

## Nicotine and Cotinine in the Cervical Mucus of Smokers, Passive Smokers, and Nonsmokers<sup>1</sup>

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### Abstract

Although epidemiological studies suggest that cigarette smoking is a risk factor for cervical cancer, further evidence is required to document the biological plausibility of this relationship. This study obtained cervical mucus, using a cervical flush technique, from 50 patients in a neoplasia clinic. Nicotine was detected in the cervical mucus of all 25 smokers and cotinine in the mucus of 84% of the smokers; nicotine and cotinine levels were correlated ( $P \leq 0.10$ ) with both the number of cigarettes usually smoked and the number smoked in the last 24 h. Nicotine and cotinine levels for passive smokers and nonexposed women were much lower than for women who currently smoked, with little difference found between the nonsmoking women who did and did not report passive smoke exposure. In the one woman who reported smokeless tobacco use, both nicotine and cotinine were detected at much higher levels than for other nonsmoking women. These results indicate that tobacco constituents do indeed reach the uterine cervix, suggesting that they could play a causal role in the development of cervical cancer.

### Introduction

Epidemiological studies suggest that cigarette smoking is a risk factor for cervical cancer, as has recently been reviewed by Winkelstein (1). However, women who smoke are also more likely to exhibit other behaviors (such as multiple sex partners and early age at first intercourse) that increase their risk of cervical cancer. Because of this problem of severe confounding and highly correlated variables, the debate continues about whether smoking is an independent risk factor for cervical dysplasia and cervical cancer (1-4).

Several lines of evidence indicate that cigarette smoking could be biologically related to cervical dysplasia and carcinoma. High levels of smoke constituents,

such as nicotine and cotinine, have been isolated in the cervical mucus of smokers (5-8). It has been suggested that nicotine can be nitrosated *in vivo* to carcinogenic nitrosamines (9), which could contribute to the development of cervical dysplasia. A recent study of passive smokers has also found that higher levels of cotinine are associated with the uptake of higher levels of carcinogens (10). Second, smoking is strongly associated with squamous cell carcinoma (most notably lung cancer), which is the predominant type of cervical cancer (1). In addition, there is some evidence that human papillomavirus could interact with cigarette smoke constituents to induce immunological changes in the cervix, leading to dysplasia (11-13). This interaction was demonstrated in a study by Herero *et al.* (14), which found that the association between smoking and invasive cervical cancer was strongest among women who tested positive for human papilloma virus.

The current study was conducted to further explore the relationship between reported exposure to tobacco smoke and the levels of nicotine and cotinine in cervical mucus.

### Materials and Methods

Fifty patients seen in the University of North Carolina Hospital neoplasia clinic between April 1987 and May 1988 participated in the study. The women were referred to the clinic by their physicians for evaluation of abnormal Papanicolaou (Pap) smears. The subjects were nonpregnant women between the ages of 18 and 65 who did not have an active vaginal infection, who were not currently menstruating, and who had not received prior treatment for dysplasia.

After eligible subjects consented to participate, a questionnaire was administered in the clinic to determine demographic characteristics, reproductive history, current and past use of tobacco products, and passive smoking exposure. The questions about tobacco exposure were quite extensive, including the amount of tobacco product used daily (e.g., number of cigarettes usually smoked and number smoked in the past 24 h), description of the product (e.g., brand name, cigarette length, presence of filter), and details of passive smoke exposure at home, at work, and elsewhere. Study enrollment continued until 25 current smokers and 25 women who were not active smokers were accrued.

The cervical mucus specimen was obtained during the clinically indicated pelvic examination, immediately following the Pap smear, and before any biopsies or other procedures were performed. For collection of the mucus, the cervix was flushed with 3 ml of normal saline, and then the solution, with any mucus present, was aspirated back into a syringe. The samples were immediately frozen at  $-70^{\circ}\text{C}$ .

Received 6/27/91.

<sup>1</sup> Presented at the 117th Annual Meeting of the American Public Health Association, Chicago, Illinois, October 22-26, 1989.

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The mucus samples were transported in one batch on dry ice to the American Health Foundation (Valhalla, NY). Laboratory assays were performed with no knowledge of the smoking status of the women. Nicotine and cotinine levels were determined by radioimmunoassays, as developed by Langone *et al.* (15). These assays use specific antisera produced by injection into rabbits of *trans*-3-succinylmethyl nicotine bound to albumin for nicotine, and *trans*-4-carboxycotinine bound to albumin for cotinine. The inter- and intraassay variations are 7%, with a sensitivity of 1 ng/ml. Nicotine and cotinine were chosen for analysis because nicotine is a measurable smoke component that is specific to tobacco, and cotinine is its major metabolite (16).

The Pap smears and biopsies were all interpreted by University of North Carolina Hospital cytopathologists and surgical pathologists as part of usual patient care.

The women were divided into three smoking status categories: (a) smokers (at least 1 cigarette/day); (b) passive smokers (exposed to cigarette smoke at work or at home in the last 24 h but who do not smoke themselves); and (c) nonsmokers (reporting no exposure to cigarette smoke). For purposes of calculating the mean, samples in which nicotine and/or cotinine could not be detected were assigned values of 0 ng/ml. The statistical significance of a difference in mean levels of nicotine and cotinine was tested by *t* tests. Correlations among the amount smoked, nicotine levels, and cotinine levels used the Spearman correlation rank order test.

## Results

Of the 50 women included in the study, 25 were smokers, 12 were passive smokers, 12 were nonsmokers, and 1 was a snuff user with passive smoke exposure. (This last woman was excluded from the comparisons among the three smoking exposure groups.) There were no significant differences in demographic or reproductive characteristics among these groups. The majority of the women were young (mean age, 27), black (59%), low-income, and unmarried (63%); their mean age at first intercourse was 16, they reported a lifetime total of 3–4 sexual partners on average, and they had had an average of two pregnancies. More than half (61%) were currently using oral contraceptives.

The Pap smears indicated benign changes for 20 of the 49 patients. Of the remaining 29 women, 21 had either mild cellular abnormalities or condylomatous changes or both. Seven patients had severe precancerous changes (cervical intraepithelial neoplasia III).

Table 1 presents the results regarding nicotine and cotinine in cervical mucus samples. All smokers had detectable levels of nicotine in their mucus, as did 58% of the passive smokers and 67% of the nonsmokers. Cotinine was present in 21 of the 25 smokers (84%) but was not detected in any passive smokers or nonsmokers. The smokeless tobacco user, who used 2 spoonfuls of snuff per day, also had detectable levels of both nicotine (198 ng/ml) and cotinine (99 ng/ml) in her mucus sample; her Pap smear indicated cervical intraepithelial neoplasia I.

The mean nicotine level for smokers was significantly different from that for passive smokers ( $P = 0.0001$ ) and for nonsmokers ( $P = 0.0002$ ), as displayed in Table 1 and Fig. 1. The mean cotinine level was also significantly different for smokers compared to both passive smokers

Table 1 Nicotine and cotinine in cervical mucus, by smoking status

	Smokers (n = 25)	Passive smokers (n = 12)	Nonsmokers (n = 12)
<b>Nicotine</b>			
No. and % in whom nicotine was detected	25 (100%)	7 (58%)	8 (67%)
Mean nicotine levels (ng/ml) <sup>a</sup>	107.2	3.6 <sup>b</sup>	6.2 <sup>b</sup>
Median (ng/ml)	56	3.5	3.5
Range (ng/ml)	4-358	ND-12 <sup>c</sup>	ND-31
<b>Cotinine</b>			
No. and % in whom cotinine was detected	21 (84%)	0 (0%)	0 (0%)
Mean cotinine levels (ng/ml) <sup>a</sup>	38.8	0 <sup>b</sup>	0 <sup>b</sup>
Median (ng/ml)	19	ND	ND
Range (ng/ml)	ND-167	ND	ND

<sup>a</sup> Computed using 0 as the value for women with levels below the detectable limit of 2 ng/ml.

<sup>b</sup> Significantly different from mean levels for smokers ( $P < 0.001$ ).

<sup>c</sup> ND, not detected.

and nonsmokers ( $P = 0.0009$ ). Comparison between the passive smokers and the nonsmokers revealed no significant differences in mean nicotine or mean cotinine levels.

Fig. 1 shows the distribution of nicotine levels by smoking status. Among smokers the nicotine values ranged from 4 to 358 ng/ml, whereas among passive smokers and nonsmokers they were generally below 14 ng/ml. The nonsmoker with a nicotine level of 31 ng/ml reported no passive smoke exposure in the last 24 h, but she was usually exposed to several hours of passive smoke a day; if this outlier is excluded from the analysis and the mean for nonsmokers is recalculated, the mean nicotine level is 3.9 ng/ml.

Among smokers the mucus nicotine and cotinine levels were significantly correlated with each other, as shown in Fig. 2 ( $r = 0.75$ ;  $P = 0.0001$ ). It is particularly noteworthy that all four of the smokers with nondetectable cotinine also had very low levels of nicotine (<20 ng/ml).

The two measures of smoking intensity, number of cigarettes smoked in the last 24 h and the usual number of cigarettes smoked per day, were also significantly correlated with each other ( $r = 0.61$ ;  $P = 0.0001$ ). The two smoking intensity measures were marginally associated both with nicotine levels (last 24 h:  $r = 0.38$ ,  $P = 0.06$ ; usual number per day:  $r = 0.33$ ,  $P = 0.10$ ) and with cotinine levels (last 24 h:  $r = 0.56$ ,  $P = 0.004$ ; usual number per day:  $r = 0.37$ ,  $P = 0.07$ ). (See Fig. 3 for correlations with number of cigarettes in last 24 h; correlations with usual number per day are not shown.) The nicotine content of the cigarette brand that the women smoked was not associated with the mucus nicotine and cotinine levels.

Among passive smokers there was no apparent association of mucus nicotine levels with amount of exposure to environmental tobacco smoke whether assessed as number of hours, number of smokers, or place of exposure.

Finally, we were interested in possible relationships between nicotine and cotinine levels and oral contraceptive use and dysplasia severity. Within smoking status

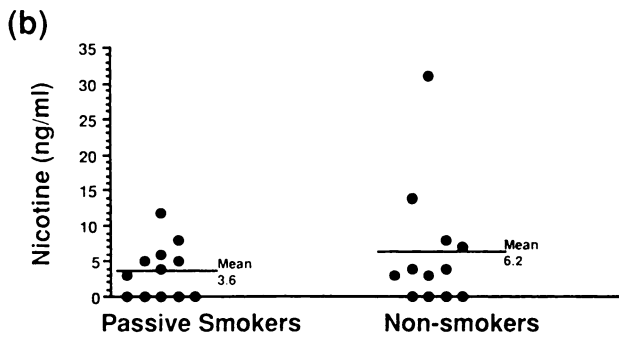
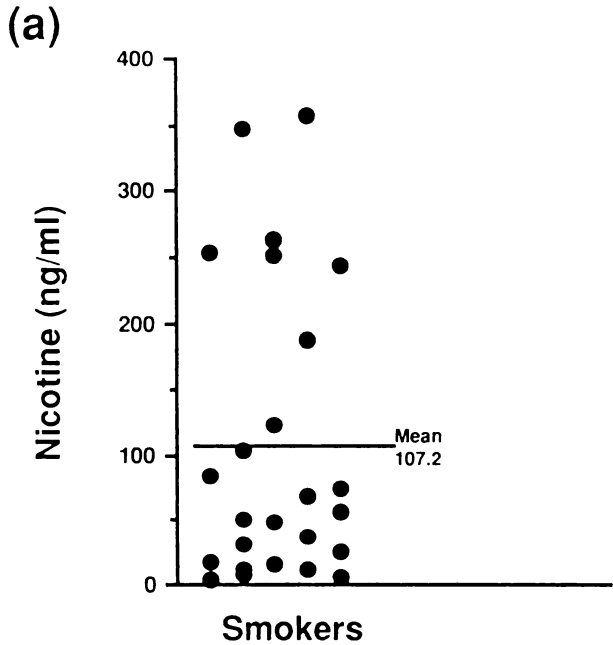


Fig. 1. Distribution and mean of nicotine levels by smoking status. a, smokers; b, passive smokers and nonsmokers.

groups, the mean nicotine and cotinine levels of oral contraceptive users were similar to the levels in women not using oral contraceptives. Dysplasia severity on Pap smear and/or biopsy was not associated with either nicotine/cotinine levels or number of years of smoking, but the number of subjects was too small for meaningful analysis.

**Discussion**

Our results show that nicotine and cotinine can be isolated in the cervical mucus of smokers, confirming the results of previous investigations (Table 2). The levels of smoke constituents among smokers were similar to those reported by Schiffman *et al.* (8), who also used the cervical flush technique for mucus sampling. The nicotine and cotinine levels in the present study are lower than in the two studies that used the direct aspiration method, presumably because of the dilution effect of the saline flush. The two smoking intensity measures were marginally associated with both nicotine and cotinine levels, showing stronger associations for smoking in the past 24 h, as in Schiffman's study (8). The strongest of these associations in the present study was between the

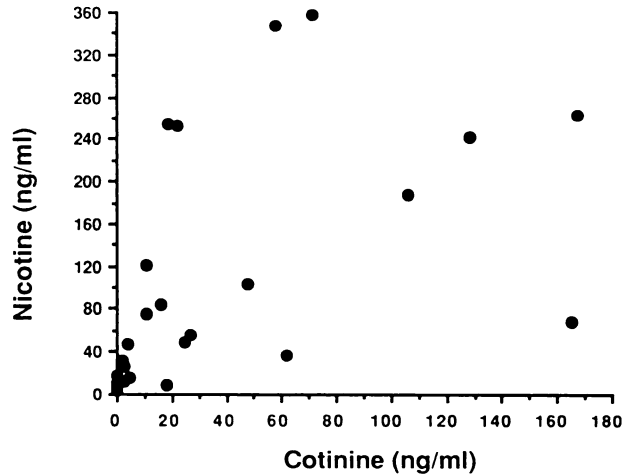


Fig. 2. Correlation of nicotine and cotinine in the cervical mucus of smokers.

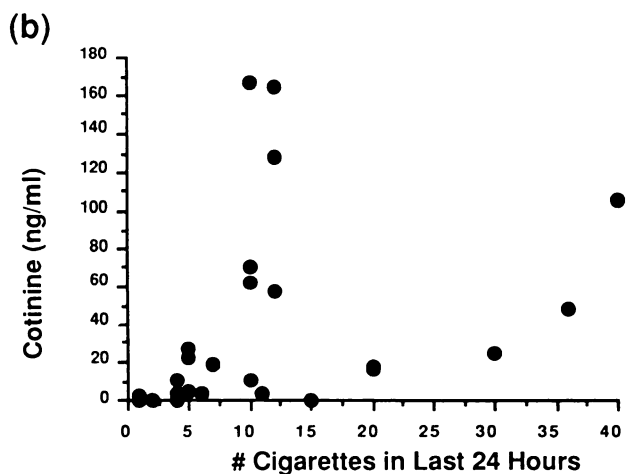
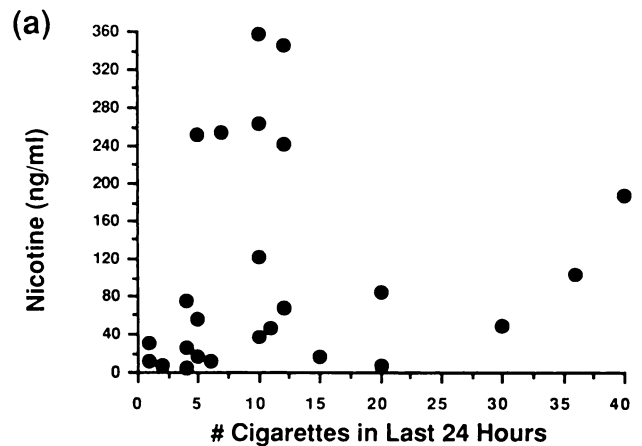


Fig. 3. Correlations of nicotine and cotinine in the cervical mucus of smokers with the number of cigarettes smoked in the last 24 h. a, nicotine; b, cotinine.

Table 2 Overview of studies of nicotine and cotinine in cervical mucus

Ref.	Mucus sampling method	Smoking status	Cervical cytology	Phase of menstrual cycle	Oral contraceptive users	Results (ng/ml)					
						Nicotine			Cotinine		
						Smokers	Passive smokers	Non-smokers	Smokers	Passive smokers	Non-smokers
7	Cervical aspiration	10 smokers 8 nonsmokers <sup>b</sup>	Normal	Preovulatory	NR <sup>a</sup>	66-2620	NR	3-37 <sup>b</sup>	161-773	NR	1-4 <sup>b</sup>
8	Cervical flush <sup>c</sup>	12 smokers 29 nonsmokers <sup>b</sup>	37 normal 4 mild dysplasia	Pre- and postovulatory	NR	12-512	NR	NR <sup>d</sup>	2-63	NR	NR <sup>d</sup>
5	Cervical aspiration	17 smokers 4 passive smokers 14 nonsmokers	9 CIN I 8 CIN II 18 CIN III	Preovulatory	Excluded	10-6652	ND-55	ND-201	ND-6662	17-124	ND-320
6	Cervical flush	74 passive smokers 70 nonsmokers	Normal	Pre- and postovulatory	NR	NR	ND-8.2	ND-3.8	NR	NR	NR
Current study	Cervical flush	25 smokers 12 passive smokers 12 nonsmokers	Benign to CIN III	Pre- and postovulatory	61%	4-358	ND-12	ND-31	ND-167	ND	ND

<sup>a</sup> NR, not reported; ND, not detected; CIN, cervical intraepithelial neoplasia.

<sup>b</sup> Includes passive smokers.

<sup>c</sup> Cervical swab sampling was also evaluated in this study but was found to be less reliable than the cervical flush technique.

<sup>d</sup> Actual values not reported, but nicotine was found for 21 of 29 nonsmokers (including passive smokers) and cotinine for 1 of 29.

last 24-h smoking exposure and the mucus levels of cotinine ( $P = 0.004$ ), reflecting the longer half-life of cotinine (18 h, compared to 2 h for nicotine) (17).

This study was also similar to the earlier studies in finding much lower levels of nicotine and cotinine for women who were not currently cigarette smokers compared with current smokers (Table 2). There was overlap of cervical mucus levels of nicotine and cotinine for passive smokers and nonsmokers who reported no passive exposure; both the percentages of women in whom nicotine and cotinine were detected and the mean levels of these chemicals were similar in the two groups. Smoking was not permitted in the waiting room of the clinic, so women would not have been exposed in the hour or so before their mucus specimens were obtained. These results are consistent with those reported by the two previous studies that separated passive smokers from nonsmokers without passive smoke exposure (5, 6). A recent study by Jones *et al.* (6) found higher nicotine levels in cervical mucus among nonsmoking women passively exposed at home than in those exposed only outside the home, and lowest levels among women reporting no passive exposure; however, there was considerable overlap among these three subgroups, there was no association between nicotine levels and various measures of the amount of passive exposure, and extremely low levels of nicotine were found.

The results of this study are consistent with studies involving other body fluids which have also found modest correlations between levels of these chemicals and degree of exposure to active and/or passive smoking (16-20). There are several reasons why these correlations are not stronger. The amount of nicotine inhaled by a smoker depends not only on number of cigarettes smoked but also on the amount of nicotine per cigarette, the smoker's inhalation pattern, and the percentage of each cigarette smoked. For example, it is well documented that the nicotine dose per cigarette as determined by smoking machines bears little relationship to

the widely varying nicotine levels per cigarette smoked by individuals (17). Among passive smokers the amount of nicotine inhaled depends on the smoking patterns of the other people sharing the same space and ventilation system and on the time spent in that space. Among both active and passive smokers there is great individual variation in the percentage of nicotine that is converted to cotinine and in the hepatic clearance of nicotine and cotinine (17), with some of this variation associated with gender (17) and race (21).

Very little is known about the transport of nicotine and cotinine throughout the body and about possible metabolism of nicotine and cotinine in more distant sites, such as the cervix, but it can be expected that there could be even greater variability in cervical mucus levels than in the more proximal fluids such as serum. There may also be some variation related to the difference in amount and consistency of cervical mucus associated with such factors as time in the menstrual cycle and oral contraceptive use. Furthermore, the data on number of cigarettes smoked and exposure to environmental tobacco smoke may not be precise because of variability over time in an individual's exposure; the timing of relevant exposures is unknown because of lack of knowledge about distribution of nicotine and cotinine to the cervix. Finally, in women with sexual partners who smoke, it is unclear what proportion of the nicotine and cotinine levels found in cervical mucus is derived from cervical contact with semen, which has recently been shown to contain cotinine,<sup>3</sup> and what proportion from inhalation of environmental tobacco smoke.

One aspect of nicotine and cotinine assessment that is different for the various body fluids is the relative levels of nicotine and cotinine. In this study, as in the other

<sup>3</sup> M. F. Vine, B. S. Hulka, P. C. Hu, *et al.* Cotinine levels in blood (serum), urine and semen of smokers and nonsmokers, paper presented at the 2nd Annual Meeting of the International Society for Environmental Epidemiology, Berkeley, California, August 1990.

studies of cervical mucus, the levels of nicotine are higher than the levels of cotinine (Table 2). In contrast, higher levels of cotinine than of nicotine are found in serum (5, 7, 16, 19). It has been speculated that nicotine may be selectively concentrated in cervical fluids because it is a stronger base than nicotine (7).

This is the first report of nicotine and cotinine being isolated from the cervical mucus of a smokeless tobacco user. While it is not possible to separate the effect of her snuff use from her passive smoke exposure, the fact that her nicotine and cotinine levels were much higher than those of any other passive smoker suggests that most of the nicotine and cotinine in the mucus can be attributable to her smokeless tobacco use. Furthermore, investigations of other body fluids have shown that smokeless tobacco users have peak nicotine and cotinine levels similar to those found for smokers and more prolonged elevation of levels than smokers (22, 23).

The majority of epidemiological studies addressing the relationship between smoking and cervical cancer risk have indicated a strong association, as reviewed by Winkelstein (1). Most recent studies confirm this association even after controlling for sexual behavior. Several studies have noted a particularly strong relationship between smoking and cervical cancer among women with no sexual experience or only one sexual partner (24–26). In one of these studies serum cotinine levels were assessed and were found to correlate well with the woman's reported status as a current cigarette smoker (26). Passive smoking has also been recently reported to have an effect on increased cervical cancer risk (26). Three other studies have found some evidence that smoking by the male partner is a risk factor (24, 27, 28).

The present study, together with the earlier studies of nicotine and cotinine in cervical mucus, supports the biological plausibility of the association between exposure to tobacco products and risk of cervical cancer. Future epidemiological research should evaluate the correlation between nicotine or cotinine levels in cervical mucus and the severity of dysplasia. Further research is also needed on the presence in the cervix of other tobacco components that are potentially carcinogenic. Other areas for further investigation include the possible metabolism of smoke constituents in distant organs, such as the cervix, and the role these metabolites play in carcinogenesis.

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# Cancer Epidemiology, Biomarkers & Prevention

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*Cancer Epidemiol Biomarkers Prev* 1992;1:125-129.

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