

Saliva Cotinine Levels in Smokers and Nonsmokers

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The authors collected by mail self-reported data on smoking habits and saliva samples that were analyzed for cotinine concentration in 222 smokers and 97 nonsmokers. Participants were members of the University of Geneva (Switzerland) in 1995. The 207 cigarette-only smokers smoked on average 10.7 cigarettes/day and had a median concentration of cotinine of 113 ng/ml. The cotinine concentration was moderately associated with the number of cigarettes smoked per day (+14 ng/ml per additional cigarette, $p < 0.001$, $F^2 = 0.45$) and was 54 ng/ml higher in men than in women after adjustment for cigarettes per day and for the Fagerström Test for Nicotine Dependence. The cotinine level was not associated with the nicotine yield of cigarettes ($r = 0.08$). In nonsmokers, the median concentration of cotinine was 2.4 ng/ml. The cotinine concentration was 1.5 times higher in nonsmokers whose close friends/spouses were smokers than in nonsmokers whose close friends/spouses were nonsmokers ($p = 0.05$). A cutoff of 7 ng/ml of cotinine distinguished smokers from nonsmokers with a sensitivity of 92.3% and a specificity of 89.7%; a cutoff of 13 ng/ml provided equally satisfactory results (sensitivity, 86.5%; specificity, 95.9%). This study provides evidence for the construct validity of both questionnaires and saliva cotinine for the assessment of active and passive exposure to tobacco smoke. *Am J Epidemiol* 2000;151:251–8.

cotinine; data collection; questionnaires; smoking

Precise estimation of exposure to tobacco smoke is a concern for epidemiologic studies. The self-reported number of cigarettes smoked per day may be inaccurate because of digit bias, over- or underreporting, variability in the amount of smoke inhaled from a cigarette, and so on. Assessment of passive exposure to tobacco smoke is even more problematic (1, 2). An indirect measure of recent exposure to cigarette smoke is the concentration of cotinine in the blood, urine, or saliva (3–5). Cotinine is the principal metabolite of nicotine and has a half-life of about 17 hours (3). The use of cotinine in epidemiologic studies is limited by the cost and difficulty of collecting body fluid samples in large numbers of individuals. However, saliva samples can be collected by mail and analyzed for cotinine concentration (6–11).

The objectives of this study were to evaluate the relation between saliva cotinine concentration and self-reported active and passive exposure to tobacco

smoke, to identify factors associated with saliva cotinine levels in smokers, and to determine an optimal cutoff for the cotinine concentration to distinguish smokers from nonsmokers.

MATERIALS AND METHODS

Study setting and population

The study population included students, faculty, and staff of the University of Geneva (Switzerland). We conducted a mail survey in a random sample of 3,000 university members to evaluate a smoking prevention intervention (9, 12). The initial mailing was sent to potential participants in November 1995 and 2,237 persons (75 percent) responded, after up to four reminder mailings. A random subsample of 1,500 persons received a saliva vial in the first mailing and were asked to return a sample of saliva. Requests for saliva samples were discontinued in reminder mailings, because our resources allowed laboratory analysis of only a limited number of samples. Saliva was collected in a plastic vial containing a sterile dental cotton roll (Salivette; Sarstedt, Nümbrecht, Germany). Respondents were asked to chew the cotton roll for 1 minute, at least one-half hour after eating or drinking, and to replace it in the tube without touching it. Upon receipt, saliva samples were frozen at -20°C .

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Abbreviation: CI, confidence interval.

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We received 845 saliva samples (56 percent of 1,500) on average 15 days after the initial mailing. A subsample of 325 vials were subjected to laboratory analysis, including all vials of current cigarette smokers ($n = 227$), a random sample of 50 vials of nonsmokers who reported exposure to environmental tobacco smoke, and a random sample of 48 vials of nonsmokers who reported no passive exposure. The concentration of saliva cotinine could be measured in 319 samples (98.2 percent); six vials contained no saliva after centrifugation.

Saliva cotinine was measured by capillary gas chromatography and nitrogen selective detection (13). The method had a between-run variation of about 5 percent and a detection limit of 0.1 ng/ml of saliva.

Questionnaire content

Questions covered smoking history, stages of change for smoking (14), age, sex, and, for smokers only, the number of cigarettes smoked per day, pipe or cigar smoking, age at initiation of daily smoking, number of years as a regular smoker, the Fagerström Test for Nicotine Dependence (15, 16), attempts to quit smoking in the past 12 months, and perceived difficulty to quit smoking, assessed by the following question: "For you, quitting smoking would be: Very easy, Easy, Difficult, Very difficult." Smokers were asked to look at their cigarette pack and report the nicotine yield written on the pack (in Switzerland in 1995, nicotine and tar yields were written on all cigarette packs).

Exposure to environmental tobacco smoke was assessed by the following questions: "Who is currently a smoker, among people around you?: Your best friend (Yes/No), Most of your friends (Yes/No), Your husband or wife or boyfriend or girlfriend (if you have one) (Yes/No)"; "Do you live with someone who smokes? (Yes/No)"; and "In university buildings, are you exposed to other people's tobacco smoke? (Never to Very often, five levels)."

Analysis plan

First, we assessed associations between cigarette smoking and saliva cotinine concentrations among the 207 smokers who smoked only cigarettes (pipe and cigar smokers were excluded to improve the homogeneity of exposure assessment).

Second, we assessed associations between saliva cotinine concentrations and self-reported passive exposure to tobacco smoke. This analysis concerned the 97 nonsmokers whose cotinine data were available. Third, we identified a cutoff level of saliva cotinine that best distinguished smokers from nonsmokers.

This analysis was conducted in 319 persons: 222 smokers who smoked only cigarettes ($n = 207$), both cigarettes and pipe or cigars ($n = 14$), or only pipe and cigars ($n = 1$); and the 97 nonsmokers. Using the self-report of smoking as the gold standard, we determined the level of cotinine that maximized the sum of sensitivity and specificity.

Statistical methods

We used t tests to compare means of continuous variables and chi-square tests to compare proportions. In nonsmokers, because of one high outlier, we chose to compare median cotinine values rather than means, and we used the Mann-Whitney U test for significance tests. Exploratory analyses of associations between continuous variables relied on scatter plots and non-parametric Lowess regression lines (17). A receiver operating characteristic curve was used to assess the ability of the saliva cotinine test to detect self-reported smoking status. Fisher's z transformation was used to compute 95 percent confidence intervals for Pearson's correlation coefficients.

RESULTS

Predictors of cotinine concentration in cigarette smokers

The 207 cigarette-only smokers in this analysis were on average 28 years old (range, 19–61 years), 43 percent were men, 85 percent were university students, and they had received 17 years of education on average. These participants smoked on average 10.7 cigarettes per day, and their score on the Fagerström Test for Nicotine Dependence averaged 1.7. They had begun to smoke daily when they were 18 years old and had been daily smokers for 9 years. All but three smokers had detectable levels of saliva cotinine. In smokers, the cotinine concentrations ranged from 0 to 838 ng/ml (mean, 166 ng/ml; standard deviation, 170 ng/ml; quartiles: 30, 113, and 264 ng/ml).

The association between the number of cigarettes smoked per day and the saliva cotinine level was almost linear (figure 1). Each additional cigarette smoked per day was associated with an increase of 14 ng/ml in saliva cotinine (Pearson's correlation: $r = 0.67$; 95 percent confidence interval (CI): 0.59, 0.74). This correlation was somewhat stronger among women ($r = 0.75$; 95 percent CI: 0.66, 0.82) than among men ($r = 0.61$; 95 percent CI: 0.46, 0.73). The cotinine concentration was higher in men than in women, particularly for smokers of >5 cigarettes per day (figure 1). There were consid-

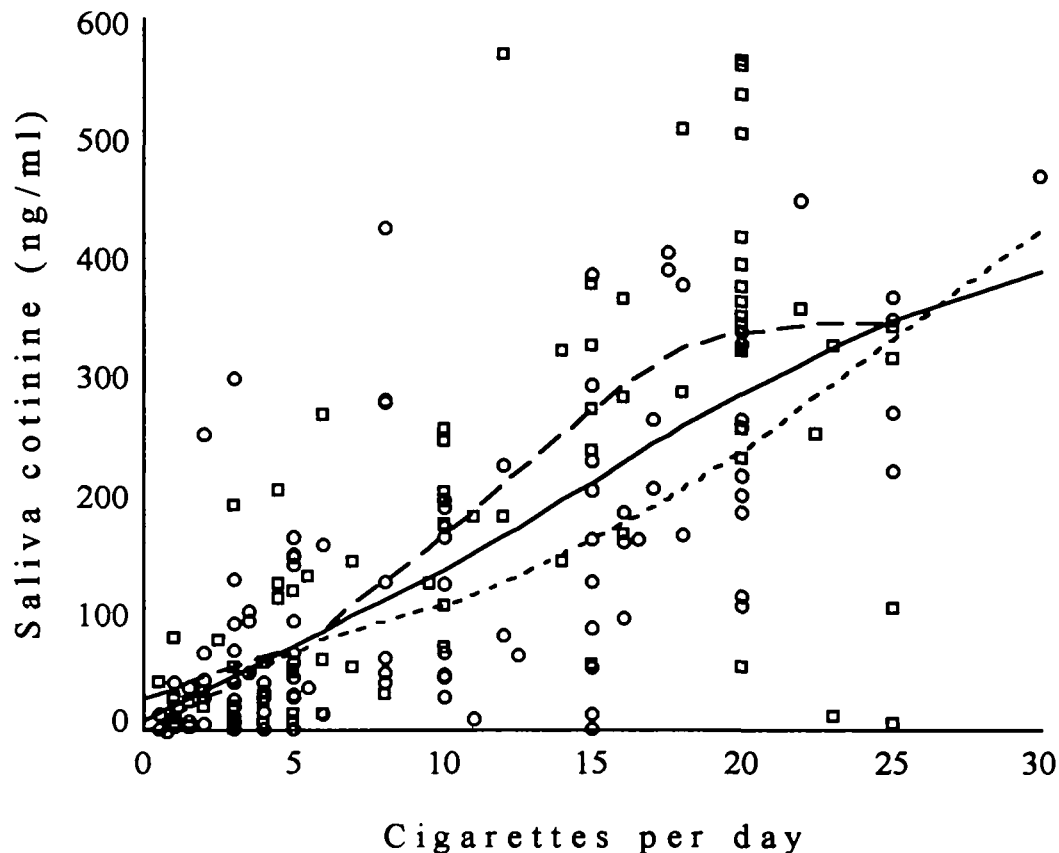


FIGURE 1. Association between the concentration of saliva cotinine and the number of cigarettes smoked per day, in men (dashed line, square symbols), women (dotted line, round symbols), and smokers of both sexes (solid line) who smoked only cigarettes (no pipes or cigars), Geneva, Switzerland, 1995.

erable variations in the saliva cotinine concentrations for similar numbers of cigarettes smoked. For instance, among 30 persons who smoked 20 cigarettes per day, the cotinine concentrations ranged from 55 to 684 ng/ml (mean, 335 ng/ml; standard deviation, 164 ng/ml). Scores on the Fagerström test were linearly associated with the cotinine concentration (correlation, 0.70; 95 percent CI: 0.62, 0.77) (figure 2).

The self-reported nicotine yield of cigarettes was not associated with saliva cotinine levels (correlation, 0.08; $p = 0.3$) (table 1). Men smoked cigarettes with a higher nicotine yield (0.65 mg) than did women (0.54 mg, $p = 0.005$), but nicotine yield was unrelated to saliva cotinine in both men and women.

Age was slightly associated with the cotinine concentration, but this association weakened after adjustment for the number of cigarettes per day (table 1). There was no association between saliva cotinine and age at initiation of daily smoking, but saliva cotinine was significantly associated with duration of daily smoking, even after adjustment for the number of cigarettes per day (table 1).

After adjustment for the number of cigarettes smoked per day, the saliva cotinine concentration was 46 ng/ml higher in smokers in the contemplation stage than in precontemplators ($p = 0.04$) and 96 ng/ml higher in the contemplation than in the preparation stage of change ($p = 0.02$).

The saliva cotinine concentration was lower in smokers who attempted to quit smoking in the previous year than in those who did not, but this association disappeared after adjustment for the number of cigarettes smoked per day (table 1).

Among 175 smokers who did not exclude that they might quit smoking, the perceived difficulty to quit smoking was strongly associated with the cotinine concentration. This association remained statistically significant after adjustment for the number of cigarettes smoked per day (table 1).

In multivariate linear regression analysis, only the number of cigarettes per day, the Fagerström test score, and sex were independently associated with saliva cotinine concentrations (table 1). These three predictors explained 54 percent of the variance in saliva cotinine concentrations.

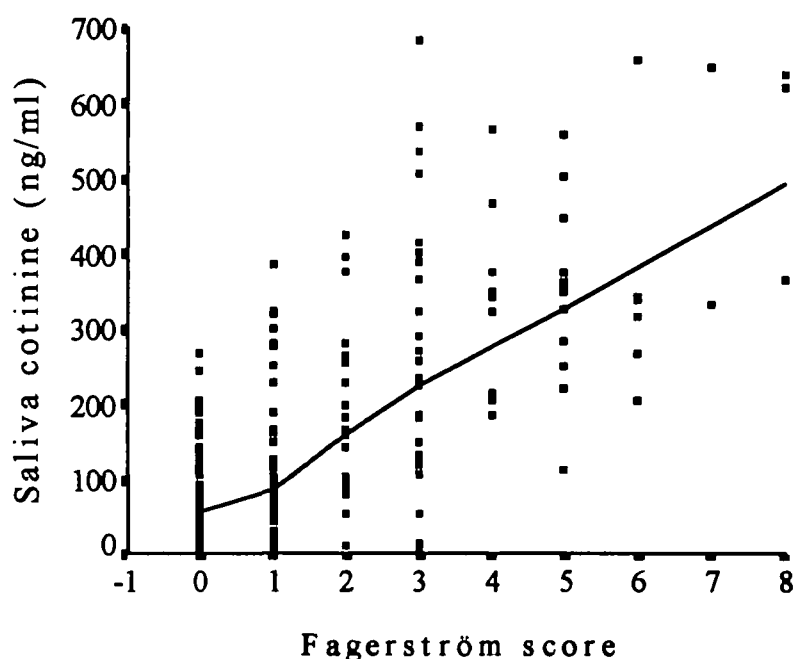


FIGURE 2. Scores on the Fagerström Test for Nicotine Dependence and the concentration of saliva cotinine in current smokers who smoked only cigarettes (no pipes or cigars), Geneva, Switzerland, 1995.

Cotinine concentrations in nonsmokers

The 97 nonsmokers included in this analysis were on average 28 years old, 34 percent were men, and 79 percent were university students. All but two nonsmokers

had detectable levels of cotinine. The cotinine concentrations ranged from 0 to 46 ng/ml, with one outlier at 236 ng/ml (mean, 6.3 ng/ml; median, 2.4 ng/ml; standard deviation, 24.2 ng/ml). The median concentrations of saliva cotinine were similar in those who never

TABLE 1. Predictors of concentration of saliva cotinine, in cigarette-only smokers, Geneva, Switzerland, 1995†

	Cotinine (ng/ml)		
	Univariate	Adjusted for cigarettes/day	Multivariate
Cigarettes/day (per cigarette)	14***		6***
Sex (men = 1, women = 0)	86***	56***	54***
Fagerström Test for Nicotine Dependence (per point on a 0–10 scale)	61***	39***	39***
Age (per year)	3*	2 (NS)‡	
Nicotine yield of cigarettes (per mg)	47 (NS)	8 (NS)	
No. of years as a smoker	4**	3*	
Attempted to quit smoking in previous year (made a quit attempt = 1, no quit attempt = 0)	-68**	-12 (NS)	
Perceived difficulty to quit smoking (per point on a four-point Likert scale, among 175 smokers who did not exclude quitting smoking)	101***	33*	
Stage of change			
Precontemplation (reference)			
Contemplation	89**	46*	
Preparation	-72 (NS)	-50 (NS)	

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

† Regression coefficients from linear models indicate the change in saliva cotinine concentration (in ng/ml) per unit increase in predictors.

‡ NS, not statistically significant.

smoked (2.4 ng/ml) and in former smokers (2.8 ng/ml, $p = 0.87$), but former smokers in the action stage of change (median, 9.5 ng/ml) had higher levels of cotinine than did former smokers in the maintenance stage (median, 2.2 ng/ml; $p = 0.02$). In nonsmokers, the median saliva cotinine concentration was similar in men (3.0 ng/ml) and in women (2.4 ng/ml, $p = 0.13$) and was not associated with age.

The saliva cotinine concentration was approximately 1.5 times higher in nonsmokers whose friends or relatives smoked than in nonsmokers whose friends/relatives did not smoke (table 2). Living with a smoker did not predict higher saliva cotinine and nei-

ther did self-reported exposure to tobacco smoke in university buildings.

Optimal cutoff to separate smokers and nonsmokers

The distributions of saliva cotinine in smokers and nonsmokers overlapped (figure 3). The sum of sensitivity and specificity did not change much for cutoff values between 7 ng/ml (sensitivity, 0.92; specificity, 0.90) and 13 ng/ml (sensitivity, 0.87; specificity, 0.96), and the area under the receiver operating characteristic curve was 0.95. Similar cutoff levels were obtained in men and women (not shown). When the cotinine test was used to detect smokers of five cigarettes/pipes/cigars per day (vs. nonsmokers), the sum of sensitivity and specificity did not change much for cutoff values between 8 ng/ml (sensitivity, 0.98; specificity, 0.90) and 40 ng/ml (sensitivity, 0.89; specificity, 0.98), and the area under the receiver operating characteristic curve was 0.98.

TABLE 2. Concentration of saliva cotinine in nonsmokers and indicators of exposure to environmental tobacco smoke, Geneva, Switzerland, 1995

	Saliva cotinine, median (ng/ml)		<i>p</i> value*
	Yes	No	
Among people around you, who is currently a smoker?			
Your best friend	3.5	2.4	0.42
Most of your friends	3.7	2.4	<0.001
If you have one, your husband/wife/boyfriend/girlfriend	3.6	2.4	0.05
Do you live with someone who smokes?	2.4	2.8	0.48

* *p* value based on the Mann-Whitney *U* test.

DISCUSSION

In this study, questionnaires and cotinine data provided very consistent information about exposure to tobacco smoke. Three variables independently predicted saliva cotinine concentrations in current smokers: the number of cigarettes smoked per day, addiction level (Fagerström test), and sex.

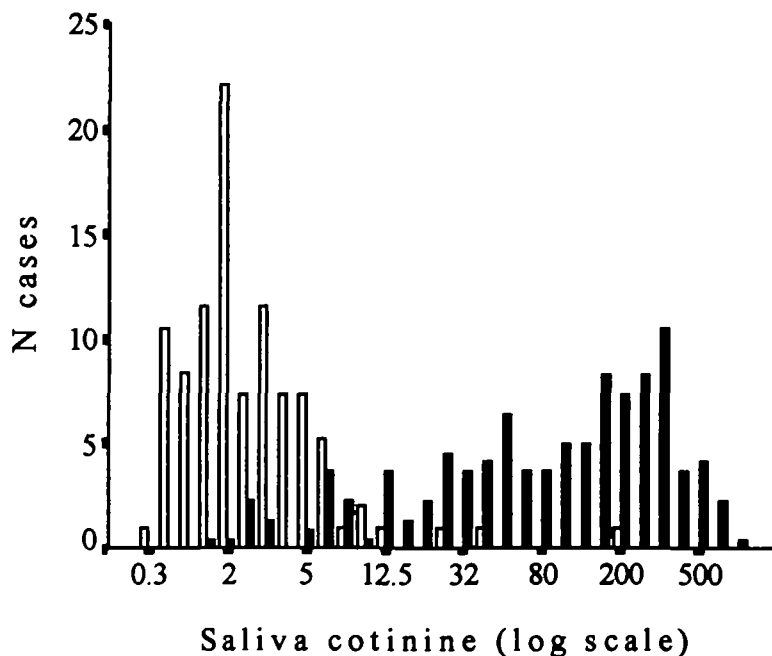


FIGURE 3. Saliva cotinine (ng/ml) in smokers (black bars) and nonsmokers (white bars), Geneva, Switzerland, 1995.

Saliva cotinine in current smokers

The saliva cotinine concentration was more strongly correlated with the number of cigarettes per day in our study ($r = 0.67$) than in published studies ($r = 0.27$ – 0.64) (18–21). This difference may have been caused by the peculiarities of our study population or by the use of a more precise measurement of cotinine. Nevertheless, 55 percent of the variance of cotinine was explained by factors other than the number of cigarettes smoked. This result underlines the necessity of developing more precise self-reported measures of intake of cigarette smoke, particularly if researchers want to quantify the amount of smoke inhaled and not merely to dichotomize individuals as smokers or nonsmokers.

More precise measurement of cotinine may also explain why saliva cotinine was more strongly correlated with the Fagerström score in our study ($r = 0.70$) than in previous studies ($r = 0.33$ and 0.39) (18, 22). The significant correlation between a dependence score and cotinine levels after adjustment for the number of cigarettes smoked is consistent with (but does not prove) a causal chain among drug intake (cigarettes smoked), internal concentration of drug (cotinine levels), and addiction to drug (Fagerström score).

Men usually smoke more cigarettes than do women and have higher cotinine levels (23–25). Our study shows that the sex difference in cotinine concentrations is not explained only by a greater number of cigarettes smoked, a higher level of nicotine dependence, or a higher nicotine yield of cigarettes smoked by men. Higher levels of cotinine in men after adjustment for cigarettes smoked can be due to sex differences in the metabolism of nicotine (25, 26), sex-specific bias in self-reported smoking habits, or a different way of smoking cigarettes (rate and depth of inhalation, unsmoked butt length, and so on).

After adjusting for the number of cigarettes per day, we found no association between age and cotinine levels. This result contradicts reports that older smokers have higher cotinine levels than do younger smokers (21). This discrepancy may be explained by either the specific smoking patterns of the highly educated older smokers in our sample or the fact that few older smokers were included in the study.

The absence of association between the self-reported nicotine yield of cigarettes and the cotinine concentration confirms that the nicotine yield of cigarettes is not a valid indicator of nicotine intake (27). Smokers may adjust their blood level of nicotine to their needs, regardless of the nicotine yield of the cigarettes they smoke (28, 29). However, a weak association between nicotine yield and saliva cotinine may have been obscured by imprecise self-report. Several

studies suggest that the smokers' knowledge and understanding of the tar content of their cigarettes are inaccurate (30–33), but equivalent data on the associations between self-reported nicotine yields and the values printed on cigarette packs are not available.

Saliva cotinine and passive smoking

We found concentrations of saliva cotinine in nonsmokers that were similar to those of previous studies (3, 34). The saliva cotinine concentration of nonsmokers was influenced by the smoking status of their close friends or spouses, which justifies the use of the partner's smoking status as an indicator of environmental tobacco smoke exposure in epidemiologic studies (3, 34–37). On the other hand, we did not replicate the finding of higher cotinine levels in nonsmokers who live with smokers (36–38).

Several factors may have weakened the associations between self-reported exposure to environmental tobacco smoke and the saliva cotinine concentration. First, the cotinine concentration reflects exposure to tobacco smoke in the last few days, whereas the questionnaire did not specify a time limit. Second, interindividual differences in nicotine and cotinine metabolism may have obscured a weak association (3). Third, the association may have been diluted by a low reliability of the questionnaire used to assess exposure to environmental tobacco smoke.

Identification of a cutoff to separate smokers and nonsmokers

In this study, the level of cotinine concentration that best divided smokers and nonsmokers (7–13 ng/ml) was somewhat lower than those in most published studies, in which cutoffs ranged between 10 and 44 ng/ml (4, 34, 39, 40), or even 100 ng/ml (34). The lower cutoff in our study may have been due to different internal laboratory standards. Alternatively, the sensitivity and specificity of the cotinine test may have been subject to spectrum bias, if the characteristics of smokers and nonsmokers differed between our study and other studies. In our study, the fact that most smokers were moderate smokers may have reduced sensitivity, and low exposure to environmental tobacco smoke in nonsmokers may have increased specificity for any given cutoff value. Both conditions would push the cutoff value lower compared with other populations.

In this study, a detailed analysis of questionnaire data showed that all self-reported smokers whose cotinine values were below the cutoff of 7–13 ng/ml smoked few cigarettes or few pipes or cigars. Conversely, all self-reported nonsmokers whose coti-

nine was above this cutoff reported a passive exposure to tobacco smoke. Only two participants who classified themselves as nonsmokers had cotinine levels typical of active smokers, but questionnaire data indicated that they were in fact occasional smokers. These results, together with the high area under the receiver operating characteristic curve, indicate that questionnaire data and cotinine measurements provided very consistent information about exposure to tobacco smoke. In addition, we have shown previously that requesting a saliva sample did not affect the sincerity of answers on smoking status and on the number of cigarettes smoked per day, but it decreased response rates (8). Thus, at least in populations of educated moderate adult smokers, verification of the participants' smoking status with biochemical tests may not be necessary. Rather, researchers should aim at improving the validity of questionnaires, in particular by assessing occasional or irregular use of tobacco (41–43).

Limitations of the study

This study has several limitations. First, we did not collect data on the use of nicotine replacement products. In Switzerland in 1995, these products were sold under medical prescription to prevent relapse in exsmokers. Thus, if some participants used these products, this would have artificially increased cotinine levels in exsmokers. This may have been the case of one former smoker who had very high cotinine levels in our survey. Second, we had incomplete data on exposure to environmental tobacco smoke, as our questions focused on university buildings. Third, cotinine is not a specific marker of tobacco use, since nicotine is found in tea, tomatoes, eggplants, potatoes, and so on (44). However, at the usual levels of food consumption, nicotine intake in food is trivial compared with even moderate exposure to environmental tobacco smoke (3). Finally, this study was conducted in young and educated participants, most of whom were university students and moderate smokers. The results may not apply to older and less educated persons or to heavier smokers.

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