表1　平成17年度歯周疾患医療費

年齢階級	平成17年度歯科医療費総額	平成17年度社会医療診療行為別換算	患者調査配分による歯周疾患医療費		平成17年患者調査(歯周疾患)	
	(億円)	医療費(歯肉炎+歯周炎)(円)	男性(円)	女性(円)	男性(人)	女性(人)
総　数	25,766	839,541,515,809	343,521,367,123	494,515,225,308	130,500	178,300
0～4歳	405	0	0	0	300	600
5～9歳	1,023	318,069,299	179,423,707	138,645,592	2,200	1,700
10～14歳	550	474,251,252	320,119,595	154,131,657	2,700	1,300
15～19歳	557	10,280,807,807	4,984,634,088	5,296,173,719	1,600	1,700
20～24歳	869	34,150,852,909	9,420,924,940	24,729,927,969	2,400	6,300
25～29歳	1,313	55,464,175,485	18,766,074,412	36,698,101,072	4,500	8,800
30～34歳	1,662	78,965,797,349	27,590,459,315	51,375,338,034	5,800	10,800
35～39歳	1,641	75,347,111,857	32,291,619,367	43,055,492,490	8,400	11,200
40～44歳	1,390	65,588,147,491	26,173,673,881	39,414,473,610	8,500	12,800
45～49歳	1,597	64,817,853,688	24,347,823,213	40,470,030,475	7,400	12,300
50～54歳	2,009	74,246,742,710	31,599,824,752	42,646,917,958	12,300	16,600
55～59歳	2,493	88,700,022,575	41,190,511,803	47,509,510,772	17,600	20,300
60～64歳	2,591	92,294,724,934	37,379,363,598	54,915,361,336	16,200	23,800
65～69歳	2,370	84,280,043,570	40,422,716,822	43,857,326,748	15,300	16,600
70～74歳	2,405	65,855,314,819	29,124,132,626	36,731,182,193	13,400	16,900
75歳以上	2,890	47,252,676,684	19,730,065,001	27,522,611,683	11,900	16,600

表2　平成17年度喫煙者と非喫煙者の歯周疾患医療費

年齢階級	平成17年患者調査(歯周疾患)(再掲)		歯周疾患患者数のうち				歯周疾患医療費 (推定値、円)			
	男性(人)	女性(人)	男性喫煙(人)	男性非喫煙(人)	女性喫煙(人)	女性非喫煙(人)	男性喫煙	男性非喫煙	女性喫煙	女性非喫煙
総　数	130,500	178,300	72,372	58,128	38,798	139,502	206,838,686,628	136,682,680,495	122,149,798,930	372,365,426,378
0～4歳	300	600	0	300	0	600	0	0	0	0
5～9歳	2,200	1,700	0	2,200	0	1,700	0	179,423,707	0	138,645,592
10～14歳	2,700	1,300	6	2,694	3	1,297	714,325	319,405,271	359,401	153,772,256
15～19歳	1,600	1,700	276	1,324	126	1,574	858,608,767	4,126,025,322	393,503,772	4,902,669,947
20～24歳	2,400	6,300	1,594	806	2,238	4,062	6,258,547,647	3,162,377,293	8,783,847,333	15,946,080,636
25～29歳	4,500	8,800	3,188	1,312	3,208	5,592	13,294,945,067	5,471,129,345	13,376,660,445	23,321,440,628
30～34歳	5,800	10,800	4,179	1,621	3,853	6,947	19,881,234,421	7,709,224,894	18,327,600,889	33,047,737,145
35～39歳	8,400	11,200	6,005	2,395	3,628	7,572	23,084,704,656	9,206,914,711	13,946,938,505	29,108,553,985
40～44歳	8,500	12,800	5,970	2,530	4,200	8,600	18,383,468,919	7,790,204,963	12,931,770,006	26,482,703,603
45～49歳	7,400	12,300	5,175	2,225	3,766	8,534	17,025,626,117	7,322,197,096	12,390,815,525	28,079,214,950
50～54歳	12,300	16,600	8,438	3,862	4,225	12,375	21,677,812,716	9,922,012,036	10,854,487,665	31,792,430,293
55～59歳	17,600	20,300	11,469	6,131	4,452	15,848	26,841,467,183	14,349,044,619	10,418,636,823	37,090,873,949
60～64歳	16,200	23,800	9,179	7,021	3,972	19,828	21,179,229,195	16,200,134,404	9,164,529,168	45,750,832,168
65～69歳	15,300	16,600	7,496	7,804	2,132	14,468	19,804,261,060	20,618,455,762	5,633,051,142	38,224,275,606
70～74歳	13,400	16,900	5,758	7,642	1,862	15,038	12,515,214,102	16,608,918,525	4,046,111,394	32,685,070,799
75歳以上	11,900	16,600	3,639	8,261	1,135	15,465	6,032,852,455	13,697,212,546	1,881,486,863	25,641,124,820

表3　平成17年度喫煙者の歯周疾患超過医療費とその歯周疾患医療費に対する割合

年齢階級	喫煙者超過医療費と歯周疾患医療費に対する超過医療費割合					
	超過医療費男女計	割合男女計	男性超過医療費	割合(男性)	女性超過医療費	割合(女性)
総　数	172,327,301,959	20.5	108,344,073,948	31.5	63,983,228,011	12.9
0～4歳	0	0.0	0	0.0	0	0.0
5～9歳	0	0.0	0	0.0	0	0.0
10～14歳	562,428	0.1	374,170	0.1	188,258	0.1
15～19歳	655,868,473	6.4	449,747,449	9.0	206,121,023	3.9
20～24歳	7,879,349,751	23.1	3,278,286,863	34.8	4,601,062,889	18.6
25～29歳	13,970,840,982	25.2	6,964,018,844	37.1	7,006,822,138	19.1
30～34歳	20,014,151,829	25.3	10,413,979,935	37.7	9,600,171,894	18.7
35～39歳	19,397,527,370	25.7	12,091,988,153	37.4	7,305,539,217	17.0
40～44歳	16,403,220,389	25.0	9,629,436,100	36.8	6,773,784,289	17.2
45～49歳	15,408,612,289	23.8	8,918,185,109	36.6	6,490,427,180	16.0
50～54歳	17,040,728,771	23.0	11,355,044,756	35.9	5,685,684,015	13.3
55～59歳	19,517,197,337	22.0	14,059,816,144	34.1	5,457,381,193	11.5
60～64歳	15,894,349,618	17.2	11,093,881,959	29.7	4,800,467,659	8.7
65～69歳	13,324,306,391	15.8	10,373,660,555	25.7	2,950,645,836	6.7
70～74歳	8,674,980,022	13.2	6,555,588,339	22.5	2,119,391,683	5.8
75歳以上	4,145,606,309	8.8	3,160,065,572	16.0	985,540,738	3.6

＊全歯科医療費に対する割合　　男女計 6.7%

された。さらに、歯科医療の総医療費に占める割合では、全体の平均で6.7%と推計された。また、年齢階級別に超過医療費および歯周疾患医療費に占める割合をみると、男性ではそれぞれ55～59歳および30～34歳に、女性ではそれぞれ30～34歳および25～29歳にピークがみられた。

考　察

本研究の結果から、喫煙がもたらす歯周疾患の超過医療費は1,723億円と見積もられた。中原ら[2]は平成17年のわが国のデータから喫煙が関わる疾患の医療費の増加を、悪性新生物（4,475億円）、高血圧疾患（3,473億円）、虚血性心疾患（1,957億円）、胃・十二指腸潰瘍（1,003億円）、脳血管疾患（937億円）、喘息（747億円）、肝疾患（277億円）、気管支炎・慢性閉塞性肺疾患（246億）と試算した。本研究によって得られた歯周疾患の超過医療費（1,723億円）は、中原ら[2]とは推計方法が異なるため直接的な比較は難しいものの、悪性新生物、高血圧疾患、虚血性疾患に次ぐものであり、歯周疾患における超過医療費が見過ごすことのできない重大な問題であることが明らかになった。

歯周疾患の超過医療費は歯周疾患全体の医療費の20.5%を占めていた。男性に限るとその割合は31.5%であった。また、歯周疾患医療費では女性の方が男性よりも多かったが、超過医療費では男性の方が女性よりも多かった。これらの結果は、歯周疾患の超過医療費を下げる主なターゲットとなる集団は女性よりも男性であることを意味している。特に20～59歳の男性はいずれも30%を超えていること、また平成20年国民健康・栄養調査[14]では29%の男性が20歳未満から喫煙を開始していることを考慮すると、学童期からの介入が必要と考えられる。

なお、今後は女性についても喫煙対策が必要と考えられる。女性の非喫煙者の歯周疾患医療費は60～64歳といういわゆる団塊の世代（人口の多い世代）でピークがみられる一方で、女性の喫煙者では30～34歳にピークがある。これは喫煙による歯周組織への影響が現れている可能性を示唆している。

女性の歯周疾患超過医療費は男性よりも低かった。また女性の総数において喫煙者は非喫煙者よりも歯周疾患医療費が少なく、男性とは逆の結果になった。これらは女性の方が男性よりも喫煙率が低いことが主な原因と思われる。

本研究の結果は一定の条件下（喫煙者・非喫煙者による受療率の差を考慮していないこと、喫煙者の過去の喫煙習慣・喫煙量にかかわらず歯周疾患になる可能性をオッズ比2.1としたこと、歯単位でなく、人単位で検討して歯周疾患医療費を配分したこと、歯周疾患に関係する他のリスク要因の影響を除外したこと、喫煙者の歯の喪失リスクを考慮していないことなど）で算出された結果はあくまでも推定値の域を脱しえない。しかしながら、本算出モデルからの算出結果が喫煙率と歯周疾患リスク（オッズ比2.1）に影響（計算式；①、②、③）される点では、今後推進が必要な歯科領域における禁煙支援活動において、喫煙率低下状況の評価が可能で、健康増進法に掲げる健康増進事業実施者の禁煙指導や禁煙サポートなどの禁煙対策推進の一助になりうる推計モデルといえる。なお、オッズ比2.1はわが国の20～59歳の労働者310名を対象に行った横断研究から得られたものであり、この対象者わが国を代表する集団とはいえない。また、歯周組織の評価はCommunity Periodontal Indexにより、代表歯を用いて行われたものである。歯周疾患の超過医療費の推計制度を高めるために、今後はこのオッズ比についてもさらに検討する必要がある。

「健康日本21」に掲げられる歯科領域（「歯の健康」）の目標は、歯の喪失防止からの国民のQOLの確保であり、歯の喪失の主要因に歯周疾患が挙げられる[2]。わが国の喫煙に関する歯科的な研究の多くは個人の喫煙習慣と受療状況からの喫煙習慣別の医療費積算の研究9)であり、喫煙状況に伴う歯の喪失とその後に必要な歯科医療費に関する研究は十分とはいえない。そのようなことから、本研究の歯科禁煙対策の喫煙率低下ならびに経済効果モデルの開発に続き、今後は、歯の喪失

に伴う歯科医療費への影響から歯科領域での禁煙治療・指導や禁煙サポートの必要性について検証する必要がある。

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Estimation of periodontal care cost savings of quitting smoking based on the national data in Japan

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Key Words : smoking, periodontal disease, health care cost, health economics, estimation

Periodontal care cost savings of quitting smoking was estimated under certain conditions based on the national data in Japan. The estimated periodontal care cost savings in 2005 was 172 billion yen in total, 108 billion in males, and 64 billion in females. The percentages of the savings in total amount of periodontal care cost in total, males and females were 20.5, 31.5 and 12.9, respectively. The percentage of savings in total amount of dental care cost was about 6.7. These results suggest that smoking have a great impact on health care cost and a measure devised to deal with the problem is necessary as soon as possible.

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Impact of a tobacco curriculum on smoking behaviour and attitudes toward smoking in dental students in Japan: a three-year follow-up study

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Aim: Dental professionals have the potential to influence global smoking rates. This study evaluated the impact of a tobacco curriculum on smoking behaviour and attitudes toward smoking in dental students. **Methods:** Immediately before and three years after the implementation of a tobacco curriculum with a no-smoking policy, a questionnaire was administered to students to obtain information about their smoking behaviour and attitudes toward smoking. **Results:** The number of students who responded to the questionnaire was 580 in 2003 and 554 in 2006. The smoking rate decreased significantly from 35% in 2003 to 26% in 2006; however, analysis of data for each school year suggested that this was due to the prevention of smoking initiation rather than quitting smoking. Attitudes toward patient smoking and public policy were more positive in non-smokers than in current smokers. Improvement in attitudes toward patient smoking was smaller in current smokers than in non-smokers. Little improvement occurred in attitudes toward public policy in both non- and current smokers. **Conclusions:** Implementation of a tobacco curriculum was effective in preventing smoking initiation and improving attitudes toward patient smoking in students. Further measures are necessary to improve attitudes toward public policy and to discourage smoking among students.

Key words: Dental student, smoking, attitude, curricula, no-smoking policy

Smoking and exposure to tobacco smoke cause death, disease and disability. Oral health and effects of various dental treatments are also affected by tobacco smoking. Roles of dental professionals and organisations in global tobacco control have been advocated[1,2]. The Japanese Dental Association adopted a code of practice for tobacco control that urged regional organisations to influence health educational centres to include tobacco control in their curricula through continued education and other training programmes.

The smoking rates of Japanese dental students were 30-43% for fourth- and fifth-year students in three schools[3], 32% for all students in one dental school[4] and 54% for fourth-year students in eight dental schools[5]. These rates are far higher than those reported for students from other developed countries: 4% in the United States[6], 7% in England[7] and 13% in Australia[8]. The high rates of smoking among dental students suggest a high rate of smoking dentists in Japan, although little information is available on the smoking rate of dentists. A decreased smoking rate of dental students has the potential to reduce the number of smoking dentists and may increase dentists' involvement in global tobacco control[9].

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Information on smoking behaviour of dental students and their attitudes toward smoking obtained in recent global cross-sectional studies[10-12] implies that tobacco curricula could reduce the number of smoking students and improve their attitudes toward smoking. To our knowledge, few studies have addressed the impact of implementing tobacco curricula on behaviours and attitudes regarding smoking. Implementation of a policy of no-smoking in workplace successfully decreased the number of smoking employees in a hospital[13]. The goal of the present prospective study was to evaluate the impact of implementing a tobacco curriculum with a policy of no-smoking in school buildings on smoking behaviour of dental students and their attitudes toward smoking in a school with high smoking rates.

Subjects and methods

A tobacco curriculum (*Table 1*) was implemented for first-, second-, third- and fifth-year students in a dental school in April 2003. These classes were organised by the Department of Preventive and Public Health Dentistry. The policy of no-smoking in school buildings was implemented on 1 July 2003. The smoking behaviour of the students and their attitudes toward smoking were surveyed using a standardised questionnaire in 633 students immediately before and 623 students three years after the initiation of these activities. The questionnaire was originally developed by WHO, the International Union against Cancer, and the American Cancer Society[14] and was then translated into Japanese and further modified with respect to use for dental students. Students in each class were asked to complete the questionnaire anonymously before a class to avoid any potential for bias.

The questionnaire consisted of four major units: smoking behaviour, reasons for not smoking, and attitudes toward smoking cessation practice and public policies regarding tobacco control including legislative action. To describe smoking behaviour, students were first categorised as current, former and never smokers. The daily and occasional smokers were further grouped as current smokers, and former and never smokers as non-smokers. Students answered each question, except for smoking behaviour, by choosing one item from a five-point Likert scale. For each question, subjects who chose one of the first two answers were classified as agreeing with the statement and having a positive attitude.

Differences between groups in the smoking rate and subjects agreeing with the statement and those with positive attitudes were analysed using the χ^2 test and statistical software (SPSS 15.0J; SPSS, Chicago, IL, USA). The level of significance was set at 5%.

Results

The number of students who responded to the questionnaire was 580 (response rate, 92%) in 2003 and 554 (89%) in 2006. The number of male students decreased from 349 in 2003 to 310 in 2006 and that of females increased from 227 in 2003 to 244 in 2006 (data not shown). The smoking rate of females was lower than that of males (*Table 2*). The overall smoking rate was 35% in 2003, which decreased significantly to 26% ($p < 0.001$) by 2006, when the smoking rate was 40% in males and 8% in females. In 2003, the smoking rate of first-year students was 20% and that of students in other school years was more than 35%, whereas in 2006, it was around 20% for first- to fourth-year students. The smoking rate of second- to fourth-year students was significantly lower in 2006 than in 2003 ($p < 0.01$ or $p < 0.05$). Almost all the students in the first, second and third years in 2003 were the same individuals as those in the fourth, fifth and sixth years in 2006, and their smoking rates were also similar in both surveys ($p > 0.05$), i.e., 20% versus 23%, 40% versus 40%, and 35% versus 33%, respectively.

Table 1 Tobacco curriculum implemented in a dental school since 2003

School year	Class	Mode and content
1	Contemporary civilisation	Lecture on general information about 'Smoking or health' and the role of dental professionals in tobacco control
2	Environmental health	Lecture on the effects of passive smoking on health
3	Public health dentistry and oral epidemiology	Lecture on the effects of smoking on oral health and dental treatment and exercise on the association of smoking with gingival melanin pigmentation
5	Preventive dentistry	Lecture on the effects of smoking on dental treatments and exercise on smoking cessation practice using role play
	Other activities	Lecture on the effects of smoking on physical exercise to captains of athletic clubs

Non-smokers had generally positive perception regarding importance of the reasons for not smoking rather than current smokers (Data not shown). The percentages of former and never smokers increased by 3 and 7 points, respectively, between the two surveys (*Table 3*). The percentage of never smokers among second-, third- and fourth-year students increased by 19, 12 and 9 points, respectively, between surveys. Comparing identical classes, the percentage of former smokers increased by 4-6 points, but the percentage of never smokers decreased by 3-7 points.

Non-smokers generally had a stronger positive perception of the importance of the reasons for not smoking than current smokers (*Table 4*). In 2003, the most important reason for not smoking among current smokers was 'symptoms' (90%) followed by 'to protect your health' (79%); less frequent reasons were 'to set a good example for health workers' (55%) and 'to set

Table 2 Comparison of smoking rates (%) in 2003 and 2006 according to the school year

School year	Male		Female		Total			p value for the identical class
	2003	2006	2003	2006	2003	2006	p value	
1	30	23	7	8	20[a]	18	NS	
2	53	34	18	9	40[b]	22	<0.01	
3	46	43	20	2	35[c]	21	<0.05	
4	56	42	15	0	42	23[a]	<0.01	NS[a]
5	46	55	7	13	36	40[b]	NS	NS[b]
6	60	44	7	18	39	33[c]	NS	NS[c]
Total	49	40	12	8	35	26	<0.001	

Almost all students in the first[a], second[b] and third[c] years in 2003 were the same individuals as those in the fourth[a], fifth[b] and sixth[c] years in 2006.

Table 3 Percentages of former and never smokers in 2003 and 2006 according to the school year

School year	Former smoker			Never smoker		
	2003	2006	Change	2003	2006	Change
1	5[a]	6		74[a]	76	
2	4[b]	3		56[b]	75	
3	2[c]	5		62[c]	74	
4	0	10[a]	+5[a]	58	67[a]	−7[a]
5	6	8[b]	+4[b]	58	52[b]	−4[b]
6	8	8[c]	+6[c]	54	59[c]	−3[c]
Total	4	7		60	67	

Almost all students in the first[a], second[b], and third[c] years in 2003 were the same individuals as those in the fourth[a], fifth[b] and sixth[c] years in 2006.

Table 4 Comparison of percentages of subjects with positive perception regarding importance of reasons for not smoking according to the smoking status

Reason for not smoking	Current smoker			Non-smoker		
	2003	2006	p value	2003	2006	p value
Occurrence of certain symptoms	90	93	NS	74	77	NS
To protect your health	79	85	NS	87	92	<0.05
Not to create discomfort to people nearby	69	67	NS	83	86	NS
To set a good example for children	60	73	<0.05	76	84	<0.05
To set a good example for health workers	55	60	NS	70	78	<0.05
To set a good example for patients	54	65	NS	70	78	<0.05
To save money	50	62	<0.05	61	71	<0.01
Self-discipline	31	34	NS	43	43	NS
Example for colleagues	21	30	NS	46	51	NS

a good example for patients' (54%). Among current smokers, the percentage of individuals with a positive perception increased significantly for two items ($p < 0.05$) between 2003 and 2006; among non-smokers, such an increase was observed for five items ($p < 0.01$ or $p < 0.05$).

More non-smokers than current smokers had a generally positive attitude toward smoking cessation practice (*Table 5*). The statement with which the highest percentage of students agreed regarding patient smoking in 2003 was that 'most people will not quit smoking even if their dentist tells them to' (63%) in current smokers and that 'dentists would be more likely to advise if they knew an approach which really worked' (70%) in non-smokers. Only one item in the list of statements regarding patient smoking was agreed with by *more* than 50% of current smokers in 2003. In contrast, only one item in the list was agreed with by *less* than 50% of non-smokers in 2003 and 2006. The statement which was the least agreed upon in both groups was 'your current knowledge is sufficient for counselling a patient who wants to quit' in 2003 and 2006. Compared to the 2003 survey, among current smokers, the percentage of student agreement increased significantly for five items from the list of statements in 2006, whereas among non-smokers, all items showed a significant increase in the percentage in agreement in 2006 ($p < 0.001$ to $p < 0.05$).

Current smokers had a less positive attitude toward public health policy on tobacco control than non-smokers (*Table 6*). The percentage of current smokers with a positive perception regarding public policy for tobacco control exceeded 50% for only one of the 10 items regarding the policy in 2003, whereas less than 20% of smoking students had a positive attitude for three items. In contrast, more than half of non-smokers had a positive attitude to all items. The percentage of

Table 5 Comparison of percentages of subjects who agreed with statements regarding patient smoking according to the smoking status

	Current smoker			Non-smoker		
	2003	2006	p value	2003	2006	p value
Most people will not quit smoking even if their dentist tells them to	63	60	NS	68	74	<0.05
Dentists would be more likely to advise if they knew an approach which really worked	46	58	NS	70	77	<0.01
Dentists should be more active in speaking to lay groups	42	56	<0.05	66	79	<0.001
It is the dentist's responsibility to convince people to stop smoking	37	54	<0.01	56	73	<0.001
Dentists should set a good example by not smoking	33	50	<0.01	64	73	<0.01
At every contact you should dissuade a patient from smoking	31	42	<0.05	51	61	<0.01
Your current knowledge is sufficient for counselling a patient who wants to quit	27	40	<0.05	23	34	<0.001

Table 6 Comparison of percentages of subjects with positive perception regarding public policy, including legislative action on tobacco control according to the smoking status

	Smoker			Non-smoker		
	2003	2006	p value	2003	2006	p value
Sales to children prohibited	62	68	NS	85	86	NS
Health warning on cigarette packages	48	46	NS	85	87	NS
Smoking in hospital restricted	41	55	<0.001	80	84	NS
Health professionals trained	41	45	NS	77	75	NS
Smoking restricted in public places	37	49	NS	83	87	NS
Non-smoking train cars increased	25	28	NS	80	81	NS
Governmental campaigns promoted	22	28	NS	69	71	NS
Vending machine restricted	16	25	NS	61	60	NS
Complete ban on advertising	13	28	<0.01	51	51	NS
Price of cigarettes increased	13	25	<0.01	53	63	<0.01

smoking students with a positive perception in 2006 was significantly greater than that in 2003 for only three items ($p < 0.01$ or $p < 0.001$).

Changes in the mean percentages of students with positive perceptions three years after implementation of anti-tobacco activities are plotted against smoking rate for each school year in *Figure 1*. Trends in negative correlation between attitudes toward anti-smoking activity and smoking rate were identical among the following three categories: reasons for not smoking (*Figure 1A*), smoking cessation practice (*Figure 1B*) and public policies regarding tobacco control (*Figure 1C*). Several classes in the questions in categories A and B showed an improvement in the percentage of students with a positive attitude, though the change in the smoking rate was the least.

Discussion

The findings of the present study confirmed that smoking behaviour influences attitudes toward smoking. The strength of the present study was its prospective approach using students from all school years. The improvements following the intervention were demonstrated by changes in several components of the questionnaire. The smoking rate of male students was found to be 49%, which was higher than the 39% reported for 1,590 students from 19 medical schools in Japan[4], but lower than the 56% reported for people from the general population in their 20s in a national survey[15]. Decreasing the number of smoking students may be an important means of improving attitudes toward the role of dentistry in global tobacco control in this population.

The smoking rate of sixth-year students (53%) was nearly twice that of the first-year students (29%) in a Romanian dental school[16]. A similar difference was observed in the present study, indicating that many students started smoking during their school years. The three-year intervention described in the present article may have contributed to the prevention of initiation of smoking during the school course by increasing the number of school-year classes with a low smoking rate and decreasing the smoking rates in the second- to fourth-year classes.

More accurate information can be obtained by observing changes in the same class. The decrease of 3-7 points in the smoking rate in never smokers in the classes we studied was less than the difference between first- and sixth-year students, which was 19 points in 2003 and 15 points in 2006. Total smoking rates were similar in both the surveys, but the percentage of former smokers increased and that of never smokers decreased during the 3-year interval. Accordingly, such an intervention could minimise the rate of starting smoking

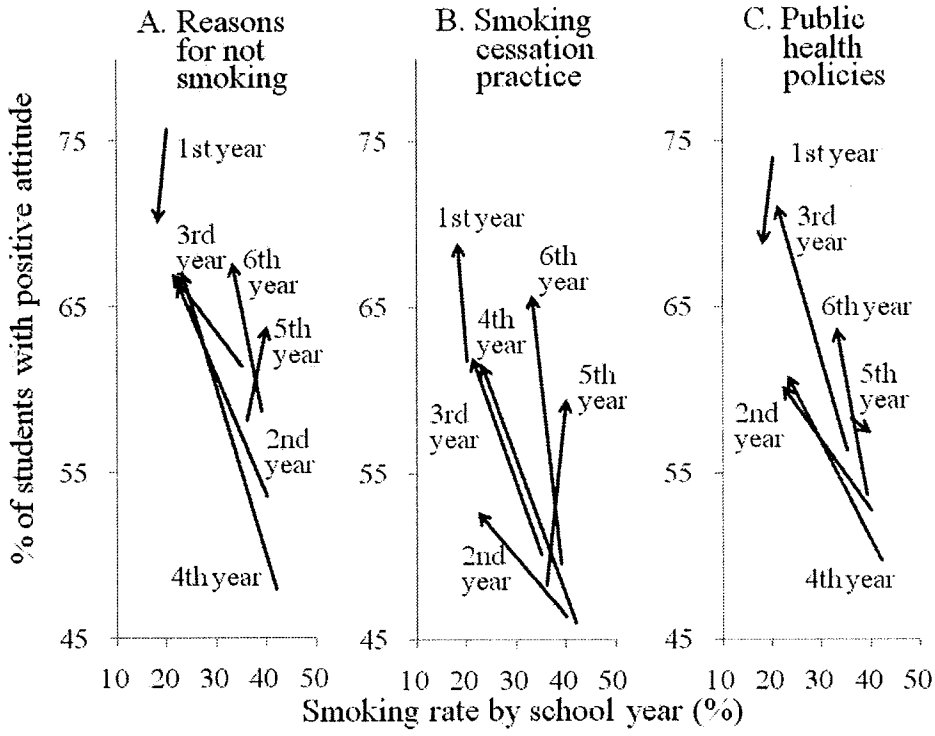

Figure 1. Changes over 3 years after implementation of anti-tobacco activities in the mean percentages of students reporting a positive perception regarding reasons for not smoking (A), smoking cessation practice (B) and public policies regarding tobacco control (C), plotted against smoking rate for each school year.

and improve the balance between starting and quitting smoking.

The impact of the intervention should be interpreted carefully because of the lack of a non-intervention group. The decreases in smoking rate in males (9 points) and females (4 points) among dental students were comparable to those of people from the general population in their 20s[15], which were 11 points in males (56–45%) and 1 point in females (19–18%), respectively. The increase in 17 female students during the 3-year interval might contribute to the improvement of smoking rate, since the smoking rate of females is far lower than that of males.

Lack of effective smoking cessation interventions for college smokers is a recognised problem[17–19]. Since the most important reasons for not smoking were relevant to personal health events, personalised feedback regarding smoking-associated oral symptoms, such as lip and gingival pigmentation, which appear in young smokers[20,21], can be used to discourage dental students from continuing to smoke. The implementation of smoking cessation counselling for incoming smoking students might have the potential to reduce the number of smoking students. Dental students have been asked to undergo training of tobacco cessation counselling as standardised patients[22,23].

Attitudes regarding patient smoking and public policy regarding tobacco control improved significantly in both current and non-smokers in the present study. Tobacco curricula would be an effective measure to improve attitudes toward smoking among students. However, changes in attitudes toward public policy were less apparent than attitudes toward smoking by patients. Similar problems were found in Chinese dental students[11], although their smoking rate (4%) was far lower than that of the population studied in the present study. The role of dentistry in tobacco control[1,2] should be further reflected in the tobacco curricula in terms of public policy.

The questionnaire we used was originally developed for a global survey of medical students[14] and was modified for dental students[3]. Recent studies in the Global Health Professions Student Survey (GHPSS)[10-12] have covered a wider range of professions: dental, medical, nursing and pharmacy students. The authors, who participated in the GHPSS in Japan, recognised that the components of the two types of questionnaire were similar. Therefore, the findings of the present study may be comparable with those of the GHPSS.

Several limitations of our study should be considered. The major limitation was the lack of a non-intervention group as a control to evaluate the effects of anti-smoking activities. Therefore, the impact of the anti-tobacco activities should be interpreted carefully. Second, the impact of a revised curriculum, which may be confounded by the parallel introduction of a no-smoking policy[24], might be overestimated. However, the influence of a policy of no-smoking in the school building would be diluted because students would be able to smoke between classes in smoking areas adjacent to the building. Third, the follow-up period was 3 years and students who were in their sixth year in 2006 therefore received the intervention during only half of their school years, and thus, the impact of the revised tobacco curriculum may have been underestimated. Finally, the findings were obtained from a study of students at a private dental school. There are 17 private and 12 public dental schools in Japan. Our findings should be interpreted carefully before being generalised.

In conclusion, the implementation of tobacco curricula with a policy of no-smoking in school buildings improved attitudes of dental students toward smoking. The impact was greater in non-smokers than in current smokers. The smoking rate decreased significantly, although the decrease may have been due to the prevention of smoking initiation rather than discouragement of smoking. Further intervention measures that would effectively discourage students from smoking and improve attitudes toward public policies regarding tobacco control should be developed and established by conducting controlled studies with an observation period longer than the duration of the school course and should be enforced in dental schools in order to encourage dental education system to become involved in global tobacco control[12,25].

Conflict of interest and source of funding

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Intensive Smoking-cessation Intervention in the Dental Setting

ABSTRACT

Smoking exerts detrimental effects on dental treatment and oral health. Our goal was to evaluate effectiveness in terms of the abstinence rate in smoking-cessation intervention delivered by dental professionals. Individuals who were willing to quit smoking were randomly assigned to either an intervention or a non-intervention group. Intensive intervention was provided, consisting of 5 counseling sessions, including an additional nicotine replacement regimen. Reported abstinence was verified by the salivary cotinine level. Thirty-three persons in the intervention and 23 in the non-intervention group started the trial. On an intent-to-treat basis, 3-, 6- and 12-month continuous abstinence rates in the intervention group were 51.5%, 39.4%, and 36.4%, respectively, while the rates in the non-intervention group were consistent at 13.0%. Adjusted odds ratios (95% confidence interval) by logistic stepwise regression analyses were 7.1 (1.8, 28.5), 8.9 (1.7, 47.2), and 6.4 (1.3, 30.7), respectively. Intensive smoking-cessation intervention in the dental setting was therefore effective.

KEY WORDS: smoking cessation, dentist, dental hygienist, randomized control trial.

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INTRODUCTION

The causal association of smoking with oral diseases has been established—for example, oral cancer and periodontal disease (US Department of Health and Human Services, 2004). Smoking is also associated with various forms of oral symptoms. Premature tooth loss is associated with smoking (Krall *et al.*, 1997; Hanioka *et al.*, 2007a), and smoking impairs the effects of dental treatments. Smoking also decreases the effects of periodontal treatment (Preber and Bergström, 1990; Kaldahl *et al.*, 1996; Grossi *et al.*, 1997). Root canal treatment (Krall *et al.*, 2006), wound healing after tooth extraction (Larsen, 1992), and dental implant failure (Chuang *et al.*, 2002) have also been shown to be affected by smoking. Smoking cessation decreases the risk of tooth loss (Dietrich *et al.*, 2007) and dental implant failure (Lambert *et al.*, 2000) and increases the speed of recovery after periodontal treatment (Preshaw *et al.*, 2005). Smoking cessation is therefore an important measure for the prevention of oral diseases and symptoms and may help to ensure that the effects of dental treatment are sustained.

Various dental organizations around the world have recommended the cessation of tobacco use. A chart of mucosal lesions was disseminated for the early detection of oral cancer (Mecklenburg *et al.*, 1994). A smoking cessation manual for dental teams was developed by the US Government (Mecklenburg *et al.*, 1991) and another by the British Dental Association (Beaglehole and Watt, 2004). At a global level, an advocacy guide for oral health professionals included smoking cessation practice (FDI/WHO, 2005). Since clinical trials with physician and dentist involvement were conducted for a comprehensive tobacco control strategy (Cohen *et al.*, 1994), the effectiveness of smoking-cessation intervention in the dental setting has been highlighted; however, standardizing the evaluation is difficult due to the variety of intervention regimens (Carr and Ebbert, 2007).

In Japan, the smoking rates for male and female adults were 39.9% and 10.0%, respectively, in 2006. The rate in men is high in developed countries and that of young females is increasing. Smoking cessation guidelines were first introduced in cooperation with 7 medical and 2 dental academies in 2005 and included the role of dental professionals; however, little information is available on smoking-cessation practices in Japan. In 2006 in Japan, smoking-cessation treatment by physicians was approved by governmental health insurance *via* the recognition of "nicotine dependence" as a disease. The protocol for intensive intervention includes the diagnosis of nicotine dependence, counseling about smoking behavior modification, and prescription of the nicotine patch. An intensive smoking-cessation intervention conducted by dental hygienists has been successful (Binnie *et al.*, 2007). In the dental setting, smoking-cessation intervention may be implemented to ensure effective treatment against dental diseases. The aim of this feasibility study was to evaluate the potential effectiveness of an intensive smoking-cessation intervention delivered by dental professionals, with the outcome measured in terms of abstinence rates.

METHODS

Two local dental associations, one in Hiroshima prefecture and one in Nagasaki city, agreed to the recruitment of dental clinics. Dentists and dental hygienists in 30 dental clinics participated in a 3-hour training course of intensive smoking-cessation intervention. The course, which consisted of a counseling lecture and an additional pharmaceutical regimen and role-playing exercises, was organized to achieve the goals of the experimental protocol. The detailed protocol for the intervention is described below. This study was approved by the ethics committee of Fukuoka Dental College.

Adults were screened by means of a questionnaire that asked about their willingness to stop smoking within 1 mo. Those who were pregnant, breast-feeding, or had a history of at least one of the following diseases were excluded: angina pectoris, myocardial infarction, arrhythmia, another heart disease, cerebral hemorrhage, subarachnoid hemorrhage, and another cerebral disease.

Patients in each clinic were assigned to intervention and non-intervention groups. Because free nicotine transdermal patches were provided to the intervention group, with no similar benefit to the non-intervention group, non-intervention group participants may have been disappointed to find that they were not being offered this benefit. Disappointment could have led to selective dropout or unwanted changes in behavior. We therefore used a modified random consent design (Kaper *et al.*, 2005); participants were blinded to the existence of the counterpart experimental group.

Participants were given brief verbal information about the study and were asked about their interest in taking part. Those who agreed to participate were assigned to the intervention or non-intervention group according to an assignment card in an envelope provided *a priori* to the clinics. After randomization, those assigned to the intervention group were told in more detail that the study examined the effectiveness of intensive smoking-cessation intervention, and those in the non-intervention group were told about the salivary test. Participants in both groups then gave written informed consent to participate. A brief intervention protocol had been recommended previously (Tomar, 2001; Gordon *et al.*, 2005).

The protocol in the intervention group consisted of 5 visits. At the first visit, participants were counseled to set a quit date, including two major regimens to prevent relapse, consisting of behavioral and pharmaceutical approaches. Self-help material and nicotine patches (Nicotinel® TTS®, Novartis Pharma K.K., Tokyo, Japan), which consisted of 3 dosage levels, were provided for the first 6 wks with information regarding nicotine gum (Nicorette®, Johnson & Johnson K.K., Consumer Company, Tokyo, Japan), which participants could purchase in a drug store. The pharmaceutical approach could reduce withdrawal symptoms. Counseling during the first visit could be performed in 2 consecutive visits, because informed consent was obtained during the visit for ordinal dental treatment, and counseling during the first visit often required a longer time than in other visits. Following the first visit, approximately 2, 4, 8 wks, and 3 mos after the quit date, smoking-cessation counseling was further conducted in a similar but concise manner to assist participants in overcoming withdrawal symptoms and preventing relapse.

Daily use of cigarettes and duration of smoking data were collected from the questionnaire. Nicotine dependence was estimated by means of the Tobacco Dependence Screener (TDS), which consists of 10 questions (Kawakami *et al.*, 1999). Smokers with a TDS score of more than 5 were estimated as being nicotine-dependent. For each participant, the times at the start and end of intervention by a dentist and dental hygienist were recorded. To verify smoking cessation, we used saliva to determine the level of cotinine, which is a metabolite of nicotine. Saliva was collected about 3 mos after the first visit from participants in both groups. After 6 and 12 months' follow-up, saliva was collected from individuals who reported smoking cessation. Each participant chewed a cotton plug (Salivette, Sarstedt Ltd., Nürnbrecht, Germany) for 1–2 min to ensure that it was fully saturated with saliva. The cotton plug was stored in a sampling tube and mailed to a laboratory. At the laboratory, samples were centrifuged to harvest saliva and plated for a competitive enzyme-linked immunosorbent assay with a solution of rabbit polyclonal anti-goat IgG (Dako, Glostrup, Denmark). A cut-off of 20 ng/mL was used to verify reported abstinence (Etzel, 1990). Participants were counted as smokers if they were lost to follow-up and failed to provide a saliva sample for the intent-to-treat analysis.

Differences in averages between groups were assessed *via* the two-tailed *t* test. Differences in distribution between groups were evaluated with the χ^2 test. Effectiveness of smoking cessation intervention was evaluated by comparison of the 3-, 6-, and 12-month continuous abstinence rates between the intervention and non-intervention groups. The continuous abstinence rate was defined, for intent-to-treat analysis, as the number of individuals who continuously stopped smoking during the observation period divided by those who participated in the study. Adjusted odds ratio (OR) and 95% confidence interval (CI) for continuous abstinence in the intervention group relative to the non-intervention group were calculated by logistic regression analysis with backward stepwise selection to eliminate non-significant factors (p value > 0.10) from among sex, age, daily use of cigarettes, and the TDS score. Statistical analyses were conducted with SPSS software (SPSS Japan Inc., Tokyo). The significance level was set at 5%.

RESULTS

Among the facilities participating in the training course, 19 clinics (63.3%) began the trial. Of the 47 and 44 participants assigned to the intervention and non-intervention groups, respectively, 33 and 23 individuals, respectively, consented to participate (Fig.). During the intervention period, 15 persons were lost to study among the 56 participants. In the intervention group, two persons did not use nicotine patches. One participant reported using nicotine gum after patches, but had ceased by the 6-month period. No adverse event regarding smoking cessation was reported.

There were no significant differences between the groups with respect to sex, age, cigarettes smoked daily, and smoking yrs (Table 1). The TDS score was lower in the non-intervention group than in the intervention group, but the differences were not significant.

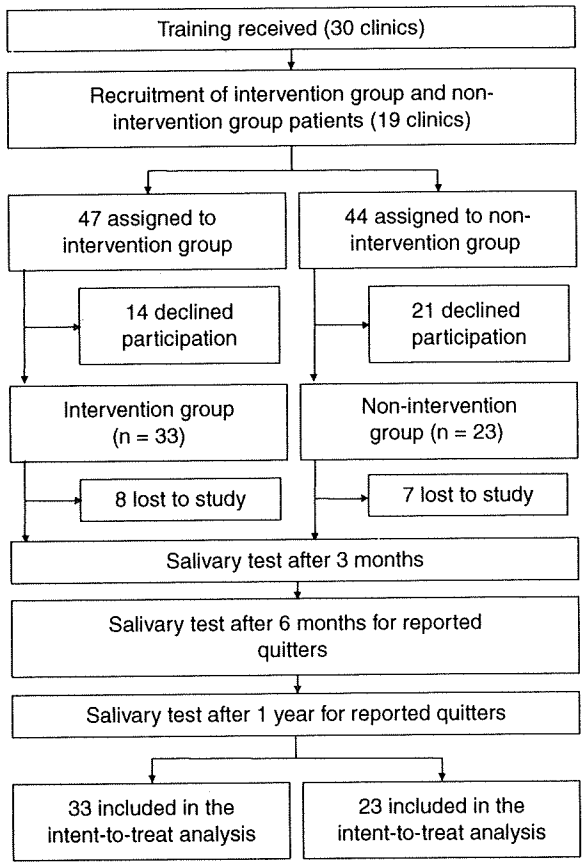

Figure. Training of intensive smoking-cessation intervention and flow of participants and salivary tests for chemical validation of abstinence in intervention and non-intervention groups.

Table 1. Comparison of Characteristics of Smokers between Intervention and Non-intervention Groups

Characteristics	Intervention Group (n = 33)	Non-intervention Group (n = 23)	p
Number of participants			
Males	26	14	
Females	7	9	NS[a]
Age (yrs)	48.0 (43.4, 52.6)[b]	46.7 (41.2, 52.3)	NS
Cigarettes smoked daily	24.3 (19.5, 29.0)	20.6 (14.9, 26.3)	NS
Yrs smoked	26.7 (22.2, 31.2)	24.1 (18.7, 29.5)	NS
TDS score[c]	7.3 (6.5, 8.1)	6.0 (5.1, 6.9)	NS

[a] Not significant between intervention and non-intervention groups.
[b] 95% confidence interval.
[c] Tobacco dependence screener (TDS) consists of 10 questions. Smoker with a TDS score of more than 5 could be assessed as a nicotine-dependent smoker.

The total intervention time *per* intervention group participant was 116.2 min on average (Table 2). The mean number of interventions *per* person was 4.6, and 63.6% of participants completed the intervention. The number of interventions received was similar between dentists and dental hygienists; however, the contact time with dentists was 1.7 times longer than with dental hygienists. Many participants (63.6%) completed the maximum visits (5 or 6 visits).

Table 2. Characteristics of Intervention Practices in Intervention Group (N = 33)

Intervention	Dentists	Dental Hygienists	Total
Mean time *per* participant (min)[a]	73.7 (53.9–93.5)[b]	42.3 (27.9–56.8)	116.2 (86.8–145.6)
Mean number *per* participant	4.4 (3.8–5.0)	4.3 (3.7–4.9)	4.6 (4.0–5.1)

[a] One record was not available, because it was incomplete.
[b] 95% confidence interval.

The effectiveness of intervention was evaluated in 33 participants in the intervention group and 23 participants in the non-intervention group according to the continuous abstinence rate on an intent-to-treat basis (Table 3). In the 3-month period, 75.8% and 69.6% were evaluated for smoking status in the intervention and non-intervention groups, respectively, and abstinence rates were 51.5% and 13.0%, respectively. Abstinence rates in the non-intervention group in the follow-up assessments at 6 and 12 mos were consistent with those at 3 mos, while the rates decreased to 39.4% at 6 mos and 36.4% at 1 yr in the intervention group. Adjusted OR (95% CI) for continuous abstinence in intervention relative to non-intervention groups at 3, 6, and 12 mos were 7.1 (1.8, 28.5), 8.9 (1.7, 47.2), and 6.4 (1.3, 30.7), respectively.

DISCUSSION

The present study demonstrated that intensive smoking-cessation intervention is effective in the dental setting in terms of the long-term abstinence rate, which was verified chemically. In the present study, participants were limited to smokers who were willing to quit within 1 mo. A brief intervention in individuals who were not willing to quit within 1 mo was about 3 times as effective in their attempt to quit (Hanioka *et al.*, 2007b); therefore, the dental clinic could be an independent facility where smokers are motivated and helped to quit effectively.

A national survey was conducted for the first time to verify the effectiveness of smoking-cessation treatment in the medical setting in 279 facilities (response rate, 61.2%) in Japan at the time of the present study, and the reported 6- and 12-month continuous abstinence rates for 2546 smokers were 40.8% and 32.6%, respectively. These numbers were similar to those for the intervention group in the present study. The number of participants who completed the maximum visits was lower in the medical setting (30.0%) than in the present study (63.6%). About 75% of participants were examined in the 3-month period in both the intervention and non-intervention groups. Most participants completed the maximum intervention. Good compliance in the dental setting may be due to the necessity of continuing dental treatment.

Dental professionals trained in smoking-cessation intervention may have influenced smoking behavior in the non-intervention group, since they might have intervened unconsciously. This type of bias, if any, and possible bias due to a lower TDS score in the non-intervention group than in the intervention group, may

Table 3. Abstinence Ratios in Intervention and Non-intervention Groups, and Adjusted Odds Ratios (OR) by Logistic Stepwise Regression Analysis

Period	Assessment	Intervention Group	Non-intervention Group	p
Registration		33 (100%)	23 (100%)	
3 mos	Days[a]	107.7 (100.3, 115.1)[b]	103.1 (93.9, 112.4)	NS
	Examined	25 (75.8%)	16 (69.6%)	NS
	Quit[c]	17 (51.5%)	3 (13.0%)	0.004
	Crude OR	7.1 (1.8, 28.5)[c]		0.006
	Adjusted OR[d]	7.1 (1.8, 28.5)		0.006
6 mos	Days	196.5 (181.8, 211.1)	204.3 (176.3, 232.3)	NS
	Quit	13 (39.4%)	3 (13.0%)	0.039
	Crude OR	4.3 (1.1, 17.6)		0.040
	Adjusted OR[e]	8.9 (1.7, 47.2)		0.010
1 yr[f]	Days	433.2 (402.2, 464.2)	453.3 (388.8, 517.9)	NS
	Quit	12 (36.4%)	3 (13.0%)	NS
	Crude OR	3.8 (0.9, 15.5)		NS
	Adjusted OR[e]	6.4 (1.3, 30.7)		0.021

[a] Based on the first day of intervention. Since setting a quit day within 1 wk after the first visit was recommended in the intervention group, the period may be approximately 7 days shorter than in the Table.
[b] 95% confidence interval.
[c] Reported abstinence was verified according to a salivary cotinine level of less than 20 ng/mL at 3, 6, and 12 mos. Salivary tests at 6 and 12 mos were performed for those who reportedly quit.
[d] No variables were entered.
[e] Age and daily use of cigarettes were entered.
[f] Assessment was delayed for approximately 2 mos due to the extension of financial support.

underestimate the effectiveness of the current intervention. The adjustments for age and daily cigarette use between groups contributed to the increases of crude odds ratio. We used random consent to minimize the overestimation of effectiveness due to participation bias, although this method has inspired debate and controversy regarding ethical issues (Homer, 2002). This method was appropriately used in a study which examined effectiveness with respect to behavior change (Kaper *et al.*, 2005). We avoided a parallel design in which participants were assigned to intervention and non-intervention clinics, since a participation bias may occur between groups.

Study designs to assess the efficacy of a smoking-cessation program in the dental setting have varied greatly (Warnakulasuriya, 2002; Carr and Ebbert, 2007), including the abstinence rate in on-treatment *vs.* intent-to-treat bases, intervention in the general population *vs.* dental patients, lack *vs.* existence of a control group, brief *vs.* intensive intervention regimen, short- *vs.* long-term observation periods, use of reported abstinence *vs.* chemical verification, and intervention by a single professional *vs.* a team approach. The team approach has been recommended, because differences in the intervention approach were identified between dental and physician settings (Cohen *et al.*, 1994). The strength of the present study was the use of more confirmative evaluation of the intervention trial, with comparison of abstinence verified chemically with the control group on an intent-to-treat basis.

A few limitations to this study should be noted. First, the number of participants in the non-intervention group was about two-thirds of that in the intervention group. This imbalance may have been due to the greater benefit of free nicotine patches in the intervention than in the non-intervention group. We cannot expect an effect on abstinence in these individuals if they participated in the trial. Second, nicotine patches have been available over the counter in Japan since May, 2008. The influence of their availability in drug stores on the effectiveness of intervention in the dental setting should be further clarified. Third, smoking-cessation counseling by dentists and dental hygienists requires a certain time commitment, and thus the efficacy of the practice should be considered. Approval for smoking-cessation practice in the health insurance system may improve efficacy in the dental setting. Further discussions are required regarding medical economics: how much and by which dental professional the intervention could save in dental expenditures by preventing dental diseases and improving dental-treatment effectiveness.

Another source for dental patients to receive intensive smoking-cessation intervention is referral services (Gordon *et al.*, 2007). In the present study, dental professionals were briefly trained in smoking-cessation intervention. Since dental professionals have the potential for behavioral and pharmaceutical approaches, dental visits are an opportunity for smokers to be effectively helped to quit smoking by trained professionals.

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TOBACCO INDUCED DISEASES

REVIEW Open Access

Destructive effects of smoking on molecular and genetic factors of periodontal disease

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Abstract

Many epidemiological evidences have proven the association between smoking and periodontal disease. The causality can be further established by linking findings of traditional epidemiological studies with the developments in molecular techniques that occurred in the last decade. The present article reviews recent studies that address the effect of smoking on molecular and genetic factors in periodontal disease. Most findings support the fact that tobacco smoking modulates destruction of the periodontium through different pathways: microcirculatory and host immune systems, connective tissue, and bone metabolism. Although smokers experience an increased burden of inflammatory responses to microbial challenges compared to non-smokers, understanding the association between smoking and periodontal diseases involves substantial problems with respect to accuracy of measurements, and particularly, sampling of many subjects. It remains unclear whether genetic susceptibility to periodontal disease is influenced by exposure to smoking or the effect of smoking on periodontal disease is influenced by genetic susceptibility. Employment of molecular techniques may play a key role in further elucidation of mechanisms linking smoking and periodontal destruction, the direct relationship as environmental factors and indirect relationship through genetic factors.

Background

Periodontal disease is defined as inflammatory destruction of periodontal tissue and alveolar bone supporting the teeth. Severe and prolonged periodontal inflammation leads to loss of teeth, thereby affecting oral functions (e.g., mastication, speech, and facial esthetics). Progression and severity of the disease depends on complex interactions between several risk factors such as microbial, immunological, environmental, and genetic factors, as well as age, sex, and race [1]. Tobacco smoking is a significant risk factor for periodontal disease [2].

Epidemiological studies concerning the association between smoking and periodontal disease have markedly increased since the 1990s. Based on epidemiological articles published from 1965 to 2000, the US Surgeon General's Report 2004, which comprehensively addressed active smoking and health issues, concluded that there is sufficient evidence to infer a causal relationship between smoking and periodontal disease [3]. Although biological plausibility is an important criterion in the Bradford-Hill criteria for assigning causality to an association [4], traditional epidemiology correlates exposure with disease outcomes, and everything between the cause and outcome is treated as a "black box" [5].

Despite numerous studies having demonstrated the causal association between smoking and periodontal disease, many questions remain unanswered. For example, what happens when periodontal tissue is exposed to tobacco smoke? How is the onset or progression of periodontal disease in smokers different from that in non-smokers? The underlying mechanisms of smoking-attributed periodontal disease can be further clarified by linking findings of traditional epidemiological studies with those of *in vitro* studies. Recently, molecular, cellular, and other biological markers (called biomarkers) have been frequently measured in epidemiological studies to reveal the mechanisms and events occurring along the theoretical continuum between exposure to tobacco smoke and the disease.

These biomarkers can be categorized according to the target of qualification, i.e., host responses and genetic factors (Table 1). Host responses can be further grouped as the microcirculatory system, host immune inflammatory response system, and connective tissue and bone metabolism. Since the application of a sampling

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Table 1 Biomarkers employed in studies on smoking and periodontal disease

Target of qualification	Biomarkers	Specimens
Host responses		
Microcirculatory system	Microcirculatory functions and intercellular adhesion molecule	Gingival microvasculature
Host immune inflammatory response systems	Immune cells and immunoglobulins	Blood serum, saliva, gingival crevicular fluid, and gingival tissue
Connective tissue and bone metabolism	Cytokines, prostanoids, and matrix metalloproteinase	
Genetic factors	Genotypes associated with the immune system, inflammation, and tissue metabolism	Blood, buccal swabs, and saliva

technique to obtain an informative biomarker is limited, particularly in non-diseased smokers [6], saliva, blood serum, and gingival crevicular fluid (GCF) are used as specimens.

Biological mechanisms of periodontal diseases are characterized by imbalance between bacterial virulence and host defense activity. The most plausible mechanism that explains the relationship between smoking and periodontal disease is that smoking, an environmental factor, interacts with host cells and affects inflammatory responses to microbial challenge [7]. Alternatively, the toxic components of tobacco smoke, e.g., nicotine, may directly or indirectly deteriorate periodontal tissue. Recently, genetic susceptibility to periodontal disease has been receiving much attention with respect to smoking-periodontal disease relationships. This review describes smoking as an environmental factor of periodontal disease and the interrelationship between smoking and genetic factors in periodontal disease in studies using molecular biology techniques.

Search strategy

The PubMed database was examined for English language publications from 1965 to 2008, using the following key words: "smoking," "smokers," "tobacco," "periodontal diseases," and "periodontitis." These terms were mainly searched as title words. Epidemiological studies not employing biological measurements and review articles were excluded. Most of the articles were published in the last 10-15 years. Consequently, 134 studies were evaluated and 60 have been included in this review.

Inflammatory host responses

Microcirculatory System

Changes in vascular formations and microcirculatory functions in periodontal tissue following smoking can influence immune function and the subsequent inflammatory reaction in the gingiva. A significantly smaller number of vessels were observed in the inflamed gingival tissues of smokers compared to non-smokers [8]. Continuous smoking has a long-term effect that impairs the vasculature of periodontal tissue. Acute exposure to cigarette smoke induces gingival hyperemia, which is caused by the concomitant increase in blood pressure against a small but significant sympathetically induced vasoconstriction in healthy gingiva [9]. Smoking even one cigarette may cause a decrease in gingival blood flow and vascular conductance [10]. Small repeated vasoconstrictive attacks and impairment of revascularization due to cigarette smoking may contribute to disruption of the immune response and delay in the healing response, leading to an increased risk of periodontal disease. Gingival blood flow in periodontally healthy regular smokers significantly increased three days after quitting, and further small increases occurred until eight weeks compared to the baseline [11].

Vascular dysfunction may be related to impairment of oxygen delivery to gingival tissue. Smokers exhibited lower function of oxygen sufficiency in healthy gingiva and reduced ability to adapt to the function in inflamed gingiva, compared to non-smokers [12]. Pocket oxygen tension was significantly lower in smokers than in non-smokers, possibly due to impaired microcirculatory function. Correlation of pocket oxygen tension to gingival oxygen saturation of hemoglobin was highly significant in non-smokers, but this association was absent in smokers [13].

Smoking-induced endothelial dysfunction may lead to inflammatory activation within the vascular wall, mediated by cytokines and adhesion molecules. Intercellular adhesion molecule-1 (ICAM-1) is expressed on the cell surface of the endothelium of the gingival vasculature and in the junctional epithelium; it is critical in leukocyte trafficking through gingival tissue. The level of soluble ICAM-1 (sICAM-1) was higher in smokers than in age-matched non-smoking controls [14]. The mean serum sICAM-1 concentration was elevated in smokers compared to non-smokers. Conversely, the mean concentration of sICAM-1 in GCF of subjects with periodontitis was significantly lower in smokers than in non-smokers [15].

Host Immune System

The number of neutrophils in GCF was lower or remained constant in smokers compared to non-

smokers [16]. However, smoking can affect neutrophil increase in blood in a dose-dependent manner [17]. Deleterious effects of smoking on the function of polymorphonuclear neutrophils, including reduced viability and phagocytosis, were observed in periodontally healthy smokers, in a dose-response manner [18]. Although there are some conflicting data, smoking may alter neutrophil behavior in periodontal tissue. It is reported that lung macrophages are functionally compromised, e.g., reduction in capacity to produce cytokines and phagocytize microorganisms [19].

Limited evidence suggests that smoking may influence lymphocyte numbers and antibody production. In a previous study, smoking was significantly associated with an increased number of CD3+ and CD4+ T cells with a clear dose-response effect, whereas CD19+ B cells were not affected by smoking [20]. The CD4+ and CD8+ T cell values after periodontal treatment were lower in smokers than in non-smokers [21]. The serum level of IgG (Immunoglobulin G), particularly IgG2, which is an important antibody against gram-negative periodontal pathogens, was decreased in periodontitis patients who were smokers [22-27]. These findings suggest that smoking decreases the proliferative capacity of T cells or T-cell-dependent antibody responses that affect B-cell function and antibody generation.

Connective Tissue and Bone Metabolism

Among several cytokines, levels of interleukin (IL)-1 in GCF have been extensively compared between smokers and non-smokers. Smokers exhibited significantly lower concentrations of IL-1α and IL-1ra in GCF than non-smokers [16,28]. The GCF level of IL-1β at deep bleeding sites was lower in smokers than in non-smokers [29]. This level was not different between smokers and non-smokers prior to periodontal therapy; however, it was significantly higher in smokers than in non-smokers at diseased sites following therapy [25]. Healthy smokers exhibited higher total amounts of IL-1β in GCF than non-smokers [30]. Serum IL-1β in patients with untreated aggressive periodontitis showed a positive correlation with smoking [31].

Other ILs, such as IL-4, IL-6, IL-8, and IL-10, and tumor necrosis factor-α (TNF-α) have also been investigated. The total amount of IL-4 in GCF was lower in smokers than in non-smokers and remained stable in smokers but decreased in non-smokers during induction of experimental gingivitis [32]. Smokers with early onset periodontitis exhibited lower levels of IL-4 in GCF than non-smokers [33]. The total amount of IL-10 in GCF at diseased sites was significantly lower in smokers than in non-smokers [25]; however, the levels of IL-6 and IL-8 in GCF were higher in smokers than in non-smokers [32,33]. Smokers exhibited a significantly higher level of TNF-α than non-smokers, though smoking was not associated with levels of IL-1β, IL-1ra, and IL-6 in GCF [34,35].

Considering these findings, smokers tend to exhibit excess production of inflammatory molecules, such as IL-6, IL-8, and TNF-α, and suppression of anti-inflammatory molecules, such as IL-4, IL-10, and IL-1ra; however, these findings are partly inconsistent.

IL-8 can attract and activate neutrophils. Findings regarding the effects of smoking on the level of neutrophil-derived proteolytic enzymes in oral specimens are inconsistent; however, smoking may increase their level in systemic circulation. Smokers had significantly higher elastase concentrations in GCF than non-smokers, regardless of pocket depths [36,37], while elastase concentrations decreased in smokers compared to non-smokers [38] and former smokers [18]. Plasma matrix metalloproteinase-9 (MMP-9) of smokers was 6.45 times higher than that of non-smokers [39]. Smoking was highly correlated with the MMP-3 level in GCF [40]. MMP-8 expression in periodontal tissue was significantly higher in smokers than in non-smokers [41], while the salivary MMP-8 level was significantly lower in current smokers than in former smokers [42]. Smoking may suppress the activities of protease inhibitors. Smokers had a significantly lower concentration of α-2-macroglobulin in GCF as well as total amounts of α-2-macroglobulin and α-1-antitrypsin than non-smokers [43]. Smoking seems to disturb the balance between proteolytic and anti-proteolytic activities in periodontal tissue.

IL-1, IL-6, and TNF-α stimulate the expression of the receptor activator of nuclear factor-κβ ligand (RANKL) and the inhibitor protein osteoprotegerin (OPG), which are essential factors for bone resorption and remodeling. Smoking did not affect the mean levels of free soluble RANKL (sRANKL) in GCF [44]. The OPG concentration was significantly lower and the sRANKL/OPG ratio was higher in smokers than in non-smokers, in saliva [45] as well as serum [46], explaining the greater potential for bone loss in smokers.

IL-1 and IL-6 induce production of prostaglandin E_2 (PGE_2) by neutrophils and macrophages, which could also promote periodontal bone resorption. However, the level of PGE_2 in GCF in smokers was similar to that in non-smokers [47,48] or even lower than that in non-smokers [49,36]. The level of salivary PGE_2 was also lower in smokers than in non-smokers [50]. Interference of prostaglandin production may be related to the vasoconstricting effect of smoking [51] (refer Microcirculatory system).

The level of free oxygen radicals in periodontal tissues was increased in smokers compared to non-smokers [52]. Oxidative stress induces tissue damage by injuring

cells such as fibroblasts. Tobacco products inhibit attachment and growth of fibroblasts derived from human periodontal ligaments [53]. Fibroblasts impaired by smoking possibly lead to delay in tissue repair and wound healing in periodontal disease.

Smoking-associated pathophysiological changes in periodontal tissue evaluated by biological measurements are summarized in Table 2. Reduction in GCF observed in smokers may influence the conflicting results between the levels of several biomarkers in GCF and blood. It remains unclear whether these changes are due to nicotine or other components of tobacco smoke and systemic or local effects of smoking. The common mechanism in periodontal and systemic disease under the influence of smoking may be revealed by markers for inflammatory responses, tissue damage, and vascular effects [54].

Genetic factors

Gene polymorphisms have been investigated as possible markers of increased susceptibility to periodontal diseases: IL-1, IL-4, IL-10; TNF-α; Fcγ receptor; human leukocyte antigen; vitamin D receptor; and N-formyl peptide receptor [55]. Relationships between smoking and genetic susceptibility to periodontal diseases have been strengthened with respect to genotypes associated with cytokines (IL-1, IL-6, and IL-10), the immune system (Fcγ receptor), bone metabolism (vitamin D receptor), and xenobiotics metabolism (N-acetyltransferase and myeloperoxidase). These studies have been listed in Table 3.

IL-1 polymorphisms have been intensively studied using a cross-sectional approach, except for one study that employed a longitudinal design [56]. The relationship with respect to smoking is controversial. The association between positive genotypes and the severity of periodontal disease was independent of smoking [57,58], suggesting no relationship between smoking and IL-1 genotypes; however, relationships between IL-1-positive genotypes and smoking was evident [59-63]. Logistic regression analysis of periodontal disease with genotype-negative non-smokers as a reference group exhibited odds ratios of 0.98 for genotype-positive non-smokers, 2.37 for genotype-negative smokers, and 4.50 for genotype-positive smokers, thus suggesting synergism between IL-1 polymorphism and smoking [64].

Non-smokers with moderate periodontitis and periodontally healthy subjects displayed a higher incidence of IL-6 G-genotype than severe periodontitis subjects [65]. The difference in the occurrence of the IL-10 GG genotype between severe chronic periodontitis and control groups was more evident in non-smokers [66]. Gene coding for the ligand-binding chain of interferon gamma receptor 1, a cytokine that plays a pivotal role in defense against infection, was significantly associated with periodontitis in combination with smoking [67]. IgG-binding factors, namely Fcγ receptors, could influence the ability of phagocytosis. Genotypes of Fcγ receptor, FcγRIIa, and FcγRIIIb, may be associated with periodontal disease in smokers [68,69]. Vitamin D receptor Taq-I TT polymorphism was moderately

Table 2 Pathophysiological changes associated with smoking

Target of qualification	Biomarkers*	Articles
Microcirculatory system	Gingival blood flow (chronic effect ↓ and acute effect ↑, quit effect ↑)	9-11
	Number of vessels in inflamed site↓ (Gingival bleeding ↓)	8
	Oxygen sufficiency ↓	12
	Pocket oxygen tension ↓	13
	sICAM-1 ? (Serum ↑ and GCF ↓)	14, 15
Host immune inflammatory response systems	PMNs or neutrophil count ? (blood↑ and GCF↓)	16, 17
	PMN function (chemotaxis, phagocytosis, and oxidative burst) ↓	18
	Macrophage function ↓	19**
	T lymphocytes ?	17, 20, 21
	IgG2 ↓	22-27
Connective tissue and bone metabolism	IL-1a/β and IL-1ra ↓	16, 25, 28-31
	IL-6 and IL-8 ↑, IL-4, and IL-10 ↓,TNF-α ↑	25, 32-35
	Elastase activity ?	18, 36-38
	MMP-9 and MMP-3 in GCF ↑	39, 40
	MMP-8 ? (GCF ↑ and saliva ↓)	41, 42
	α-2-Macroglobulin	43
	↓ OPG ↓ and sRANKL/OPG ratio ↑	44-46
	Prostaglandin E_2 ↓	36, 47-50
	Free radicals ↑	52
	Gingival fibroblast ↓ (Tissue repair and wound healing ↓)	53

*↑: increase, ↓: decrease, ?: uncertain. **Lung macrophages

ICAM-1: intercellular adhesion molecule-1, GCF: gingival crevicular fluid, PMN: polymorphonuclear neutrophil, IgG: immunoglobulin G, IL: interleukin, TNF-α: tumor necrosis factor-α, MMP: matrix metalloproteinase, OPG: osteoprotegerin, RANKL: receptor activator of nuclear factor-κβ ligand