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Misclassification of smoking status among women in relation to exposure to environmental tobacco smoke

E. Riboli*, N.J. Haley**, J. Trédaniel*, R. Saracci*, S. Preston-Martin+, D. Trichopoulos++

Misclassification of smoking status among women in relation to exposure to environmental tobacco smoke. E. Riboli, N.J. Haley, J. Trédaniel, R. Saracci, S. Preston-Martin, D. Trichopoulos. ©ERS Journals Ltd 1995.

ABSTRACT: In studies of the health effects of exposure to environmental tobacco smoke (ETS), misclassification of active smokers has the potential to bias the estimates of disease risk. Biochemical validation of exposure to ETS can provide objective evidence of current smoking status in epidemiological studies. Intrinsic to this effort is the establishment of appropriate cut-off points for the measurements of tobacco biomarkers.

Within a collaborative study on ETS co-ordinated by the International Agency for Research on Cancer, questionnaire data and urine samples were collected from 1,369 women at 13 centres in 10 countries. Forty seven of these women had urine cotinine levels above 50 ng·mg^{-1} creatinine, a level used to discriminate smokers from nonsmokers in previous studies.

The distributions of the subjects across cotinine values and self-reported exposure to ETS was consistent with the association, at one extreme, of moderate cotinine levels (50–150 ng·mg^{-1}) with very high exposure to ETS, and, at the other extreme, of very high cotinine levels indicating actual use of nicotine-containing products in women with low ETS exposure. Using the cut-off point of 150 ng·mg^{-1}, only 1.5% of the alleged nonsmokers were reclassified as current light smokers.

Potential bias due to smoker misclassification is very unlikely to be responsible for the increased health risks observed in epidemiological studies on ETS.

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*International Agency for Research on Cancer, Lyon, France. **American Health Foundation, Valhalla, NY, USA. +Dept of Preventive Medicine, University of South California, Los Angeles, USA. ++Harvard School of Public Health, Boston, MA, USA.

Correspondence: E. Riboli
International Agency for Research on Cancer
150 Cours Albert-Thomas
69372 Lyon Cedex 08
France

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A collaborative study on environmental tobacco smoke (ETS) was initiated by the International Agency for Research on Cancer to compare and contrast questionnaire and biochemical data on ETS exposure in nonsmoking women across 13 local settings in 10 countries [1]. The primary objective of the study was to validate self-reported exposure to ETS from different sources by analysis of urinary cotinine levels.

The number of studies investigating the associations of ETS exposure and cancer of the lung as well as other cancers has increased in recent years [2, 3]. The majority of studies found an association, but questions on possible misclassification of subjects according to current or former smoking status as well as methodological considerations have maintained the need for biochemically validated analyses of self-reported data [4].

The objectives of our primary study were to explore determinants of urinary cotinine excretion in nonsmoking women exposed to ETS from residential and nonresidential sources across several local settings. In our previous paper [5], we excluded 47 cases from the study group of 1,369 due to cotinine excretion of more than 50 ng·mg^{-1} creatinine, and we discussed the necessity for such exclusion to ensure that our exposure measures of ETS were not confounded by possible inclusion of currently active smokers. This group of 47 women and their

Participating centres

A.H. Wu-Williams (Dept of Preventive Medicine, University of South California, Los Angeles, CA, USA); (Harvard School of Public Health, Boston, MA, USA); H. Becher (Division of Epidemiology, German Cancer Research Centre, Heidelberg, Germany); J.D. Burch (NCIC Epidemiology Unit, Toronto, Ontario, Canada); E.T.H. Fontham (Dept of Pathology, Louisiana State University Medical Center, New Orleans, LA, USA); Y-T. Gao (Shanghai Cancer Institute, Shanghai, People's Republic of China); S.K. Jindal (Dept of Chest Diseases, Postgraduate Institute of Medical Education and Research, Chandigarh, India); L.C. Koo (Dept of Community Medicine, University of Hong Kong, Hong Kong); L. Le Marchand (Cancer Center of Hawaii, University of Hawaii, Honolulu, Hawaii, USA); N. Segnan (Unit of Cancer Epidemiology, Dept of Oncology, San Giovanni Hospital A.S., Turin, Italy); H. Shimizu (Gifu University, School of Medicine, Gifu, Japan); G. Stanta (Istituto di Anatomia, Università di Trieste, Ospedale Maggiore, Trieste, Italy); W. Zatonski (Unit of Epidemiology, Institute of Oncology, Warsaw, Poland).

self-reported exposure to ETS constitutes the subject of this report.

Subjects and methods

Thirteen centres located in Canada (Toronto), People's Republic of China (Shanghai), Greece (Athens), Federal Republic of Germany (Bremen), Hong Kong, India (Chandigarh), Italy (Turin and Trieste), Japan (Sendai), Poland (Warsaw) and the United States of America (Los Angeles, New Orleans and Hawaii) took part in the study. If numbers permitted, 50% of the women recruited into the study were to be currently married to smokers, and the other 50% to nonsmokers; within each of these categories, 50% of the women were to be currently employed outside the home.

To be eligible for the study, women had to report abstinence from any tobacco product for at least 2 yrs before interview. Each subject was interviewed according to a standardized questionnaire, which had been pilot tested and translated into seven languages. The details of the interview have been published previously [6]. In brief, the questionnaire included questions about exposure to smoking in the home, at work, during travel and social situations during the preceding 8 days. Very detailed information was obtained on a daily basis for the 4 days preceding the interview.

The survey data were correlated with biochemical measurements of urinary cotinine. Cotinine is one of the major metabolites of nicotine, and is specific for exposure to nicotine, primarily from tobacco or tobacco smoke. It has been used increasingly as a short-term marker in epidemiological studies because it has a relatively longer half-life (18 h) than nicotine, is not susceptible to fluctuations during smoke exposure, and can be measured in urine and saliva [2, 7–10]. There is a strong correlation, including a dose-response relationship, between urinary cotinine levels and self-reported exposure to tobacco smoke [11, 12].

Immediately following the interview, a urine sample was collected from each subject. The procedures for collection and shipping of these samples have been described previously [13]. Samples were frozen on the day of collection and stored at the centres until shipment to the American Health Foundation Clinical Biochemistry Laboratory in Valhalla, New York. Each urine sample was analysed for cotinine and creatinine.

The 47 women included in this analysis came from the total cohort of 1,369 and represent 3.4% of the total group. The formation of this group came from examination of several studies which suggested that a cotinine level of 50 $ng \cdot mg^{-1}$ creatinine might be an appropriate cut-off point to discriminate between active smokers and nonsmokers exposed to ETS [2, 4, 10, 14, 15]. For the primary purpose of our study on determinants of passive smoking in women across cultural settings, this cut-off point was utilized to minimize misclassification of active smokers as passive smokers, in the conservative view of avoiding artefacts in the overestimation of the effect of exposure by inclusion of any possible active smokers in the study group.

Biochemical methods

Samples were stored at -20°C until time of analysis. Batches of samples (250–300 ml each) were defrosted and analysed for cotinine and urinary creatinine. Duplicate analyses and quality control maintained accurate measures across centres and analyses.

Cotinine was determined by radioimmunoassay using polyclonal antisera raised in rabbits as described previously [5, 16], WALL *et al.* [15] having shown that adjustment of urinary cotinine levels for urinary creatinine concentrations affords the best separation of a group of nonsmokers from passive smokers. Creatinine was determined on a Kodak Ektachem 400 Clinical Chemistry Analyzer using single slide methodology.

Statistical analysis

Data on cotinine concentrations were adjusted by taking the ratio over creatinine concentration (ng cotinine/mg creatinine). Means and cross-tabulations were computed using SAS procedures. Chi-square for trend was computed following the methods described by ROTHMAN and BOICE [17].

Results

The distribution of the 47 subjects by centre is shown in table 1. The largest number of subjects included in this analysis by centre came from Trieste, Warsaw and Hong Kong (8, 7 and 6, respectively) with only one or no women with cotinine levels above 50 $ng \cdot mg^{-1}$ creatinine being found in the Athens, Shanghai or Honolulu centres.

Table 2 presents details on this subgroup and on the entire study population to show the number of persons within each centre with cotinine/ creatinine levels below or above 50 $ng \cdot mg^{-1}$. The corresponding age-adjusted means of cotinine levels observed for each centre are shown.

The determinants of cotinine levels above 50 $ng \cdot mg^{-1}$ creatinine could include: 1) very high ETS exposure; 2) possible infrequent active smoking and/or high ETS exposure; or 3) probable smoking behaviour. To determine whether these possibilities could be discriminated, the relationship between cotinine in subjects whose levels were greater than 50 $ng \cdot mg^{-1}$ and indices of self-reported exposure were examined.

These indices included average daily duration of exposure over the 4 days preceding the interview (table 3), and the number of cigarettes to which the subject reported having been exposed during this period (table 4).

Distribution of subjects according to their reported duration of exposure during the past 4 days showed that the majority of subjects (16 out of 27) with cotinine/creatinine levels between 50–150 $ng \cdot mg^{-1}$ reported rather long daily exposure to ETS ($\geq 5\ h \cdot day^{-1}$). When questioned about the past 8 days, 14 of these subjects maintained a report of long exposure periods (data not shown).

Table 1. – Distribution of subjects with cotinine levels above 50 ng·mg^{-1} by centre

	Cotinine/creatinine#							
Ln ng·mg^{-1}: ng·ml^{-1}+:	3.9–4.2 50–70	4.2–4.6 70–100	4.6–5.0 100–150	5.0–5.4 150–220	5.4–5.8 220–330	5.8–6.2 330–500	≥6.2 >500	Total
Bremen		1	2	1	1			5
Torino	1		1					2
Trieste	1	2		1	3		1	8
Warsaw			1	1		3	2	7
Athens	1							1
Chandigarh		1				1	3	5
Hong Kong	2	3				1		6
Shanghai					1			1
Sendai	2						1	3
Honolulu								0
Los Angeles	1	1						2
New Orleans	2	2	1					5
Toronto	1		1					2
Total	11	10	6	3	5	5	7	47

Intervals are of equal width on logarithmic scale. #: interval cut-off points were defined as (≥3.9–4.2<) *etc*. and (≥50–70<), *etc*. +: rounded values corresponding to logarithmic scale intervals.

Table 2. – Average cotinine levels in all women in the study and those with cotinine (COT) ≥50 ng·mg^{-1} creatinine

	No. of subjects		Average cotinine ng·mg^{-1}	
Centre	COT <50	COT ≥50	COT <50	COT ≥50
Bremen	90	5	7.9	162.0
Torino	91	2	8.1	98.5
Trieste	89	8	14.5	265.0
Warsaw	124	7	10.5	443.0
Athens	100	1	9.7	54.3
Chandigarh	92	5	6.2	2389.2
Hong Kong	97	6	10.4	129.2
Shanghai	98	1	4.4	288.9
Sendai	145	3	8.2	1068.8
Honolulu	99	-	3.5	-
Los Angeles	98	2	10.4	68.3
New Orleans	101	5	7.4	84.7
Toronto	98	2	6.3	93.2
All subjects	1322	47	8.3	494.6

Averages were based on log transformed values, and adjusted for age and retransferred to the normal scale.

In contrast, among subjects with cotinine/creatinine levels above 150 ng·mg^{-1}, 11 out of 20 reported moderate exposure (≤2 h·day^{-1}) or none.

The hypothesis that groups of subjects with cotinine levels below or above 150 ng·mg^{-1} differ in their distribution by levels of exposure to ETS was statistically tested by dichotomizing the cotinine levels, below or above 150 ng·mg^{-1}, and by computing χ^2 for trend. The tests indicated that the two subpopulations differed significantly, as the subjects with cotinine levels below 150 ng·mg^{-1} are exposed to ETS for more hours per day (p=0.015).

When total number of cigarettes smoked in the presence of the subject was used as the criterion of exposure (table 4), a similar picture emerged. Eight subjects out of 20 reported exposure to fewer than 8 cigarettes·day^{-1} yet had cotinine/creatinine levels greater than 150 ng·mg^{-1}, whereas 19 out of 27 subjects with cotinine/creatinine levels of 50–150 ng·mg^{-1} reported daily exposure to more than 8 cigarettes (χ^2 test for trend: p=0.04).

Examination of the determinants of urinary cotinine in our study of nonsmoking women (1,322 with cotinine <50 ng·mg^{-1}) revealed that the smoking behaviour of the husband was most predictive of cotinine excretion [7]. The source of self-reported exposure to ETS was, therefore, examined in the 47 women considered in the present paper: 38 out of the 47 women with cotinine levels above 50 ng·mg^{-1} creatinine reported that they had been

Table 3. – Distribution of subjects by cotinine levels and by self-reported duration of exposure during the 4 days preceding interview

Cotinine/creatinine ng·mg^{-1}	Exposure h·day^{-1}#								Total
	<0.5	1	2	3	4	5	6	≥6.5	
50–70	1	1	3	1		1	1	3	11
70–100			2	1	1		2	4	10
100–150		1				2	2	1	6
150–220	1		1		1				3
220–330	1					1	2	1	5
330–500	2	2						1	5
>500	3	1	1			1	1		7
Total	8	5	7	2	2	5	8	10	47

#: interval cut-off points were defined as (0–<0.5), (≥0.5–>1.5), (≥1.5–<2.5), *etc*. For a cut-off point of 150 ng·mg^{-1} χ^2 for trend=5.871; p=0.015.

Table 4. – Distribution of subjects by cotinine levels and by self-reported number of cigarettes to which they were exposed daily during the 4 days preceding the interview

Cotinine/creatinine ng·mg^{-1}	Average number of cigarettes·day^{-1}					Total
	<2	2–<4	4–<8	8–<16	≥16	
50–70	2		3	3	3	11
70–100			2	2	6	10
100–150		1		1	4	6
150–220	1			2		3
220–330	1			3	1	5
330–500	2			2	1	5
>500	3		1	1	2	7
Total	9	1	6	14	17	47

For a cut-off point of 150 ng·mg^{-1} χ^2 for trend=4.203; p=0.04.

exposed to the smoking behaviour of their husband during the past 4 days, with 14 of these women being exposed to smoke from both their colleagues at work and their husband. Across all centres, the majority of women were exposed to their husband's smoking, with only 3 out of the 47 reporting exposure only at work, and 6 no exposure at work or to the smoking of their husband.

The study included information on exposure from other sources including vehicles, public places, social occasions or visitors to the home. This was analysed in relation to ETS exposure from the husband and cotinine level (table 5). Three subjects who reported no exposure to husband's ETS and who had cotinine levels of 50–150 ng·mg^{-1} reported exposure from other sources, whilst five women also not exposed to husband's smoking and having cotinine levels above 150 ng·mg^{-1} reported no other exposures; the difference in distribution was statistically significant (p=0.03). In those women married to smokers, other sources of exposure were reported by 7 out of 24 women with cotinine levels of 50–150 ng·day^{-1}, whilst only one woman out of 14 with levels above 150 ng·mg^{-1} reported exposure to ETS from other sources. The difference did not, however, reach statistical significance (p=0.113).

Table 5. – Exposure to other sources: vehicles, public places, other smokers at home (for a total of ≥4 h)

	Exposed to ETS from husband			
	No (n=9)		Yes (n=38)	
Exposed to other sources	No	Yes	No	Yes
50–150 cotinine	0	3	17	7
>150 cotinine	5	1	13	1
Fisher exact test	χ^2=5.00; p=0.03 p=0.048		χ^2=2.512; p=0.113 p=0.216	

Discussion

Research into the relationship between exposure to ETS and lung cancer has intensified since the publication of the first two studies by TRICHOPOULOS *et al*. [18] and HIRAYAMA [19], and many reviews have been written on the evidence and biological plausibility of such an association [2, 3, 7, 20–22]. Knowledge of the nature of the carcinogens and toxins contained in tobacco smoke, the materials absorbed during passive smoking, and the quantitative relationship between dose and effect suggest that passive smoking can give rise to risk for lung cancer [20]. In epidemiological studies, it is critical to classify the study participants accurately as to their history of both active and passive smoking. Of particular concern are former and current smokers who claim to be nonsmokers but may be at higher risk for lung cancer than true nonsmokers because of a history of smoking, not just because of exposure to ETS. If this misclassification occurs more often among cases than controls, it may lead to falsely high estimates of the risk of passive smoking in relation to lung cancer. From this point of view, concordance of smoking habits in married couples is of special importance: a woman who claims to be a nonsmoker is more likely to be, or to have been, an actual smoker if married to a smoker than if married to a nonsmoker. Questionnaire data on smoking status are clearly limited, and variations in validity of reports have been shown to depend on the source of

information (case or surrogate) [23], or the choice of control [24].

The present study is an analysis of a subset of 47 women (from 1,369 interviewed in 13 local centres across 10 countries) who reported no use of tobacco or nicotine-containing products for at least 2 yrs. They were excluded from the main analysis since, in the light of the literature on cotinine, their cotinine excretion was considered too high to be compatible with only passive smoking. It was, therefore, feared that their inclusion might bias the results of the main analysis.

Cotinine is one of the major metabolites of nicotine and, whilst it is generally considered specific for tobacco use, possible contributions to a body burden of nicotine and its metabolites can come from the use of nicotine-containing chewing gum or sources unsuspected by the subject. In this study, subjects were excluded if they reported use of nicotine gum or other smoking cessation aids which might contain nicotine. Whilst it is possible that, in such an international study, very heavy consumption of members of the Salonacea species, such as tomatoes or egg plant [25], could contribute nicotine to the diet of selected groups, we observed no prevalence of higher cotinine levels in vegetarian or agrarian cultures. Tobacco use remains the overwhelming source of nicotine exposure [26], despite recent comments about its possible low-level presence in certain foods [27].

Across centres, a higher proportion of subjects with elevated cotinines were found in Chandigarh, Trieste and Hong Kong, with the lowest proportions seen in Honolulu, Shanghai and Athens. Recent studies in women have shown racial differences in nicotine metabolism [28] in active smokers, and indications of similar differences in persons exposed to ETS [29]. Furthermore, it is possible that variability in the manner of questioning by the interviewers influenced report of smoking status or ETS exposure. It is also possible that local customs may be responsible for cross-centre variation. For example, four women in Chandigarh had cotinine levels greater than 300 ng·mg^{-1}, a level clearly consistent with tobacco use. They had been questioned about use of betal quid containing tobacco, but perhaps they were unaware of the presence of tobacco in this product. In contrast, 5 of the 6 Hong Kong subjects with elevated cotinines had levels of 50–100 ng·mg^{-1}, positively consistent with their reports of very long duration of exposure.

Examination of self-reporting of exposure to ETS clearly showed two populations across centres: those subjects with cotinine levels of 50–150 ng·mg^{-1}, the majority of whom reported heavy exposure from their husbands and from other sources; and those with higher cotinine levels not consistent with self-reported exposure to ETS. This effect was noted for both reported daily duration of exposure and number of cigarettes smoked around the subject during the previous 4 days.

These results suggest that some subjects with cotinine levels above 50 ng·mg^{-1} creatinine could have been heavily exposed to ETS on the days preceding the interview, and might not have been actively using tobacco products. At the other extreme, it seems plausible that the high cotinine levels in subjects reporting light or no exposure can only be due to active smoking or chewing of tobacco, or use of other nicotine-containing products.

Exposure to their husbands' tobacco smoke was the major factor in this subgroup of women as it was for the subjects with cotinine values below 50 ng·mg^{-1}, indicating that for these women the husbands' smoking is the main source of ETS in the environment. The home may, therefore, represent a particularly important source of tobacco smoke pollution.

Additionally, 14 out of 38 women reporting exposure to their husbands' smoking had cotinine levels above 150 ng·mg^{-1}. This could partly be explained by concordance of behaviours, as discussed by LEE [4], where smokers are more likely to marry smokers. The high cotinine levels noted in most of these women are consistent with active use of tobacco products.

Thus, the cut-off point of 50 ng·mg^{-1} may be too low, excluding from the population of nonsmokers some subjects who are heavily exposed to ETS. On the other hand, the majority of subjects with levels above 150 mg·mg^{-1} creatinine are probably smokers, although light smokers because the cotinine level of heavy smokers is generally very high, more than several hundred ng·mg^{-1} creatinine [11, 15, 21]. From this point of view, 20 subjects can be considered smokers, which represents 1.5% of the total study population.

These results are in agreement with data available previously. FONTHAM *et al.* [30] found that 0.8% of lung cancer cases, 2.6% of colon cancer cases and 2% of population controls who claimed to be nonsmokers had high cotinine/creatinine levels (>100 ng·mg^{-1}), suggesting that they were actually current smokers. The same cut-off point was used in a recent study in Poland [31]. The National Research Council (NRC) Report [2], following the work of WALD and co-workers [32], assumed that the category "never smokers" includes up to 5% of ex-smokers. Such approximations have, however, been disputed [33, 34]. Following a different approach, the Environmental Protection Agency (EPA) Report [21] made an adjustment on the proportion of misclassified active smokers separately for each study. Both results show that the potential bias due to smoker misclassification is unlikely to be responsible for the increased risk for lung cancer observed in epidemiological studies on ETS.

Finally, it must be stressed that, because exposure to ETS is so widespread, the potential upward bias in the relative disease risks which may be due to smoker misclassification is counterbalanced by the downward bias from background ETS exposure among the supposedly unexposed group.

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