THEORY AND METHODS

Validation of self reported smoking by serum cotinine measurement in a community-based study

E Vartiainen, T Seppälä, P Lillsunde, P Puska

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See end of article for authors' affiliations

Correspondence to: Professor E Vartiainen, National Public Health Institute, Mannerheimintie 166, FIN-00300 Helsinki, Finland; erkki.vartiainen@ktl.fi

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Study objective: The validity of self reported smoking in population surveys remains an important question. An associated question is what would be the value of measuring serum cotinine concentrations in such surveys to obtain validated smoking data.

Design: Cross sectional analysis of data on self reported smoking and serum cotinine among a random population sample of 5846 persons aged 25 to 64 years, who participated in the FINRISK-92 survey.

Main results: Among self reported regular smokers, 97.2% of men and 94.9% of women had a cotinine concentration of 10 ng/ml or higher in serum. Of those participants who reported to have smoked at any time during their life but not during the previous month, 6.3% of men and 5.2% of women had a serum cotinine concentration of at least 10 ng/ml. Among never smokers 2.5% of men and 2.7% of women had detectable level of cotinine in their serum. The validity of self reporting was similar among subjects from different areas, ages, and socioeconomic groups.

Conclusions: In a sample of the general population in Finland the validity of self reported smoking is high, and most of the few self reported non-smokers who had cotinine in their serum had only low or moderate levels.

Both in clinical and in community settings there has been a concern about the validity of self reported smoking.[1 2] Mainly, three biological measurements have been used to validate self reported smoking: carbon monoxide, thiocyanate, and cotinine.[3] The aim of our paper is to study the validity of self reported smoking in a cardiovascular risk factor population survey by comparing self reports with results of measurements of cotinine levels in serum.

Nicotine metabolises rapidly and extensively, primarily in the liver. N-oxidation of nicotine to nicotine-1′-N-oxide occurs in humans. This metabolite has been shown to convert back to nicotine. In humans, the urinary elimination phase of the metabolite parallels that of the parent nicotine, indicating a formation rate limited excretion. It has been estimated that approximately 4% of the nicotine dose is excreted as nicotine-1′-N-oxide. Furthermore, it has been estimated that the quantitative disposition of nicotine is as follows: an average of 9% of the dose seems to be excreted as intact nicotine, and about 70% of nicotine seems to be converted to cotinine. Cotinine is the major plasma metabolite of nicotine and persists for a considerable time period in plasma, with a half life of approximately 16 hours. Only a minor fraction of the generated cotinine is excreted by the kidneys, but cotinine is further metabolised to more polar water soluble substances. According to recent human data the major metabolite found in urine is hydroxylated cotinine.[4 5]

In the CARDIA study self reported smoking prevalence was 31%, and the measured prevalence of serum cotinine with 14 ng/ml as the cut off point was 32%.[6] The proportion of reported non-smokers with a cotinine level of at least 14 ng/ml was 4.2%. The misclassification was larger among subjects who were black, had a high school education or less, or were former smokers. The possible reasons for misclassification were reporting errors, environmental tobacco smoke, or an inappropriate cut off point for delineating smoking status.

Self reported smoking and serum cotinine were compared among 743 Mexican American participants in the Hispanic Health and Nutrition Examination Survey.[7] Of 189 self reported non-smokers 6.3% were defined as biochemical smokers and possible misclassifications by self report. Among the 547 self reported smokers 12.1% were found to have serum cotinine levels less than 14 ng/ml and were possible misclassifications by self report. The cotinine level cut off points to determine smoking has varied from 3 ng/ml to 40.5 ng/ml among studies.[8] The most commonly used cut off points are between 10 ng/ml and 20 ng/ml. From the review of 16 studies it was concluded that the maximum sensitivity was near the cut off point of 8.8 ng/ml.[9] The aim of this paper is to describe how valid self reported smoking is in an area with a community-based cardiovascular prevention programme and in other areas of Finland as well as in different demographic groups.

METHODS

In 1992 the FINRISK survey was carried out to assess cardiovascular risk factor levels and to assist the monitoring of trends in Finland. The survey represents the third and final FINMONICA survey and is used to evaluate the long term effects of the North Karelia project.[10] The survey was conducted in four areas of Finland. In eastern Finland these areas were the provinces of North Karelia and Kuopio. The North Karelia and Kuopio provinces have populations of 180 000 and 250 000, respectively. The third survey area in south western Finland encompasses the city of Turku, the small town of Loimaa, and 12 small rural municipalities with a total population of roughly 210 000 people. Two cities in the Helsinki capital area, Helsinki and Vantaa, were included in the study. Helsinki's and Vantaa's populations are 500 000 and 170 000, respectively.

In 1992 the sampling frame followed the WHO MONICA protocol. A random sample of 2000 people from each of the survey areas was drawn from the National Population Register. The sample included people aged 25–64. The sample was stratified by 10 year age groups and by sex. Each cell contained 250 people. The participation rates are shown in table 1.

The survey included a self administered questionnaire (mainly covering questions on socioeconomic factors, medical

Table 1 Subjects and participation rate

	Men			Women		
	Subjects	Participated	%	Subjects	Participated	%
North Karelia province	988	673	68.1	994	803	80.8
Kuopio province	990	752	76.0	991	830	83.8
South western Finland	994	749	75.4	995	832	83.6
Helsinki capital area	993	675	68.0	982	737	75.1

history, health behaviour, and psychological factors) and a cardiovascular risk factor examination conducted by specially trained nurses.

Smoking was assessed with a set of questions. Two types of indices were used to categorise the smokers. In the first index the following questions were used: Have you ever smoked in your life? (1) no, (2) yes. Those who answered no were classified as never smokers. Those, who answered yes were asked the following question: When was the last time you smoked? (1) Today or yesterday, (2) Between two days and. one month ago, (3) Between one month and half a year ago, (4) From half a year and one year ago, (5) More than one year ago. Based on this the first index contained the following four groups: (1) those who had smoked today or yesterday ("current smokers"), (2) those who had smoked two days to one month ago, (3) those who had smoked longer than one month ago or (4) those who had never smoked. For the second index the participants were asked: Do you now smoke (1) regularly? (2) occasionally? (3) not at all? (4) 1 have never smoked. The number of daily cigarettes, pipes smoked and cigars consumed were asked from those who reported to have smoked within the past month. The number of smoking times in a day were calculated.

Blood samples were taken in the seated position and in a smoke free place as part of the risk factor examination. Fresh serum samples were sent to the laboratory at the National Public Health Institute where they were frozen. Cotinine was measured by a Hewlett Packard gas chromatography (5890) mass spectometre (5970, GC/MS) with a selected ion monitoring mode. Half a millilitre of serum was shaken with 1 ml of 0.5 M NaOH and 5 ml of dichlormethane with pyribenzamine (5 µg/100 ml) as the internal standard. After centrifugation the organic layer was transferred into a clean test tube and evaporated. The residue was dissolved in 100 µl of ethanol, and 1 µl was injected, into the GC/MS column. A fused silicone capillary column coated with HP 1 (Hewlett Packard, 12 m×0.2 mm×0.33 mm) was used. The initial oven temperature was 60°C, maintained for one minute, and then raised by 30°C per minute to 300°C and followed by linear programming. The injector was maintained at 250°C, and the detector at 280°C. The carrier gas was helium, with a flow of 0.5–1.0 ml/min. The minimum detectable level was 10 ng/ml.

The principal fragment ions (98 and 176 for cotinine, 91 for pyribenzamine) were monitored. The cotinine's coefficient of variation (cv) was 6.6% (n=10) at a level of 200 ng/mg and 19% at a level of 20 ng/ml. The extraction recovery was 98%.

RESULTS

Among those participants who reported to have smoked today or yesterday, 96.4% of men and 92.6% of women had a serum cotinine level of 10 ng/ml or higher, which was the minimum detectable level of the method. Most of them had serum cotinine level higher than 50 ng/ml (table 2). Of these participants who reported to have smoked today or yesterday (=1489), 77 subjects did not have a measurable level of cotinine in serum, 31 reported that they smoke occasionally, 23 said they smoked 10 times or less per day, and 21 reported to smoke more than 10 times per day. From one area seven of those who reported to smoke at least 10 cigarettes per day every day, and reported to smoke regularly were asked to give a new blood sample. Two

Table 2 Self reported last smoking time and serum cotinine level (ng/ml)

Cotinine level (ng/ml)	Smoked today or yesterday %	Smoked 2 days – 1 month ago %	Smoked longer time than a month ago %	Never %	Total %
Men					
0	3.6	62.6	93.7	97.3	64.4
10–19	1.5	3.6	1.1	0.8	1.3
20–49	5.7	15.8	3.1	0.8	3.9
50+	89.2	18.0	2.1	1.0	30.4
Mean	258	33	5	2	
SD	172	67	30	15	
N	881	139	906	828	2754
Total	32.0	5.0	32.9	30.1	100.0
Women					
0	7.4	59.5	94.8	97.3	77.5
10–19	1.6	7.6	1.2	1.2	1.6
20–49	5.6	14.5	1.5	0.9	2.5
50+	85.4	18.3	2.5	0.6	18.4
Mean	198	38	6	2	
SD	149	93	50	24	
N	608	131	671	1680	3090
Total	19.7	4.2	21.7	54.4	100.0

Table 3 Percentage of self reported non-smokers (had not smoked in the past month) having serum cotinine higher than 10 ng/ml by sociodemographic groups

Sex		NS*
Men	4.6	
Women	3.4	
Age		NS
25–34	3.2	
35–44	4.3	
45–54	3.4	
55–64	4.5	
Area		NS
North Karelia	4.1	
Kuopio province	3.3	
South western Finland	4.2	
Helsinki capital area	4.0	
Marital status		NS
Married	3.8	
Single	3.5	
Divorced	5.1	
Widow	4.1	
Education		NS
Basic education	3.9	
Vocational school	3.7	
Medium level	4.0	
Academic level	3.9	

*χ^2 test between the groups.

subjects did not come to the survey, one had stopped smoking, two current daily smokers had cotinine in serum, and two others did not have cotinine in serum although they reported to continue their daily smoking.

The percentage of people who had a serum cotinine level of at least 10 ng/ml and reported not to have smoked in the past month was 3.9%. Out of these 159 persons 12 had used nicotine chewing gum or a transdermal patch. Most of those who reported not smoking but had cotinine in serum only exhibited a low or moderate level (between 10 ng/ml and 50 ng/ml).

The validity of self reported smoking was analysed in different demographic and socioeconomic groups (table 3) There were no statistically significant differences between age, sex, marital status, or educational groups in the percentage of subjects who reported not to have smoked in the past month but still had a measurable level of cotinine in serum. This percentage was similar in different areas.

Key points

- Self reported smoking is quite reliable in Finnish population.
- Small proportion of daily smokers do not have cotinine in their serum for an unknown reason.
- Validation by cotinine is needed to asses if self reporting of smoking is changing overtime.

The differences between the areas in smoking were very similar by using different criteria of self reported smoking or different cut off points in cotinine level (table 4).

Among those who reported to smoke at least once per day, the serum cotinine had a correlation of 0.45 with the number of self reported smoking times in a day. When we recorded non-smokers as 0 the correlation increased to 0.75.

DISCUSSION

The main concern in the validity of self reported smoking has been the possible under reporting. This has been of particular concern in a situation where there is a strong social pressure against smoking like in community-based disease prevention and health promotion programmes, smoking cessation trials, or clinical settings.[11 12] In Finland a long term, community-based cardiovascular disease prevention programme has been carried out in North Karelia,[13] one of the four districts that participated in this FINRISK-92 survey.

The differences between areas were very similar when assessed either by self reports in a questionnaire or by cotinine concentration in serum. This indicates that a more intensive programme in one area does not affect self reporting. The social pressure for people not to smoke is probably lower in community-based programmes with cross sectional random samples than in clinical settings where cotinine measurements may be more important. In their report, Jarvis *et al*[2] found that 19% of smoking hospital patients reported themselves to be non-smokers. When those people were added to the number of smokers the smoking prevalence increased from 43% to 54%.

Our data indicated that 6.3% (78 of 1713) of self reported male non-smokers had cotinine in serum al least 10 ng/ml. lf we assume that all these men smoke regularly or occasionally the percentage of smokers increases from 32% to 34%. In the CARDIA study 4% of self reported non-smokers had more

Table 4 Percentage of smokers by different smoking criteria (regular smokers, smoked today or yesterday) and by different cut off points in serum cotinine level

	North Karelia	Kuopio province	South western Finland	Helsinki capital area	Total	χ^2
Men						
Regular smokers	28	31	32			p=0.33*
Occational smokers	7	8	9	29	30	
Smoked today or yesterday	30	33	35	8	8	
Cotinine 10+	33	36	40	30	32	p=0.12
Cotinine 15+	32	36	40	33	35.7	P=0.009
Cotinine 20+	32	35	39	33	35	p=0.013
Cotinine 50+	27	32	34	32	34.4	p=0.008
				29	30.5	p=0.037
Women						
Regular smokers	12	14	19	24	17	p<0.001
Occational smokers	7	8	6	9	7	
Smoked today or yesterday	14	17	22	26	20	p<0.001
Cotinine 10+	18	19	23	30	23	
Cotinine 15+	17	18	23	29	22	p<0.001
Cotinine 20+	17	18	22	29	21	p<0.001
Cotinine 50+	14	15	20	25	18	p<0.001

*χ^2 test between the areas.

than 14 ng/ml of cotinine, and the respective increase in smoking prevalence was from 31% to 34%.[6]

Among Mexican Americans in the Hispanic Health and Nutrition Examination Survey 12% of the self reported smokers had a serum cotinine level lower than 14 ng/ml.[7] In a commercially run community survey, Piers and his colleagues found that 12% of smokers had a cotinine level lower than 25 ng/ml. The possible explanations proposed in the discussion have been low or occasional smoking, errors in the laboratory or with completing the questionnaire. In our study 5% of those who reported to have smoked "today or yesterday" did not have cotinine in serum. Most of this was explained by the fact that they were occasional smokers who may have smoked "today or yesterday" in relation to the time of completing the questionnaire but did not smoke on the day of or day before the examination. There is also intraindividual variation how well serum cotinine is describing nicotine intake. Different people convert different percent of nicotine to cotinine. Usually this varied between 55% and 92% and also the cotinine clearance varied from 19 to 75 ml/min.[14] In their report Benowitz and colleagues reported a person with deficient c-oxidation of nicotine.[5] This is associated with a long half time of nicotine and low level of cotinine in plasma compared with nicotine. It is unknown whether this or other similar conditions could explain the very low cotinine values of some smokers observed in many large epidemiological studies.

A special survey was done to assess the demographic factors and health behaviour of non-participants by a short postal questionnaire and by phone if they did not respond to the mailed questionnaire. About 50% of non-respondents were contacted. There were more non-participants in younger men and in cities. Smoking was slightly more prevalent among non-participants. No differences were observed in other health behaviours. Participants were not directly informed that self reported smoking will be validated by cotinine. Hence, the results reflect the general situation how people are reporting smoking. However, the self reporting may change over time when the norms in the society are changing. This survey was done in 1992, it may be useful to repeat the validation in future surveys to assess if the self reporting is changing.

The actual percentage of smokers depends on the cotinine cut off point, on the formulation of questions in the questionnaire, and on the subsequent definition of a smoker. A relatively large proportion of smokers report that they smoking occasionally.

Years ago, smoking used to be a more clearly defined habit: people were either smokers or non-smokers. This seems to be changing. About 20% of male smokers and 30% of female smokers reported in our survey that they smoking occasionally. About half of the self reported occasional smokers did not have cotinine in serum, and most of the rest had only moderate levels. If this will change over time requires a new survey in the future. This also means that classic calculations of sensitivity and specificity are not as appropriate as they were when people were more clearly classified as smokers or non-smokers.

The effect of passive smoking on cotinine level is small, the usual level being between 0.5 ng/ml to 10 ng/ml.[15–18] Thus, it is not likely that passive smoking could explain the high cotinine level among some self reported non-smokers. Nicotine replacement therapy explained a few of those high values. Use of smokeless tobacco was not included in the questionnaire, which may be one explanation for this discrepancy. On the other hand, these people were from both sexes and all age groups, and use of snuff is common only among young men in Finland. Thus, it is very likely that most of these people are underreporting their smoking. The small number of these people shows that self reported smoking is very reliable. Other studies have come to similar conclusions.[6 7] This raises the question of whether costly biochemical validation procedures are needed in population-based surveys. Cotinine measurement describes only one aspect of smoking: exposure to nicotine within the past few days. Questionnaires must inquire about the complete smoking history of people, with appropriately designed questions.

The main conclusion is that in a general population survey with self administered questionnaires the validity of self reported smoking is high in Finland and attempts to validate that by general measurement of cotinine is probably not worth the costs entailed. However, it may be useful to repeat the validation to a subsample of participants in the future surveys to assess if the self reporting is changing overtime.

Authors' affiliations
E Vartiainen, T Seppälä, P Lillsunde, P Puska, National Public Health Institute, Helsinki, Finland

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