Belgian heart disease prevention project: comparison of self-reported smoking behaviour with serum thiocyanate concentrations

MARCEL KORNITZER,¹ ANNE VANHEMELDONCK,¹ PIERRE BOURDOUX,² AND GUY DE BACKER³

From the Laboratory of Epidemiology and Social Medicine,¹ Free University of Brussels, the Laboratory of Radio Isotopes,² St Pieters Hospital, Brussels, and the Laboratory of Hygiene and Social Medicine,³ State University, Ghent, Belgium

SUMMARY At the end of a multifactorial cardiovascular preventive trial serum thiocyanate was measured in random samples of 1035 cases and 1087 controls. A cut-off point 0.45 mg/dl (77.6/μmol/l) gave a sensitivity of 82.1% among the cigarette smokers in the control group and a specificity of 91.0% among the non-smokers. When the intervention and control groups are compared in terms of self-reported smoking behaviour non-significant differences in mean thiocyanate concentration are observed for those who never smoked, ex-cigarette smokers, actual cigarette smokers, and in four different cigarette smoking categories. Our results fail to confirm the reported pessimistic views concerning the validity of self-reported smoking behaviour in subjects taking part in intervention trials.

It has been argued that self-reported smoking behaviour should be interpreted with caution, particularly when subjects are taking part in a controlled trial.¹ An objective evaluation of self-reported smoking behaviour would be important when differences between experimental and control groups are small and expressed in numbers of cigarettes smoked daily.

In the Belgian Heart Disease Prevention Project significant differences in the percentage of smokers as well as in the amount smoked was observed in a group of high-risk subjects after two years of follow-up.² No significant difference in the percentage of smokers was observed between total intervention and control groups, but the self-reported number of cigarettes smoked daily was significantly lower in the intervention group compared with the control group: consequently we suspected that differences at end-screening, if any, would be detectable only in the mean number of cigarettes smoked daily. We decided, therefore, to use serum thiocyanate as an objective measure of reported smoking behaviour in random samples of both the intervention and control groups.

Material and methods

Details of the study population and screening

techniques have been described elsewhere.³ Thirty factories were paired according to type of industry, and one member of each pair was randomly allocated to the intervention group with the other serving as a control. There were 19 409 men aged 40–59 listed, of whom 16 222 (83.7%) took part in the base-line examination. In the intervention group—of 7398—all subjects were initially screened for risk factors (systolic blood pressure, resting ECG, weight and height, serum cholesterol concentration, and smoking habits). In the control group of 8824, 10% of all subjects in each factory were randomly selected to undergo the same initial examination as all the subjects in the intervention group; in the other 90% only an ECG at rest was recorded. For all the subjects in the intervention group and for 10% of the total control group who underwent the same thorough initial examination, risk scores were established based on the initial results. The 600 subjects belonging to the top 21% of the risk score distribution were arbitrarily designated as the high-risk group, while the others were called the lower-risk group.

In the intervention group the high-risk subjects received twice a year face-to-face counselling whereas the lower-risk group received written information on their particular risk factors and benefited from the mass campaign. Subjects who smoked five or more cigarettes a day were

encouraged to quit. At the six-year end screening, random samples of the intervention and control group had serum thiocyanate measured: (1035 of the intervention group and 1087 of the control group). Serum thiocyanate was measured according to the technique of Aldrige⁴ modified by Michajlovsky and Linger⁵: 0.5 ml serum were mixed with 2 ml 15% trichloroacetic acid and centrifuged for 10 minutes. An aliquot of the supernate (1.5 ml) was transferred to a glass-fitted tube; standards were prepared by mixing 0.3 ml KSCN solutions (0.1, 0.25, 0.5, 0.75, 1.0, and 1.25 mg SCN/dl) with 1.2 ml 15% trichloroacetic acid. The following reagents were then added suquentially to each tube: 0.2 ml saturated bromine water, 0.2 ml 4% As₂O₃ in 2% NaOH, 1.6 ml 1% benzidine 2 HCl in water, and 2 ml pyridine. After 30 minutes optical density was read against blank at 525 mm. A serum sample measured in 27 different assays gave a mean $\pm$ SD of 0.61 $\pm$ 0.02 mg/dl (Interassay CV = 3.5%).

Results

The incidence of ex-smokers during the six years of the trial was almost identical in both the intervention (26.5%) and control (26.5%) groups; the incidence was slightly but not significantly higher among the high-risk subjects of the intervention group (30.9%) compared with the high-risk control group (28.0%).

The change between base-line and end-screening in the mean number of cigarettes smoked daily among subjects who smoked cigarettes at base-line (= Δ cigarettes/day) was calculated. No differences were observed in Δ cigarettes/day between total intervention and 10% random sample of the control group. Nevertheless a significant difference in Δ cigarettes/day was observed between the high-risk subjects of the intervention group compared with the high-risk control subjects (table 1). When the serum thiocyanate concentrations of the control group are taken as a reference we observed the following results: the lowest mean thiocyanate concentration was found in those who reported having never smoked, a slightly higher mean was observed in ex-cigarette smokers, whereas a significantly higher level was found in those who switched from cigarettes to cigar or pipe, or both; the thiocyanate

concentration in the latter group was almost the same as that observed in genuine cigar or pipe smokers, or both (fig 1).

Fig 1 Serum thiocyanate concentrations in 1035 control subjects of the Belgian Heart Disease Prevention Project, according to self-reported smoking behaviour, at final screening.

In fig 2 the mean thiocyanate concentrations (and SEM) are given for non-smokers and for current cigarette smokers by number of cigarettes; a significant gradient is found with increasing numbers of cigarettes smoked; even smokers of one to five cigarettes a day show a significant higher mean thiocyanate concentration compared with non-smokers. The correlation coefficient between thiocyanate concentrations and number of cigarettes smoked a day is 0.41.

When thiocyanate concentrations in ex-smokers are compared with those in current cigarette smokers the same difference and gradient are observed.

We evaluated the sensitivity and specificity of the technique in subjects of the control group, as it is

Table 1 Change in number of cigarettes smoked a day by smokers seen at the initial screening and after six years

	Intervention group		Control group (10%)		p
	No of smokers	Mean difference	No of smokers	Mean difference	
Total	2182	-1.5	282	-1.0	NS*
High-risk group	539	-3.7	82	-1.4	<0.05

NS = Not significant.

Fig 2 Serum thiocyanate concentrations in 1035 control subjects of the Belgian Heart Disease Prevention Project, according to self-reported smoking behaviour, at final screening.

assumed that they reported their smoking behaviour accurately (table 2). A cut-off point of 0.45 mg/dl ($77.6/\mu\text{mol/l}$) gives a sensitivity of 82.1% among self-reported cigarette smokers, this figure being almost the same for light (< 15 cig/day) and heavy (≥ 15 cig/day) smokers; whereas specificity in non-smokers and ex-smokers is respectively 91% and 88.3%.

Cigarette smokers who switched to cigar or pipe, or both, and genuine cigar or pipe smokers or both, are very similar to current cigarette smokers in terms of thiocyanate concentrations: approximately 84% of them have levels at or above 0.45 mg/dl.

When the intervention and control groups are compared in terms of self-reported smoking behaviour non-significant differences in mean

thiocyanate concentrations are observed for those who never smoked, ex cigarette smokers, ex-cigarette smokers who switched to cigar or pipe, or both, and steady cigar or pipe smokers, or both (fig 3).

Fig 3 Serum thiocyanate concentrations in control and intervention subjects of the Belgian Heart Disease Prevention Project according to self-reported smoking behaviour at final screening. NS = Not significant.

Furthermore, in none of the four different cigarette smokers' categories, nor in the total group of cigarette smokers were significant differences in thiocyanate concentrations found between the intervention and control groups.

Finally in table 3 the thiocyanate concentrations are presented for random subgroups of 3036 subjects in the intervention group and 393 in the control group who reported cigarette smoking at base-line and who attended the end-screening: no significant differences in thiocyanate concentrations are

Table 2 Specificity and sensitivity of thiocyanate measure in the control group

	No of subjects with thiocyanate				Total
	≥0.45 mg/dl		<0.45 mg/dl		
	No	%	No	%	
Never smoked	18	9	181	91	199
Ex-cigarette smokers:					
Non-smokers	21	11.7	158	88.3	179
Cigar/pipe smokers	89	84.8	16	15.2	105
Steady cigar/pipe smokers	86	84.3	16	15.7	102
Cigarette smokers:	412	82.1	90	17.9	502
<15/day*	112	82.3	24	17.7	136
≥15/day*	299	83.3	60	16.7	359

*Seven missing values.

Table 3 Mean thiocyanate (mg/dl) of initial cigarette smokers at six-year screen

Status at six-year screen	Intervention group 3036 = No of initial cigarette smokers = 393			Control group (10%)			p
	No	n*	Mean thiocyanate	No	n*	Mean thiocyanate	
Non-smokers	462	84	0.32	62	16	0.27	NS
Cigar or pipe smokers, or both	319	66	0.53	41	7	0.67	NS
Cigarette smokers	2182	444	0.72	283	56	0.89	<0.01
Average No of cigarettes a day	17.9			20.1			<0.01

*Random subsample with thiocyanate measure.

observed when the intervention group is compared with the control group for ex-smokers and those who switched to cigar or pipe, or both; however, the lower mean number of daily smoked cigarettes reported by subjects in the intervention group as compared with the control group goes along with a significantly lower mean thiocyanate concentrations in the former as compared with the latter.

Discussion

In this study the majority (90%) of the subjects in the control group attended the cardiovascular screening examination for the first time at end-screening. Therefore we assumed that the smoking behaviour as reported by them was unbiased; from these data criteria for specificity and sensitivity concerning thiocyanate concentrations could be established. Thus with a cut-off point of 0.45 mg/dl only 9% of those reporting having never smoked were false-positives. Some of them may have been very moderate and irregular smokers or alternatively were consuming food products resulting in thiocyanate, such as cauliflower, horseradish, or broccoli. Cohen and Bartsch⁶ reported in 426 smokers and 191 non-smokers a specificity of 81% and a sensitivity of 93%. With a cut-off point of 100/ μ mol/l (0.58 mg/dl) Vogt *et al*⁷ correctly classified 93.3% of non-smokers and 81% of smokers. The correlation coefficient between daily smoked cigarettes and thiocyanate concentrations as observed in this study (0.41) lies between a low 0.25 of Cohen and Bartsch⁶ and a somewhat higher 0.46 of Butts *et al*⁸ and 0.48 Vogt *et al*.⁷

It seems that the greatest part of thiocyanate variance is not explained by the number of cigarette smokers but by other variables related to smoking behaviour such as depth of inhalation, frequency of puff, or puff size.⁹

The advantage of thiocyanate over carboxyhaemoglobin as an objective marker of smoking is related to its biological half-life of 14 days, so that recent ex-smokers for some time still have raised thiocyanate concentrations. On the other hand, thiocyanate seems to be resorbed, at least

partially, through the oral mucosa, which made us unable to discriminate between cigarettes, cigar, or pipe smokers or between inhalers and non-inhalers. Hence, ex-cigarette smokers who switched to cigar or pipe cannot be divided according to inhalation by thiocyanate concentrations.

The ratio of mean thiocyanate concentration between cigarette smokers and non-smokers was three, comparable to what has been observed in other studies.^{10 11}

Several authors have questioned the validity of self-reported behaviour. Thus Sillet *et al*¹ observed that respectively 22% and 40% of subjects taking part in clinical trials who reported to have stopped smoking had a high serum carboxyhaemoglobin concentration. In another study, however, 17 out of 19 subjects (89.5%) who reported at the follow-up to have stopped smoking had low thiocyanate concentrations.¹² Under-reporting of number of cigarettes smoked daily in clinical trials has been suggested by several authors on the basis of thiocyanate concentrations. Thus in the study of Kirk *et al*¹² subjects who reported a decrease in number of cigarettes smoked had an initial thiocyanate concentration of 142/ μ mol/l and 147/ μ mol/l at follow-up.

In a sample of the multiple risk factor intervention trial 102 non-smokers and 162 smokers were followed up during one year with base-line and follow-up measurements of thiocyanate concentrations.¹³ The cigarette smokers were given an intervention programme consisting of 10 weekly or bi-weekly meetings of two hours' duration each. Among the subjects who reported a decrease in numbers of cigarettes smoked the authors observed an increase of 75% in thiocyanate concentration per smoked cigarette. The authors suggest an individual titration to tobacco smoke or alternatively a false under-reporting of smoking behaviour that could be called a "social conforming behaviour." In their final report concerning risk factor modification the multiple risk factor intervention trial reported serum thiocyanate concentrations as measured, both in special intervention and usual care groups at entry and at 12, 24, 36, and 48 months.¹⁴ Compared with

thiocyanate concentrations for initial non-smokers those for cigarette quitters, both in the special intervention and usual care groups, were much higher. Thus while under-reporting appeared in both groups it was relatively more important in the special intervention group. The authors also question the sensitivity of the thiocyanate method for the detection of smoking reduction in participants who continue to smoke.

We did not perform serial thiocyanate measurements over time which hampers comparison with other studies. Nevertheless, our results fail to confirm the reported pessimistic views concerning the validity of self-reported smoking behaviour in subjects taking part in an epidemiological intervention trial. Indeed, both for ex-cigarette smokers as for subgroups of cigarette smokers no significant differences in thiocyanate concentrations were observed between intervention and control groups. Furthermore, in a subsample of smokers differences in mean number of cigarettes smoked between intervention and control groups were in parallel with significant differences in thiocyanate concentrations. It should be remembered, however, that due to a less aggressive and individualised prevention programme as compared with the multiple risk factor intervention trial study, the results at end-screening in terms of differences between intervention and control groups were weak. The soft intervention procedures perhaps did not induce a feeling of social conforming behaviour in the intervention subjects, hence their more "honest" self-reporting of smoking behaviour.

Study granted by the Belgian "Fonds National de la Recherche Scientifique" (Grant No 20.202).

References

- ¹ Sillett RW, Wilson MB, Malcolm RE, Ball KP. Deception among smokers. *Br Med J* 1978; ii: 1185-6.
- ² Kornitzer M, Dramaix M, Kittel F, De Backer G. The Belgian heart disease prevention project: changes in smoking habits after two years of intervention. *Prev Med* 1980; 9: 496-503.
- ³ Kornitzer M, De Backer G, Dramaix M, Thilly C. The Belgian heart disease prevention project: modification of the coronary risk profile in an industrial population. *Circulation* 1980; 61: 18-25.
- ⁴ Aldridge WN. The estimation of microquantities of cyanide and thiocyanate. *The Analyst (London)* 1945; 70: 474-5.
- ⁵ Michajlovsky N, Langer P. Studien über Beziehungen zwischen Rhodanbildung und kropfbildender Eigenschaft von Nahrungsmitteln. I: Gehalt einiger Nahrungsmittel an präformierten Rhodanid. *Zeitschrift für Physiologische und Chemie* 1958; 312: 26-30.
- ⁶ Cohen JD, Bartsch GE. A comparison between carboxyhemoglobin and serum thiocyanate determinations as indicators of cigarette smoking. *American Journal of P H* 1980; 70: 284-6.
- ⁷ Vogt TM, Selvin S, Widdowson G, Hulley SB. Expired air carbon monoxide and serum thiocyanate as objective measures of cigarette exposure. *Am J Public Health* 1977; 67: 545-9.
- ⁸ Butts WC, Kuehneman M, Widdowson GM. Automated method for determining serum thiocyanate to distinguish smokers from nonsmokers. *Clin Chem* 1974; 20: 1344-8.
- ⁹ Gritz ER, Baer-Weiss V, Jarvick ME. Titration of nicotine intake with full-length and half-length cigarettes. *Clin Pharmacol Ther* 1976; 20: 552-6.
- ¹⁰ Densen PM, Davidow B, Bass HE, Jones EW. A chemical test for smoking exposure. *Arch Environ Health* 1967; 14: 865-74.
- ¹¹ Borgers D, Burckhard J. Thiocyanate as an indicator of tobacco smoking. *Prev Med* 1979; 8: 351-7.
- ¹² Kirk CJC, Lund VJ, Woolcock NE, Greenhalgh RM. The effect of advice to stop smoking on arterial disease patients, assessed by serum thiocyanate levels. *J Cardiovasc Surg* 1980; 21: 568-9.
- ¹³ M R F I T Group. The multiple risk factor intervention trial (MRFIT): a national study of primary prevention of coronary heart disease. *JAMA* 1976; 235: 825-7.
- ¹⁴ Neaton JD, Broste S, Cohen L, Fishman EL, Kjelsberg MO, Schoenberger J. (for the MRFIT). The multiple risk factor intervention trial VII. A comparison of risk factor changes between the two study groups. *Prev Med* 1981; 10: 519-43.