit the conclusion that not only should smoking status always be assessed as a key parameter to indicate the periodontal disease risk for an individual patient, but smoking cessation counselling should form an integral part of periodontal therapy²⁰¹. The principal findings of studies that have investigated the effect of smoking cessation on periodontal status are shown in *Table 6*^{32,41,93,109,191-193,204-211}.

The effect of smoking cessation on periodontal treatment outcomes

A small number of studies have investigated the efficacy of periodontal treatment in former smokers as compared to current smokers or never smokers, and these also provide indirect evidence of the benefit of smoking cessation on periodontal treatment outcomes. Taken collectively these studies confirm that treatment outcomes in former smokers are generally similar (if sometimes slightly inferior) to those that can be expected in never smokers, but are usually better than those that can be expected in current smokers. The principle findings of these studies are shown in *Table 7*²¹²⁻²¹⁷.

Intervention studies

A small number of intervention studies have been conducted that have investigated the effect of smoking cessation on the periodontium. These studies have indicated that smoking has a negative impact on the gingival microvasculature and that these changes are reversible on quitting smoking. To date, only one interventional study to assess the impact of smoking cessation on outcomes following non-surgical periodontal therapy has been conducted¹⁹⁴. This study achieved a 20% quit rate at 12 months, which confirms the effectiveness of dental healthcare professionals in providing smoking cessation counselling (*Table 8*)^{194,218,219}. In this study, those individuals who successfully quit smoking had the best periodontal treatment response. The treatment response in the failed quitters (i.e. the 'oscillators', who initially quit smoking but then resumed) was not significantly different from that seen in those who did not manage to quit.

The potential benefit of smoking cessation on the periodontium is likely to be mediated through a number of different pathways such as a shift towards a less pathogenic subgingival microflora, recovery of the gingival microcirculation, and improvements in aspects of the immune-inflammatory responses. In general terms, periodontal status and response to treatment in former smokers is intermediate to that seen in never smokers and current smokers, and is usually closer to that seen in never smokers. From the small number of studies to date, it appears that the periodontal status of former smokers approximates that of never smokers after around 10 years since quitting smoking.

Tooth loss

Few studies have investigated the association between smoking cessation and tooth loss risk. In the study by Ahlqvist *et al.*⁸⁹, the mean number of teeth lost in the 12 year period of follow-up was similar between never smokers and former smokers who had quit any time before baseline. In the VA DLS population, Krall *et al.*⁹⁴ demonstrated an association between time since cessation of cigarette smoking and tooth loss risk, suggesting that it may take up to 13 years after smoking cessation for the risk of tooth loss to drop to that of never smokers. These results are consistent with the results reported by Dietrich *et al.*⁹⁰ for the male USA health professionals, where the risk of tooth loss declined exponentially soon after smoking cessation but remained significantly elevated by about 20% even after 10+ years of smoking cessation (*Figure 3*).

Effect of cessation on dental implants

Only one article was identified with regard to the potential effect of smoking cessation on the outcome of implant treatment²²⁰. The study reported that four out of 34 implants (12%) in subjects who refrained from smoking in conjunction with implant placement surgery showed early implant failure (implant loss or >50% bone loss) as compared to five of 13 (38%) implants in subjects who continued to smoke. Because the number of subjects involved and affected by implant loss was not given, the finding must be interpreted with great caution.

Effect of cessation on other disorders

Mucosal hyperpigmentation can decrease and disappear after a successful attempt to quit smoking¹⁹⁹. In a population of 30,118 adults from Sweden, the prevalence of oral pigmentation was found to increase during the first year of smoking. After cessation this effect resolved, and after a period of more than six years the pigmentation returned to the level found among non-smokers ($\approx 3\%$)^{132,197}.

Table 6 The effect of smoking cessation on periodontal status.

Author, year	Study	Sample	Results
Bergstrom, 1991 ²⁰⁴	Cross-sectional	210 subjects (dental hygienists aged 24-60 years old). 30% current smokers, 32% former smokers, and 38% never smokers.	The mean distance from the CEJ to interproximal bone crest was significantly greater for current smokers (1.71 ± 0.08 mm) compared to never smokers (1.45 ± 0.04 mm). The corresponding measurement for former smokers was 1.55 ± 0.05 mm, intermediate to that seen in the other two groups.
Haber, 1993 ²⁰⁵	Cross-sectional	132 subjects with type 1 diabetes (28% current smokers, 13% former smokers and 59% never smokers) and 95 age- and sex-stratified non-diabetic subjects (22% current smokers, 19% former smokers and 59% never smokers).	In the non-diabetic subjects aged 19-30 years, 36% of former smokers had periodontitis (defined by at least one site with probing depth ≥ 5 mm and attachment loss ≥ 2 mm) compared to 12% of never smokers and 46% of current smokers. In those aged 31-40 years, 50% of former smokers had periodontitis, compared to 33% of never smokers and 88% of current smokers. In both age groups, the difference between current and never smokers was statistically significant. A similar pattern was also seen in the diabetic patients. There were no differences between current and never smokers in the proportion of sites with plaque.
Jette, 1993 ¹⁰⁹	Cross-sectional	1156 community-dwelling adults aged ≥ 70 years. Of the men, 18% were current smokers, and 65% were former smokers. Of the women, 8% were current smokers, and 37% were former smokers.	Duration of exposure to tobacco products (current smokers versus former smokers) was a statistically significant risk factor for tooth loss and periodontal disease, regardless of other social and behavioural factors.
Bolin, 1993 ²⁰⁶	Prospective cohort, 10 year follow-up	349 subjects examined at two intervals, 10 years apart.	Bone loss was calculated as percent loss in bone height from the first examination to the second examination. Bone loss in smokers over the 10 years was 6.0%, compared to 3.9% in never smokers. Former smokers (i.e. those who were smoking at examination one, but who had quit by examination two) demonstrated 4.4% bone loss, which was significantly less than that in the smokers.
Tomar, 2000 ¹⁹³	Cross-sectional	12,329 dentate subjects ≥ 18 years old from NHANES III, of whom 27.9% were current smokers and 23.3% were former smokers.	Current smokers were 4 times more likely (odds ratio 3.97) and former smokers nearly twice as likely (odds ratio 1.68) than never smokers to have periodontitis, after adjusting for potential confounding variables. In the current smokers, there was a highly significant dose-response relationship between cigarettes smoked per day and the odds of having periodontitis. In former smokers, the odds of having periodontitis declined with the number of years since quitting, from an odds ratio of 3.22 for 0 to 2 years since quitting to an odds ratio of 1.15 (95% CI, 0.83-1.60) after ≥ 11 years since quitting. The authors concluded that 41.9% of periodontitis cases in the U.S. adult population were attributable to current cigarette smoking and 10.9% to former smoking.
Bergstrom, 2000 ²⁰⁷	Cross-sectional	257 dentally aware adults aged 20-69 years. 50 current smokers, 61 former smokers and 133 non-smokers	The mean frequency of sites with probing depths ≥ 4 mm was 6.6 in the former smokers compared with 16.8 in the current smokers and 5.2 in the never smokers (significantly greater in the current smokers compared to the other two groups). Periodontal bone height (% of root length with bone) was 82.0% in former smokers compared to 81.3% in current smokers and 84.5% in never smokers (significantly lower in the current smokers compared to the other two groups). The periodontal status of former smokers was thus intermediate to that of current and never smokers.

Table 6 continued on next page ...

Table 6 continued

Bergstrom, 2000 ¹⁹¹	Prospective cohort, 10-year follow-up	257 dentally aware adults examined in 1982 and 1992. 10-year follow-up of data from Bergstrom 2000 ²⁰⁷ .	The frequency of sites with probing depths \geq 4 mm decreased from 11.1% to 7.8% in the former smokers, compared with a decrease from 8.7% to 6.6% in never smokers and an increase from 18.7% to 41.6% in the current smokers over the 10 year period (the frequency of such sites was significantly greater in the current smokers compared to the other two groups at the second examination). Periodontal bone height decreased from 80.7% to 79.6% in former smokers, compared with a decrease from 85.1% to 84.1% in never smokers and a decrease from 80.3% to 76.5% in current smokers. Overall, the periodontal status of former smokers was similar to that of non-smokers and remained stable (in terms of probing depths and bone height), suggesting that smoking cessation is beneficial to periodontal health.
Haffajee, 2001 ²⁰⁸	Cross-sectional	289 patients aged 20-86 years with chronic periodontitis.	Current smokers had significantly more attachment loss, missing teeth, deeper pockets and fewer sites exhibiting bleeding on probing than former or never smokers. Increasing age and smoking status were significantly related to mean attachment level and the effect of these parameters was additive.
Jansson, 2002 ⁹³	Prospective cohort, 20-year follow up	507 individuals who were examined in 1970 and 1990.	Interproximal bone levels were assessed from radiographs obtained in 1970 and 1990. In 1970, 50.7% were smokers and this decreased to 31.0% in 1990. Smoking was significantly correlated with alveolar bone loss over the 20 years. Individuals who quit smoking between 1970 and 1990 lost significantly less bone than those who smoked continuously.
Baljoon, 2004 ²⁰⁹	Prospective cohort, 10-year follow-up	257 dentally aware adults examined in 1982 and 1992. Same population as Bergstrom 2000 ²⁰⁷ .	The prevalence of vertical bone defects in 1982 was 47% for current smokers, 49% for former smokers, and 24% for non-smokers. In 1992, the prevalence was 42%, 28%, and 19% for current smokers, former smokers, and non-smokers, respectively. Both in 1982 and 1992 the prevalence of vertical defects was significantly related to smoking status.
Paulander, 2004 ²¹⁰	Prospective cohort, 10-year follow-up	295 subjects who were 50 years old when examined in 1988, and who were examined again in 1998.	The relative risk for a mean loss of alveolar bone height \geq 0.5 mm was 3.69 (95% CI: 2.33-5.85) in current smokers and 0.70 (95% CI: 0.31-1.59) in former smokers
Baljoon, 2005 ¹⁹²	Prospective cohort, 10-year follow-up	91 individuals examined in 1982 and 1992. 24 smokers, 24 former smokers, and 43 non-smokers. Sub-group of population from Bergstrom 2000 ²⁰⁷ .	A statistically significant increase in the proportion of vertical defects was observed in all groups but was particularly associated with smoking. In particular, the difference between smokers and never smokers was significant, whereas former smokers did not differ from never smokers.
Torrunguang, 2005 ²¹¹	Cross-sectional	1960 subjects aged 50-73 years. 14.4% current smokers, 36.9% former smokers, and 48.7% never smokers.	Current smokers had more plaque, greater probing depths and more loss of attachment than former smokers and never smokers. Current smokers were 4.8 times more likely to have severe periodontitis than never smokers and former smokers were 1.8 times more likely. Quitting smoking reduced the odds of having periodontitis. For quitters who had < 15 pack-years of smoking, their odds for severe periodontitis reverted to the level of non-smokers when they had quit smoking for \geq 10 years. For those with \geq 15 pack-years of smoking, the odds of having severe periodontitis did not differ from those of non-smokers when they had quit smoking for \geq 20 years.
Thomson, 2007 ⁴¹	Prospective cohort, 6 year follow up	810 individuals in a longstanding cohort study examined at age 26 and age 32. 31.5% were current smokers, 17.4% were former smokers, and 51.1% were never smokers.	Smokers had 5-7 times increased risk for having at least one site with \geq 5 mm attachment loss compared to never smokers. Two-thirds of new cases of periodontitis after age 26 were attributable to smoking. There were no significant differences in periodontal health between never smokers and those who had quit smoking after age 26.
Do, 2008 ³²	Cross-sectional	3161 individuals examined as part of an Australian national oral health survey. 15% current smokers, 23% former smokers, and 62% never smokers.	The overall prevalence of periodontitis was 23%. In unadjusted analyses, former and current smokers had significantly higher prevalence of periodontitis than never smokers. Relative to non-smokers, adjusted prevalence ratios (95% CI) for periodontitis were as follows: former smokers: 1.22 (1.03-1.46), moderate smokers (5-15 pack years): 1.63 (1.16-2.30); and heavy smokers (> 15 pack years): 1.64 (1.27-2.12).

Table 7 The effect of smoking cessation on periodontal treatment outcomes.

Author, year	Study	Sample	Results
Kaldahl, 1996 ²¹²	Prospective cohort, 7-year follow-up	74 patients with periodontitis. 31 heavy smokers, 15 light smokers, 15 former smokers and 18 never smokers.	Heavy and light smokers demonstrated less favourable treatment outcomes than former smokers or never smokers.
Grossi, 1997 ²¹³	Cross-sectional (3 month evaluation of treatment outcomes)	143 patients with periodontitis. 60 current smokers, 55 former smokers and 28 never smokers.	Mean probing depth reductions in former smokers were 0.49 mm (full mouth) and 1.7 mm (pockets > 5mm at baseline), almost identical to the probing depth reductions seen in never smokers (0.49 mm and 1.8 mm, respectively), and better than those observed in current smokers (0.33 mm and 1.3 mm, respectively). The probing depth reductions were significantly lower for the current smokers compared to the other two groups.
Ryder, 1999 ²¹⁴	Prospective cohort, 9-month follow up of patients from two 9-month multicentre clinical trials that compared scaling and root planing to local delivery of doxycycline	358 patients with periodontitis. 121 current smokers, 137 former smokers, and 100 never smokers.	In the scaling and root planing group, mean probing depth reductions in former smokers (1.05 mm in pockets \geq 5 mm and 1.58 mm in pockets \geq 7 mm) were almost identical to those seen in current smokers (1.02 mm and 1.48 mm, respectively) and were significantly less than those observed in never smokers (1.43 mm and 2.06 mm, respectively). In the doxycycline treated group, there were no marked significant differences in clinical attachment gain or probing depth reduction among the 3 smoking groups.
Preshaw, 1999 ²¹⁵	Prospective cohort, 6 month follow-up	41 patients with periodontitis. 15 current smokers, 14 former smokers, and 12 never smokers.	Current smokers, former smokers and never smokers did not differ significantly in plaque scores, bleeding scores, attachment levels, or radiographic bone loss. Mean probing depths were significantly greater in current smokers than in never and former smokers. Probing depths were reduced comparably in all 3 smoking subgroups following treatment, with no significant differences between groups (mean full mouth probing depth reductions were 0.55 mm in never smokers, 0.67 mm in former smokers and 0.78 in current smokers).
Meinberg, 2001 ²¹⁶	Prospective cohort, 1-year follow-up	95 patients with treated chronic periodontitis in a 3-monthly maintenance programme.	Mean baseline radiographic interproximal bone loss in former smokers (4.89 mm) was intermediate to that seen in current smokers (5.75 mm) and never smokers (4.64 mm). Over 1 year, bone loss occurred in 5% of the sites, but was not significantly different between the smoking sub-groups.
Hughes, 2006 ²¹⁷	Prospective cohort, 10 weeks follow-up	79 patients with generalised aggressive periodontitis. 20 were current smokers, 19 were former smokers and 40 were never smokers.	Treatment outcomes were poorer in smokers (mean probing depth reduction 1.75 ± 0.56 mm) than in the former smokers and never smokers combined (mean probing depth reduction 2.23 ± 0.87 mm). There were no significant differences in treatment responses between former smokers (mean probing depth reduction 2.1 ± 0.84 mm) and never smokers (mean probing depth reduction 2.3 ± 0.89 mm).

Table 8 Interventional studies of the effect of smoking cessation on the periodontium.

Author, year	Study	Sample	Results
Nair, 2003 ²¹⁸	Interventional study, short term (4-6 weeks) investigation of effect of smoking cessation on gingival bleeding	27 smokers participating in a quit smoking programme who had no signs of advanced periodontitis.	Data for the 27 quitters revealed a statistically significant increase in the proportion of sites that bled on (constant force) probing from 15.7% to 31.9% as a result of quitting. At the same time, a significant decrease in the proportion of sites with plaque occurred, from 38.9% to 28.1%.
Morozumi, 2004 ²¹⁹	Interventional study, short term (8 weeks) investigation of effect of smoking cessation on gingival vasculature	16 male, periodontally healthy smokers.	11 of the 16 subjects successfully quit smoking for 8 weeks (and the other 5 subjects dropped out of the study). Gingival blood flow (determined by laser Doppler flow) and gingival crevicular fluid volume increased significantly following smoking cessation in the 11 quitters.
Preshaw, 2005 ¹⁹⁴	Interventional study, 12 month follow-up	49 smokers with chronic periodontitis who wished to quit smoking.	After 12 months, of patients with complete data, 10 had continuously quit (20% quit rate), 10 continued smoking and six were 'oscillators' (patients who quit and then resumed smoking). Analysis of probing depth reductions between baseline and month 12, and comparing quitters with the other two groups combined, demonstrated a significant benefit of quitting on mean probing depth reductions (additional mean reduction of 0.32 mm in the quitters). Quitters were significantly more likely to demonstrate probing depth reductions ≥ 2 and ≥ 3 mm than non-quitters and oscillators. Thus, quitters had increased odds (relative risk = 1.67) of demonstrating probing depth reductions ≥ 2 mm compared with the other two groups, and more than twice the odds of demonstrating probing depth reductions ≥ 3 mm (relative risk = 2.36).

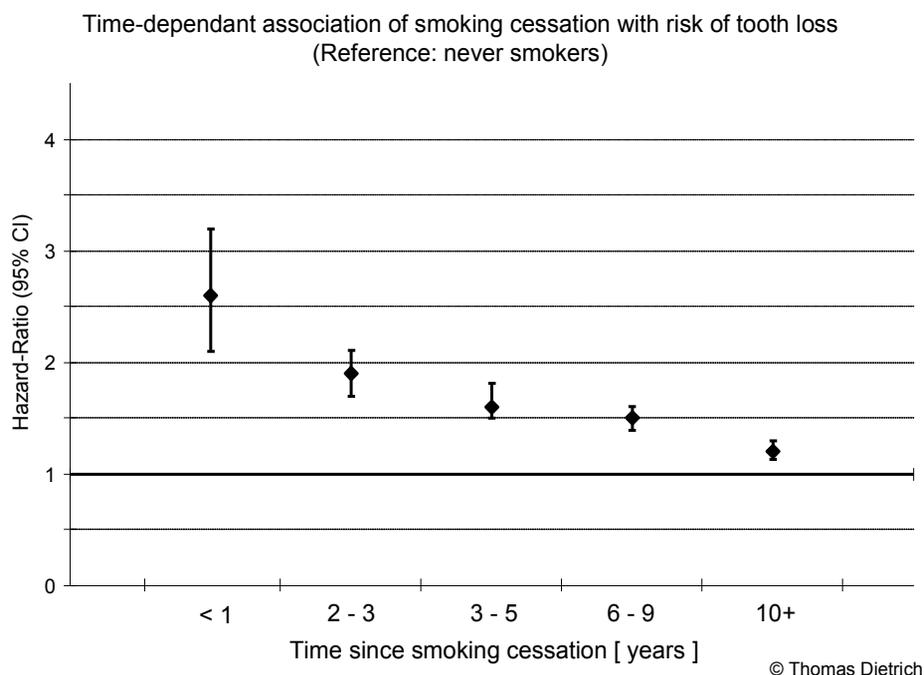


Figure 3. Hazard ratios and 95% confidence intervals (CI) for the time-dependent association between cessation of cigarette smoking and risk of tooth loss in the Health Professionals Follow-up Study, United States, 1986-2002. (Used with permission)

Conclusion

There is considerable evidence suggesting that former smokers have smaller risks of tobacco related oral diseases than current smokers. Reduction of risk following smoking cessation appears to be a function of time since cessation. While marked benefits of smoking cessation can be expected in the short-term, it may take several years of abstinence for the risk to decline to that of never smokers. However, robust data to estimate the decline in risk as a function of time since cessation are lacking for several oral health endpoints (Table 5). Nevertheless, it is evident that substantial oral health benefits can be expected from successful smoking cessation in a wide variety of populations across all ages.

The effectiveness of interventions in a dental setting to achieve smoking cessation is considered by Needleman *et al.*²²¹. Although few intervention studies have specifically evaluated the effect of smoking cessation on oral health endpoints the group felt that planning and conducting randomised controlled trials in the future on the effectiveness of smoking cessation to improve oral health outcomes may not be feasible due to many difficulties including ethical considerations because of the generally well documented benefits of smoking cessation as well as large sample sizes and long follow-up needed to document improvements in oral health outcomes. However, the group firmly believed that properly designed studies of the effects of smoking cessation interventions (for example, prospective observational studies of the effect of quitting) should continue to be performed to increase further the evidence base to support the benefits of tobacco use cessation and to provide further information on matters such as the length of time since quitting by which disease risks are reduced to be similar to those of non-smokers. In fact after completion of our workshop and prior to this publication, new evidence emerged that quitting smoking for 1-4 years resulted in oral cancer risk reduction (OR 0.65 95% CI 0.52-0.80) compared with current smokers, with risk reduction due to smoking cessation after 20 years (OR 0.19 95% CI 0.15-0.24) reaching level of never smokers²²².

In summary, the findings of this review demonstrate robust evidence that avoidance or cessation of smoking, results in substantial improvements in oral health status at all ages.

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References

1. *Tobacco smoke and involuntary smoking*. Lyon: IARC; 2004. International Agency for Research on Cancer.
2. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol* 2009; **45**: 309-316.
3. Gandini S, Botteri E, Iodice S *et al.* Tobacco smoking and cancer: a meta-analysis. *Int J Cancer* 2008 **122** 1: 155-164.
4. Nordlund LA, Carstensen JM, Pershagen G. Cancer incidence in female smokers: a 26-year follow-up. *Int J Cancer* 1997 **73** 5: 625-628.
5. Negri E, La Vecchia C, Franceschi S *et al.* Attributable risk for oral cancer in northern Italy. *Cancer Epidemiol Biomarkers Prev* 1993 **2** 3: 189-193.
6. Llewellyn CD, Johnson NW, Warnakulasuriya KA. Risk factors for oral cancer in newly diagnosed patients aged 45 years and younger: a case-control study in Southern England. *J Oral Pathol Med* 2004 **33** 9: 525-532.
7. Hashibe M, Brennan P, Benhamou S *et al.* Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst* 2007 **99** 10: 777-789.
8. Talamini R, Franceschi S, Barra S *et al.* The role of alcohol in oral and pharyngeal cancer in non-smokers, and of tobacco in non-drinkers. *Int J Cancer* 1990 **46** 3: 391-393.
9. Shanks TG. *Disease consequences of cigar smoking*. Bethesda, MD: National Cancer Institute; 1998.
10. Rahman M, Sakamoto J, Fukui T. Bidi smoking and oral cancer: a meta-analysis. *Int J Cancer* 2003 **106** 4: 600-604.
11. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000 **100** 1: 57-70.
12. Bartsch H, Rojas M, Nair U *et al.* Genetic cancer susceptibility and DNA adducts: studies in smokers, tobacco chewers, and coke oven workers. *Cancer Detect Prev* 1999 **23** 6: 445-453.
13. Bartsch H, Nair U, Risch A *et al.* Genetic polymorphism of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. *Cancer Epidemiol Biomarkers Prev* 2000 **9** 1: 3-28.
14. Lazarus P, Park JY. Metabolizing enzyme genotype and risk for upper aerodigestive tract cancer. *Oral Oncol* 2000 **36** 5: 421-431.
15. Geisler SA, Olshan AF. GSTM1, GSTT1, and the risk of squamous cell carcinoma of the head and neck: a mini-HuGE review. *Am J Epidemiol* 2001 **154** 2: 95-105.
16. Jones NJ, McGregor AD, Waters R. Detection of DNA adducts in human oral tissue: correlation of adduct levels with tobacco smoking and differential enhancement of adducts using the butanol extraction and nuclease P1 versions of 32P postlabeling. *Cancer Res* 1993 **53** 7: 1522-1528.
17. Stone JG, Jones NJ, McGregor AD *et al.* Development of a human biomonitoring assay using buccal mucosa: comparison of smoking-related DNA adducts in mucosa versus biopsies. *Cancer Res* 1995 **55** 6: 1267-1270.
18. Hecht SS. Cigarette smoking and lung cancer: chemical mechanisms and approaches to prevention. *Lancet Oncol* 2002 **3** 8: 461-469.
19. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med* 2007 **36** 10: 575-580.

20. Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. *J Oral Pathol Med* 2008 37 1: 1-10.
21. Warnakulasuriya S, Reibel J, Bouquot J *et al*. Oral epithelial dysplasia classification systems: predictive value, utility, weaknesses and scope for improvement. *J Oral Pathol Med* 2008 37 3: 127-133.
22. Morse DE, Katz RV, Pendry DG *et al*. Smoking and drinking in relation to oral epithelial dysplasia. *Cancer Epidemiol Biomarkers Prev* 1996 5 10: 769-777.
23. Kulasegaram R, Downer MC, Jullien JA *et al*. Case-control study of oral dysplasia and risk habits among patients of a dental hospital. *Eur J Cancer B Oral Oncol* 1995 31B 4: 227-231.
24. Jaber MA, Porter SR, Gilthorpe MS *et al*. Risk factors for oral epithelial dysplasia--the role of smoking and alcohol. *Oral Oncol* 1999 35 2: 151-156.
25. Siegel MA. *Premalignant lesions*. In: Ord RA, Blanchard Jr. RH, editors. *Oral cancer: The dentist's role in diagnosis, management, rehabilitation and prevention*. Chicago: Quintessence; 1999. p. 49-63.
26. van der Waal I, Reichart PA. Oral proliferative verrucous leukoplakia revisited. *Oral Oncol* 2008 44 8: 719-721.
27. Bergstrom J. Periodontitis and smoking: an evidence-based appraisal. *J Evid Based Dent Pract* 2006 6 1: 33-41.
28. Al-Bayaty FH, Wahid NA, Bulgiba AM. Tooth mortality in smokers and nonsmokers in a selected population in Sana'a, Yemen. *J Periodontol Res* 2008 43 1: 9-13.
29. Baharin B, Palmer RM, Coward P *et al*. Investigation of periodontal destruction patterns in smokers and non-smokers. *J Clin Periodontol* 2006 33 7: 485-490.
30. Borges-Yanez SA, Irigoyen-Camacho ME, Maupome G. Risk factors and prevalence of periodontitis in community-dwelling elders in Mexico. *J Clin Periodontol* 2006 33 3: 184-194.
31. Buduneli N, Kardesler L, Isik H *et al*. Effects of smoking and gingival inflammation on salivary antioxidant capacity. *J Clin Periodontol* 2006 33 3: 159-164.
32. Do LG, Slade GD, Roberts-Thomson KF *et al*. Smoking-attributable periodontal disease in the Australian adult population. *J Clin Periodontol* 2008 35 5: 398-404.
33. Kibayashi M, Tanaka M, Nishida N *et al*. Longitudinal study of the association between smoking as a periodontitis risk and salivary biomarkers related to periodontitis. *J Periodontol* 2007 78 5: 859-867.
34. Levin L, Baev V, Lev R *et al*. Aggressive periodontitis among young Israeli army personnel. *J Periodontol* 2006 77 8: 1392-1396.
35. Linden GJ, Mullally BH. Cigarette smoking and periodontal destruction in young adults. *J Periodontol* 1994 65 7: 718-723.
36. Nicolau B, Netuveli G, Kim JW *et al*. A life-course approach to assess psychosocial factors and periodontal disease. *J Clin Periodontol* 2007 34 10: 844-850.
37. Ojima M, Hanioka T, Tanaka K *et al*. Relationship between smoking status and periodontal conditions: findings from national databases in Japan. *J Periodontol Res* 2006 41 6: 573-579.
38. Okamoto Y, Tsuboi S, Suzuki S *et al*. Effects of smoking and drinking habits on the incidence of periodontal disease and tooth loss among Japanese males: a 4-yr longitudinal study. *J Periodontol Res* 2006 41 6: 560-566.
39. Rosa GM, Lucas GQ, Lucas ON. Cigarette smoking and alveolar bone in young adults: a study using digitized radiographs. *J Periodontol* 2008 79 2: 232-244.
40. Shimazaki Y, Saito T, Kiyohara Y *et al*. The influence of current and former smoking on gingival bleeding: the Hisayama study. *J Periodontol* 2006 77 8: 1430-1435.
41. Thomson WM, Broadbent JM, Welch D *et al*. Cigarette smoking and periodontal disease among 32-year-olds: a prospective study of a representative birth cohort. *J Clin Periodontol* 2007 34 10: 828-834.
42. Van der Velden U, Abbas F, Armand S *et al*. Java project on periodontal diseases. The natural development of periodontitis: risk factors, risk predictors and risk determinants. *J Clin Periodontol* 2006 33 8: 540-548.
43. Vered Y, Livny A, Zini A *et al*. Periodontal health status and smoking among young adults. *J Clin Periodontol* 2008 35 9: 768-772.
44. Wang QT, Wu ZF, Wu YF *et al*. Epidemiology and preventive direction of periodontology in China. *J Clin Periodontol* 2007 34 11: 946-951.
45. Ylostalo P, Suominen-Taipale L, Reunanen A *et al*. Association between body weight and periodontal infection. *J Clin Periodontol* 2008 35 4: 297-304.
46. Biddle AJ, Palmer RM, Wilson RF *et al*. Comparison of the validity of periodontal probing measurements in smokers and non-smokers. *J Clin Periodontol* 2001 28 8: 806-812.
47. Linden G, Patterson C, Evans A *et al*. Obesity and periodontitis in 60-70-year-old men. *J Clin Periodontol* 2007 34 6: 461-466.
48. Bergstrom J. Tobacco smoking and chronic destructive periodontal disease. *Odontology* 2004 92 1: 1-8.
49. Bergstrom J. Tobacco smoking and risk for periodontal disease. *J Clin Periodontol* 2003 30 2: 107-113.
50. Cuff MJ, McQuade MJ, Scheidt MJ *et al*. The presence of nicotine on root surfaces of periodontally diseased teeth in smokers. *J Periodontol* 1989 60 10: 564-569.
51. Chen X, Wolff L, Aepli D *et al*. Cigarette smoking, salivary/gingival crevicular fluid cotinine and periodontal status. A 10-year longitudinal study. *J Clin Periodontol* 2001 28 4: 331-339.
52. Kinane DF, Chestnutt IG. Smoking and periodontal disease. *Crit Rev Oral Biol Med* 2000 11 3: 356-365.
53. Palmer RM, Wilson RF, Hasan AS *et al*. Mechanisms of action of environmental factors--tobacco smoking. *J Clin Periodontol* 2005 32 Suppl 6: 180-195.
54. Rivera-Hidalgo F. Smoking and periodontal disease. A review of the literature. *J Periodontol* 1986 57 10: 617-624.
55. Rivera-Hidalgo F. Smoking and periodontal disease. *Periodontol* 2000 2003 32: 50-58.
56. Theilade E, Wright WH, Jensen SB *et al*. Experimental gingivitis in man. II. A longitudinal clinical and bacteriological investigation. *J Periodontol Res* 1966 1: 1-13.
57. Hanioka T, Tanaka M, Takaya K *et al*. Pocket oxygen tension in smokers and non-smokers with periodontal disease. *J Periodontol* 2000 71 4: 550-554.
58. van Winkelhoff AJ, Bosch-Tijhof CJ, Winkel EG *et al*. Smoking affects the subgingival microflora in periodontitis. *J Periodontol* 2001 72 5: 666-671.
59. Van der Velden U, Varoufaki A, Hutter JW *et al*. Effect of smoking and periodontal treatment on the subgingival microflora. *J Clin Periodontol* 2003 30 7: 603-610.
60. Kazor CE, Mitchell PM, Lee AM *et al*. Diversity of bacterial populations on the tongue dorsa of patients with halitosis and healthy patients. *J Clin Microbiol* 2003 41 2: 558-563.
61. Mombelli A. Periodontitis as an infectious disease: specific features and their implications. *Oral Dis* 2003 9 Suppl 1: 6-10.
62. Gunsolley JC, Pandey JP, Quinn SM *et al*. The effect of race, smoking and immunoglobulin allotypes on IgG subclass concentrations. *J Periodontol Res* 1997 32 4: 381-387.
63. Loos BG, Roos MT, Schellekens PT *et al*. Lymphocyte numbers and function in relation to periodontitis and smoking. *J Periodontol* 2004 75 4: 557-564.
64. Ryder MI. The influence of smoking on host responses in periodontal infections. *Periodontol* 2000 2007 43: 267-277.
65. Ryder MI, Wu TC, Kallaos SS *et al*. Alterations of neutrophil f-actin kinetics by tobacco smoke: implications for periodontal diseases. *J Periodontol Res* 2002 37 4: 286-292.

66. Tangada SD, Califano JV, Nakashima K *et al.* The effect of smoking on serum IgG2 reactive with *Actinobacillus actinomycetemcomitans* in early-onset periodontitis patients. *J Periodontol* 1997 68 9: 842-850.
67. Egelberg J. The blood vessels of the dento-gingival junction. *J Periodontol Res* 1966 1 3: 163-179.
68. Preber H, Bergstrom J. Effect of non-surgical treatment on gingival bleeding in smokers and non-smokers. *Acta Odontol Scand* 1986 44 2: 85-89.
69. Dietrich T, Bernimoulin JP, Glynn RJ. The effect of cigarette smoking on gingival bleeding. *J Periodontol* 2004 75 1: 16-22.
70. Mavropoulos A, Aars H, Brodin P. Hyperaemic response to cigarette smoking in healthy gingiva. *J Clin Periodontol* 2003 30 3: 214-221.
71. Meekin TN, Wilson RF, Scott DA *et al.* Laser Doppler flowmeter measurement of relative gingival and forehead skin blood flow in light and heavy smokers during and after smoking. *J Clin Periodontol* 2000 27 4: 236-242.
72. Mirbod SM, Ahing SI. Tobacco-associated lesions of the oral cavity: Part I. Nonmalignant lesions. *J Can Dent Assoc* 2000 66 5: 252-256.
73. Rezavandi K, Palmer RM, Odell EW *et al.* Expression of ICAM-1 and E-selectin in gingival tissues of smokers and non-smokers with periodontitis. *J Oral Pathol Med* 2002 31 1: 59-64.
74. Payne JB, Johnson GK, Reinhardt RA *et al.* Nicotine effects on PGE2 and IL-1 beta release by LPS-treated human monocytes. *J Periodontol Res* 1996 31 2: 99-104.
75. Krall EA, Dawson-Hughes B. Smoking increases bone loss and decreases intestinal calcium absorption. *J Bone Miner Res* 1999 14 2: 215-220.
76. Michalowicz BS, Diehl SR, Gunsolley JC *et al.* Evidence of a substantial genetic basis for risk of adult periodontitis. *J Periodontol* 2000 71 11: 1699-1707.
77. Meisel P, Schwahn C, Gesch D *et al.* Dose-effect relation of smoking and the interleukin-1 gene polymorphism in periodontal disease. *J Periodontol* 2004 75 2: 236-242.
78. Meisel P, Siegemund A, Dombrowa S *et al.* Smoking and polymorphisms of the interleukin-1 gene cluster (IL-1alpha, IL-1beta, and IL-1RN) in patients with periodontal disease. *J Periodontol* 2002 73 1: 27-32.
79. Meisel P, Timm R, Sawaf H *et al.* Polymorphism of the N-acetyltransferase (NAT2), smoking and the potential risk of periodontal disease. *Arch Toxicol* 2000 74 6: 343-348.
80. Johnson GK, Guthmiller JM. The impact of cigarette smoking on periodontal disease and treatment. *Periodontology* 2000 2007 44: 178-194.
81. Axelsson P, Paulander J, Lindhe J. Relationship between smoking and dental status in 35-, 50-, 65-, and 75-year-old individuals. *J Clin Periodontol* 1998 25 4: 297-305.
82. Daniell HW. Postmenopausal tooth loss. Contributions to edentulism by osteoporosis and cigarette smoking. *Arch Intern Med* 1983 143 9: 1678-1682.
83. Gilbert GH, Duncan RP, Crandall LA *et al.* Attitudinal and behavioral characteristics of older Floridians with tooth loss. *Community Dent Oral Epidemiol* 1993 21 6: 384-389.
84. Krall EA, Dawson-Hughes B, Garvey AJ *et al.* Smoking, smoking cessation, and tooth loss. *J Dent Res* 1997 76 10: 1653-1659.
85. Mundt T, Schwahn C, Mack F *et al.* Risk indicators for missing teeth in working-age Pomeranians: an evaluation of high-risk populations. *J Public Health Dent* 2007 67 4: 243-249.
86. Hanioka T, Ojima M, Tanaka K *et al.* Relationship between smoking status and tooth loss: findings from national databases in Japan. *J Epidemiol* 2007 17 4: 125-132.
87. Ojima M, Hanioka T, Tanaka K *et al.* Cigarette smoking and tooth loss experience among young adults: a national record linkage study. *BMC Public Health* 2007 7 147: 313.
88. Ylostalo P, Sakki T, Laitinen J *et al.* The relation of tobacco smoking to tooth loss among young adults. *Eur J Oral Sci* 2004 112 2: 121-126.
89. Ahlqwist M, Bengtsson C, Hollender L *et al.* Smoking habits and tooth loss in Swedish women. *Community Dent Oral Epidemiol* 1989 17 3: 144-147.
90. Dietrich T, Maserejian NN, Joshipura KJ *et al.* Tobacco use and incidence of tooth loss among US male health professionals. *J Dent Res* 2007 86 4: 373-377.
91. Eklund SA, Burt BA. Risk factors for total tooth loss in the United States; longitudinal analysis of national data. *J Public Health Dent* 1994 54 1: 5-14.
92. Holm G. Smoking as an additional risk for tooth loss. *J Periodontol* 1994 65 11: 996-1001.
93. Jansson L, Lavstedt S. Influence of smoking on marginal bone loss and tooth loss—a prospective study over 20 years. *J Clin Periodontol* 2002 29 8: 750-756.
94. Krall EA, Dietrich T, Nunn ME *et al.* Risk of tooth loss after cigarette smoking cessation. *Prev Chronic Dis* 2006 3 4: A115.
95. Copeland LB, Krall EA, Brown LJ *et al.* Predictors of tooth loss in two US adult populations. *J Public Health Dent* 2004 64 1: 31-37.
96. Krall EA, Garvey AJ, Garcia RI. Alveolar bone loss and tooth loss in male cigar and pipe smokers. *J Am Dent Assoc* 1999 130 1: 57-64.
97. Hinode D, Tanabe S, Yokoyama M *et al.* Influence of smoking on osseointegrated implant failure: a meta-analysis. *Clin Oral Implants Res* 2006 17 4: 473-478.
98. Klokkevold PR, Han TJ. How do smoking, diabetes, and periodontitis affect outcomes of implant treatment? *Int J Oral Maxillofac Implants* 2007 22 Suppl: 173-202.
99. Strietzel FP, Reichart PA, Kale A *et al.* Smoking interferes with the prognosis of dental implant treatment: a systematic review and meta-analysis. *J Clin Periodontol* 2007 34 6: 523-544.
100. Ellegaard B, Baelum V, Kolsen-Petersen J. Non-grafted sinus implants in periodontally compromised patients: a time-to-event analysis. *Clin Oral Implants Res* 2006 17 2: 156-164.
101. Fransson C, Wennstrom J, Berglundh T. Clinical characteristics at implants with a history of progressive bone loss. *Clin Oral Implants Res* 2008 19 2: 142-147.
102. Kinsel RP, Liss M. Retrospective analysis of 56 edentulous dental arches restored with 344 single-stage implants using an immediate loading fixed provisional protocol: statistical predictors of implant failure. *Int J Oral Maxillofac Implants* 2007 22 5: 823-830.
103. Mesa F, Munoz R, Noguero B *et al.* Multivariate study of factors influencing primary dental implant stability. *Clin Oral Implants Res* 2008 19 2: 196-200.
104. Moy PK, Medina D, Shetty V *et al.* Dental implant failure rates and associated risk factors. *Int J Oral Maxillofac Implants* 2005 20 4: 569-577.
105. Mundt T, Mack F, Schwahn C *et al.* Private practice results of screw-type tapered implants: survival and evaluation of risk factors. *Int J Oral Maxillofac Implants* 2006 21 4: 607-614.
106. Roos-Jansaker AM, Lindahl C, Renvert H *et al.* Nine- to fourteen-year follow-up of implant treatment. Part I: implant loss and associations to various factors. *J Clin Periodontol* 2006 33 4: 283-289.
107. Wagenberg B, Froum SJ. A retrospective study of 1925 consecutively placed immediate implants from 1988 to 2004. *Int J Oral Maxillofac Implants* 2006 21 1: 71-80.
108. Zitterbart PA, Matranga LF, Christen AG *et al.* Association between cigarette smoking and the prevalence of dental caries in adult males. *Gen Dent* 1990 38 6: 426-431.
109. Jette AM, Feldman HA, Tennstedt SL. Tobacco use: a modifiable risk factor for dental disease among the elderly. *Am J Public Health* 1993 83 9: 1271-1276.

110. Ravald N, Birkhed D, Hamp SE. Root caries susceptibility in periodontally treated patients. Results after 12 years. *J Clin Periodontol* 1993 20 2: 124-129.
111. Bergstrom J. Oral hygiene compliance and gingivitis expression in cigarette smokers. *Scand J Dent Res* 1990 98 6: 497-503.
112. Andrews JA, Severson HH, Lichtenstein E *et al.* Relationship between tobacco use and self-reported oral hygiene habits. *J Am Dent Assoc* 1998 129 3: 313-320.
113. Sakki TK, Knuutila ML, Vimpari SS *et al.* Association of lifestyle with periodontal health. *Community Dent Oral Epidemiol* 1995 23 3: 155-158.
114. Zappacosta B, Persichilli S, Mordente A *et al.* Inhibition of salivary enzymes by cigarette smoke and the protective role of glutathione. *Hum Exp Toxicol* 2002 21 1: 7-11.
115. Eriksen HM, Nordbo H. Extrinsic discoloration of teeth. *J Clin Periodontol* 1978 5 4: 229-236.
116. Asmussen E, Hansen EK. Surface discoloration of restorative resins in relation to surface softening and oral hygiene. *Scand J Dent Res* 1986 94 2: 174-177.
117. Pasquali B. Menstrual phase, history of smoking, and taste discrimination in young women. *Percept Mot Skills* 1997 84 3 Pt 2: 1243-1246.
118. Meraw SJ, Mustapha IZ, Rogers RS, 3rd. Cigarette smoking and oral lesions other than cancer. *Clin Dermatol* 1998 16 5: 625-631.
119. Meechan JG, Macgregor ID, Rogers SN *et al.* The effect of smoking on immediate post-extraction socket filling with blood and on the incidence of painful socket. *Br J Oral Maxillofac Surg* 1988 26 5: 402-409.
120. Holmstrup P, Bessermann M. Clinical, therapeutic, and pathogenic aspects of chronic oral multifocal candidiasis. *Oral Surg Oral Med Oral Pathol* 1983 56 4: 388-395.
121. Morris AG. Archaeological evidence of 'pipe-smoker's wear'. *J Dent Assoc S Afr* 1988 43 8: 361-364.
122. Rivera-Hidalgo F, Shulman JD, Beach MM. The association of tobacco and other factors with recurrent aphthous stomatitis in an US adult population. *Oral Dis* 2004 10 6: 335-345.
123. Axell T, Henricsson V. The occurrence of recurrent aphthous ulcers in an adult Swedish population. *Acta Odontol Scand* 1985 43 2: 121-125.
124. Salonen L, Axell T, Hellden L. Occurrence of oral mucosal lesions, the influence of tobacco habits and an estimate of treatment time in an adult Swedish population. *J Oral Pathol Med* 1990 19 4: 170-176.
125. Tuzun B, Wolf R, Tuzun Y *et al.* Recurrent aphthous stomatitis and smoking. *Int J Dermatol* 2000 39 5: 358-360.
126. Rosenberg M. Clinical assessment of bad breath: current concepts. *J Am Dent Assoc* 1996 127 4: 475-482.
127. Alomari Q, Barrieshi-Nusair K, Said K. Smoking prevalence and its effect on dental health attitudes and behavior among dental students. *Med Princ Pract* 2006 15 3: 195-199.
128. Nalcaci R, Baran I. Factors associated with self-reported halitosis (SRH) and perceived taste disturbance (PTD) in elderly. *Arch Gerontol Geriatr* 2008 46 3: 307-316.
129. Christen AG. The impact of tobacco use and cessation on oral and dental diseases and conditions. *Am J Med* 1992 93 1A: 25S-31S.
130. Bornstein MM, Stocker BL, Seemann R *et al.* Prevalence of halitosis in young male adults. A study in Swiss Army recruits comparing self-reported and clinical data. *J Periodontol* 2009; 80: 24-31
131. Hedin CA. Smokers' melanosis. Occurrence and localization in the attached gingiva. *Arch Dermatol* 1977 113 11: 1533-1538.
132. Axell T, Hedin CA. Epidemiologic study of excessive oral melanin pigmentation with special reference to the influence of tobacco habits. *Scand J Dent Res* 1982 90 6: 434-442.
133. Hedin CA, Axell T. Oral melanin pigmentation in 467 Thai and Malaysian people with special emphasis on smoker's melanosis. *J Oral Pathol Med* 1991 20 1: 8-12.
134. Nwhator SO, Winfunke-Savage K, Ayanbadejo P *et al.* Smokers' melanosis in a Nigerian population: a preliminary study. *J Contemp Dent Pract* 2007 8 5: 68-75.
135. Reibel J. Tobacco and oral diseases. Update on the evidence, with recommendations. *Med Princ Pract* 2003 12 Suppl 1: 22-32.
136. van Wyk CW. Nicotinic stomatitis of the palate: a clinicohistological study. *J Dent Assoc S Afr* 1967 22 4: 106-111.
137. Reichart PA. Primarprvention des Mundhohlenkarzinoms und oraler Prakanzerosen. *Mund Kiefer Gesichtschir* 2000 4 6: 357-364.
138. Philipsen HP, Petersen JK, Simonsen BH. Necrotizing sialometaplasia of the palate. Ulcerative or necrotizing stage of leukokeratosis nicotina palati? *Int J Oral Surg* 1976 5 6: 292-299.
139. Critchley JA, Unal B. Health effects associated with smokeless tobacco: a systematic review. *Thorax* 2003 58 5: 435-443.
140. Wasnik KS, Ughade SN, Zodpey SP *et al.* Tobacco consumption practices and risk of oro-pharyngeal cancer: a case-control study in Central India. *Southeast Asian J Trop Med Public Health* 1998 29 4: 827-834.
141. Brown A, Ravichandran K, Warnakulasuriya S. The unequal burden related to the risk of oral cancer in the different regions of the Kingdom of Saudi Arabia. *Community Dent Health* 2006 23 2: 101-106.
142. Idris AM, Ahmed HM, Malik MO. Toombak dipping and cancer of the oral cavity in the Sudan: a case-control study. *Int J Cancer* 1995 63 4: 477-480.
143. Weitkunat R, Sanders E, Lee PN. Meta-analysis of the relation between European and American smokeless tobacco and oral cancer. *BMC Public Health* 2007 7: 334.
144. Boffetta P, Hecht S, Gray N *et al.* Smokeless tobacco and cancer. *Lancet Oncol* 2008 9 7: 667-675.
145. Winn DM, Blot WJ, Shy CM *et al.* Snuff dipping and oral cancer among women in the southern United States. *N Engl J Med* 1981 304 13: 745-749.
146. Blot WJ, McLaughlin JK, Winn DM *et al.* Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 1988 48 11: 3282-3287.
147. Lewin F, Norell SE, Johansson H *et al.* Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck: a population-based case-referent study in Sweden. *Cancer* 1998 82 7: 1367-1375.
148. Luo J, Ye W, Zendehdel K *et al.* Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet* 2007 369 9578: 2015-2020.
149. Rosenquist K, Wennerberg J, Schildt EB *et al.* Use of Swedish moist snuff, smoking and alcohol consumption in the aetiology of oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. *Acta Otolaryngol* 2005 125 9: 991-998.
150. Schildt EB, Eriksson M, Hardell L *et al.* Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. *Int J Cancer* 1998 77 3: 341-346.
151. Roosaar A, Johansson AL, Sandborgh-Englund G *et al.* Cancer and mortality among users and nonusers of snus. *Int J Cancer* 2008 123 1: 168-173.
152. Roosaar A, Johansson AL, Sandborgh-Englund G *et al.* A long-term follow-up study on the natural course of snus-induced lesions among Swedish snus users. *Int J Cancer* 2006 119 2: 392-397.
153. Cnattingius S, Galanti R, Grafstrom R *et al.*, editors. Health risks from Swedish snuff. Stockholm: Karolinska Institute; 2005.
154. *Smokeless tobacco and some tobacco-specific N-nitrosamines*. Lyon: IARC; International Agency for Research on Cancer. 2007.

155. Jansson T, Romert L, Magnusson J *et al.* Genotoxicity testing of extracts of a Swedish moist oral snuff. *Mutat Res* 1991 **261** 2: 101-115.
156. Whong WZ, Stewart JD, Ong T. Formation of bacterial mutagens from the reaction of chewing tobacco with nitrite. *Mutat Res* 1985 **158** 3: 105-110.
157. Niphadkar MP, Bagwe AN, Bhisey RA. Mutagenic potential of Indian tobacco products. *Mutagenesis* 1996 **11** 2: 151-154.
158. Warnakulasuriya KA, Ralhan R. Clinical, pathological, cellular and molecular lesions caused by oral smokeless tobacco--a review. *J Oral Pathol Med* 2007 **36** 2: 63-77.
159. Gupta PC, Mehta FS, Daftary DK *et al.* Incidence rates of oral cancer and natural history of oral precancerous lesions in a 10-year follow-up study of Indian villagers. *Community Dent Oral Epidemiol* 1980 **8** 6: 283-333.
160. Bhonsle RB, Murti PR, Daftary DK *et al.* An oral lesion in tobacco-lime users in Maharashtra, India. *J Oral Pathol* 1979 **8** 1: 47-52.
161. Thomas G, Hashibe M, Jacob BJ *et al.* Risk factors for multiple oral premalignant lesions. *Int J Cancer* 2003 **107** 2: 285-291.
162. Idris AM, Ibrahim SO, Vasstrand EN *et al.* The Swedish snus and the Sudanese toombak: are they different? *Oral Oncol* 1998 **34** 6: 558-566.
163. Tyldesley WR. Tobacco chewing in english coal miners. A preliminary report. *Br J Oral Surg* 1971 **9** 1: 21-28.
164. Sinusas K, Coroso JG, Sopher MD *et al.* Smokeless tobacco use and oral pathology in a professional baseball organization. *J Fam Pract* 1992 **34** 6: 713-718.
165. Robertson PB, Walsh M, Greene J *et al.* Periodontal effects associated with the use of smokeless tobacco. *Journal of Periodontology* 1990 **61**: 438-443.
166. Grady D, Greene J, Daniels TE *et al.* Oral mucosal lesions found in smokeless tobacco users. *J Am Dent Assoc* 1990 **121** 1: 117-123.
167. Tomar SL, Winn DM, Swango PA *et al.* Oral mucosal smokeless tobacco lesions among adolescents in the United States. *J Dent Res* 1997 **76** 6: 1277-1286.
168. Roed-Petersen B, Pindborg JJ. A study of Danish snuff-induced oral leukoplakias. *J Oral Pathol* 1973 **2** 6: 301-313.
169. Jungell P, Malmstrom M. Snuff-induced lesions in Finnish recruits. *Scand J Dent Res* 1985 **93** 5: 442-447.
170. Axell T. A prevalence study of oral mucosal lesions in an adult Swedish population. *Odontol Revy Suppl* 1976 **36**: 1-103.
171. Offenbacher S, Weathers DR. Effects of smokeless tobacco on the periodontal, mucosal and caries status of adolescent males. *Journal of Oral Pathology* 1985 **14**: 169-181.
172. Wolfe MD, Carlos JP. Oral health effects of smokeless tobacco use in Navajo Indian adolescents. *Community Dentistry & Oral Epidemiology* 1987 **15**: 230-235.
173. Lavstedt S, Modåcer T, Welander E. Plaque and gingivitis in a group of Swedish schoolchildren with special reference to tooth-brushing habits. *Acta Odontologica Scandinavica* 1982 **40**: 307-311.
174. Modeer T, Lavstedt S, Ahlund C. Relation between tobacco consumption and oral health in Swedish schoolchildren. *Acta Odontologica Scandinavica* 1980 **38**: 223-227.
175. Rolandsson M, Hellqvist L, Lindqvist L *et al.* Effects of snuff on the oral health status of adolescent males: a comparative study. *Oral Health & Preventive Dentistry* 2005 **3**: 77-85.
176. Andersson G, Axell T. Clinical appearance of lesions associated with the use of loose and portion-bag packed Swedish moist snuff: a comparative study. *Journal of Oral Pathology & Medicine* 1989 **18**: 2-7.
177. Montén U, Wennström JL, Ramberg P. Periodontal conditions in male adolescents using smokeless tobacco (moist snuff). *Journal of Clinical Periodontology* 2006 **33**: 863-868.
178. Fisher MA, Taylor GW, Tilashalski KR. Smokeless tobacco and severe active periodontal disease, NHANES III. *Journal of Dental Research* 2005 **84**: 705-710.
179. Bergstrom J, Keilani H, Lundholm C *et al.* Smokeless tobacco (snuff) use and periodontal bone loss. *J Clin Periodontol* 2006 **33** 8: 549-554.
180. Payne JB, Johnson GK, Reinhardt RA *et al.* Smokeless tobacco effects on monocyte secretion of PGE2 and IL-1 beta. *Journal of Periodontology* 1994 **65**: 937-941.
181. Johnson GK, Poore TK, Payne JB *et al.* Effect of smokeless tobacco extract on human gingival keratinocyte levels of prostaglandin E2 and interleukin-1. *Journal of Periodontology* 1996 **67**: 116-124.
182. Poore TK, Johnson GK, Reinhardt RA *et al.* The effects of smokeless tobacco on clinical parameters of inflammation and gingival crevicular fluid prostaglandin E2, interleukin-1 alpha, and interleukin-1 beta. *Journal of Periodontology* 1995 **66**: 177-183.
183. Bernzweig E, Payne JB, Reinhardt RA *et al.* Nicotine and smokeless tobacco effects on gingival and peripheral blood mononuclear cells. *Journal of Clinical Periodontology* 1998 **25**: 246-252.
184. Seyedroudbari SA, Khan MM. In vitro effects of smokeless tobacco extract on tumor necrosis factor-alpha (TNF-alpha) and interleukin-1beta (IL-1beta) production, and on lymphocyte proliferation. *Toxicol* 1998 **36**: 631-637.
185. Furie MB, Raffanello JA, Gergel EI *et al.* Extracts of smokeless tobacco induce pro-inflammatory changes in cultured human vascular endothelial cells. *Immunopharmacology* 2000 **47**: 13-23.
186. Robertson PB, Walsh MM, Greene JC. Oral effects of smokeless tobacco use by professional baseball players. *Adv Dent Res* 1997 **11** 3: 307-312.
187. Tomar SL, Winn DM. Chewing tobacco use and dental caries among U.S. men. *Journal of the American Dental Association* 1999 **130**: 1601-1610.
188. Going RE, Hsu SC, Pollack RL *et al.* Sugar and fluoride content of various forms of tobacco. *Journal of the American Dental Association* 1980 **100**: 27-33.
189. La Vecchia C, Franceschi S, Bosetti C *et al.* Time since stopping smoking and the risk of oral and pharyngeal cancers. *J Natl Cancer Inst* 1999 **91** 8: 726-728.
190. Schlecht NF, Franco EL, Pintos J *et al.* Effect of smoking cessation and tobacco type on the risk of cancers of the upper aero-digestive tract in Brazil. *Epidemiology* 1999 **10** 4: 412-418.
191. Bergstrom J, Eliasson S, Dock J. A 10-year prospective study of tobacco smoking and periodontal health. *Journal of Periodontology* 2000 **71**: 1338-1347.
192. Baljoon M, Natto S, Bergstrom J. Long-term effect of smoking on vertical periodontal bone loss. *Journal of Clinical Periodontology* 2005 **32**: 789-797.
193. Tomar SL, Asma S. Smoking-attributable periodontitis in the United States: findings from NHANES III. National Health and Nutrition Examination Survey. *Journal of Periodontology* 2000 **71**: 743-751.
194. Preshaw PM, Heasman L, Stacey F *et al.* The effect of quitting smoking on chronic periodontitis. *Journal of Clinical Periodontology* 2005 **32**: 869-879.
195. Roed-Petersen B. Effect on oral leukoplakia of reducing or ceasing tobacco smoking. *Acta Derm Venereol* 1982 **62** 2: 164-167.
196. Poate TW, Warnakulasuriya S. Effective management of smoking in an oral dysplasia clinic in London. *Oral Dis* 2006 **12** 1: 22-26.
197. Hedin CA, Pindborg JJ, Axell T. Disappearance of smoker's melanosis after reducing smoking. *J Oral Pathol Med* 1993 **22** 5: 228-230.
198. Bosetti C, Gallus S, Peto R *et al.* Tobacco smoking, smoking cessation, and cumulative risk of upper aerodigestive tract cancers. *Am J Epidemiol* 2008 **167** 4: 468-473.

199. Macfarlane GJ, Zheng T, Marshall JR *et al.* Alcohol, tobacco, diet and the risk of oral cancer: a pooled analysis of three case-control studies. *Eur J Cancer B Oral Oncol* 1995 31B 3: 181-187.
200. Gupta PC, Murti PR, Bhonsle RB *et al.* Effect of cessation of tobacco use on the incidence of oral mucosal lesions in a 10-yr follow-up study of 12,212 users. *Oral Dis* 1995 1 1: 54-58.
201. Tonetti MS. Cigarette smoking and periodontal diseases: etiology and management of disease. *Annals of Periodontology* 1998 3: 88-101.
202. Ramseier CA. Potential impact of subject-based risk factor control on periodontitis. *Journal of Clinical Periodontology* 2005 32: 283-290.
203. Heasman L, Stacey F, Preshaw PM *et al.* The effect of smoking on periodontal treatment response: a review of clinical evidence. *Journal of Clinical Periodontology* 2006 33: 241-253.
204. Bergstrom J, Eliasson S, Preber H. Cigarette smoking and periodontal bone loss. *Journal of Periodontology* 1991 62: 242-246.
205. Haber J, Wattles J, Crowley M *et al.* Evidence for cigarette smoking as a major risk factor for periodontitis. *Journal of Periodontology* 1993 64: 16-23.
206. Bolin A, Eklund G, Frithiof L *et al.* The effect of changed smoking habits on marginal alveolar bone loss. A longitudinal study. *Swedish Dental Journal* 1993 17: 211-216.
207. Bergstrom J, Eliasson S, Dock J. Exposure to tobacco smoking and periodontal health. *J Clin Periodontol* 2000 27 1: 61-68.
208. Haffajee AD, Socransky SS. Relationship of cigarette smoking to attachment level profiles. *Journal of Clinical Periodontology* 2001 28: 283-295.
209. Baljoon M, Natto S, Bergstrom J. The association of smoking with vertical periodontal bone loss. *Journal of Periodontology* 2004 75: 844-851.
210. Paulander J, Wennstrom JL, Axelsson P *et al.* Some risk factors for periodontal bone loss in 50-year-old individuals. A 10-year cohort study. *Journal of Clinical Periodontology* 2004 31: 489-496.
211. Torrungruang K, Nisapakultorn K, Sutdhibhisal S *et al.* The effect of cigarette smoking on the severity of periodontal disease among older Thai adults. *Journal of Periodontology* 2005 76: 566-572.
212. Kaldahl WB, Johnson GK, Patil KD *et al.* Levels of cigarette consumption and response to periodontal therapy. *Journal of Periodontology* 1996 67: 675-681.
213. Grossi SG, Zambon J, Machtei EE *et al.* Effects of smoking and smoking cessation on healing after mechanical periodontal therapy. *Journal of the American Dental Association* 1997 128: 599-607.
214. Ryder MI, Pons B, Adams D *et al.* Effects of smoking on local delivery of controlled-release doxycycline as compared to scaling and root planing. *Journal of Clinical Periodontology* 1999 26: 683-691.
215. Preshaw PM, Lauffart B, Zak E *et al.* Progression and treatment of chronic adult periodontitis. *Journal of Periodontology* 1999 70: 1209-1220.
216. Meinberg TA, Canarsky-Handley AM, McClenahan AK *et al.* Outcomes associated with supportive periodontal therapy in smokers and nonsmokers. *Journal of Dental Hygiene* 2001 75: 15-19.
217. Hughes FJ, Syed M, Koshy B *et al.* Prognostic factors in the treatment of generalized aggressive periodontitis: II. Effects of smoking on initial outcome. *Journal of Clinical Periodontology* 2006 33: 671-676.
218. Nair P, Sutherland G, Palmer RM *et al.* Gingival bleeding on probing increases after quitting smoking. *Journal of Clinical Periodontology* 2003 30: 435-437.
219. Morozumi T, Kubota T, Sato T *et al.* Smoking cessation increases gingival blood flow and gingival crevicular fluid. *Journal of Clinical Periodontology* 2004 31: 267-272.
220. Bain CA. Smoking and implant failure--benefits of a smoking cessation protocol. *Int J Oral Maxillofac Implants* 1996 11 6: 756-759.
221. Needleman IG, Vivian IB, Ainamo A *et al.* Improving the effectiveness of tobacco use cessation (TUC). *Int Dent J* 2010 60: 30-58.
222. Marron M, Boffettap, Zhang ZF *et al.* Cessation of alcohol drinking, tobacco smoking and reversal of head and neck cancer risk. *Int J Epidemiol* 2010 39: 182-196

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