Int Arch Occup Environ Health (1995) 67:287–294
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ORIGINAL ARTICLE

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"Marriage to a smoker" may not be a valid marker of exposure in studies relating environmental tobacco smoke to risk of lung cancer in Japanese non-smoking women

Received: 24 September 1994/Accepted: 28 April 1995

Abstract There is no direct evidence that workplace environmental tobacco smoke (ETS) increases lung cancer risk. Demands for regulation of workplace smoking are based on studies reporting increased risk in non-smoking women whose husbands smoke. Although denying smoking can artificially elevate risk estimates, and although many studies reporting an increase have been conducted in Asia, no previous study of smoking habit misclassification has been conducted there. In this study 400 married Japanese women answered questions on smoking and ETS exposure and supplied urine for cotinine analysis. Of 106 with a cotinine/creatinine ratio (CCR) indicating current smoking (> 100 ng/mg), 22 reported never smoking. These misclassified smokers had a median CCR (1408 ng/mg) similar to the 78 self-reported current smokers (1483 ng/mg). Of current smokers, 89.7% had a currently smoking husband, while this was true of 51.0% of non-smokers. Among 264 confirmed non-smokers (with CCR < 100 ng/mg), CCR was non-significantly *lower* if the husband smoked (11.51 vs 17.98 ng/mg) and was unrelated to various indices of smoking by the husband. Japanese epidemiological studies using "marriage to a smoker" to index ETS exposure may therefore have compared groups with similar ETS exposure, suggesting that associations reported between lung cancer and this index in some of these studies may result from bias. While other biases, including confounding, may also be important, bias resulting from smoking misclassification combined with husband/wife smoking concordance is shown to be of major concern. The high misclassification rates in Japan, much higher than in Western populations, undermine conclusions from epidemiological studies conducted there.

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Key words Bias(epidemiology) · Cotinine–urine · Lung neoplasms · Tobacco smoke pollution

Introduction

In the early 1980s Hirayama [10–12] reported that risk of lung cancer among self-reported lifelong non-smoking women was significantly, 1.45, times higher if the husband had ever smoked than if he had never smoked. Since then, more than 30 studies, about half conducted in Asian populations, have investigated a possible relationship of lung cancer to environmental tobacco smoke (ETS) exposure using "marriage to a smoker" as an index of ETS exposure [18, 31]. While only a few of the studies have reported a statistically significant relationship, most have reported relative risks in excess of 1, though generally below 2. This had led some reviewers [e.g. 22, 31, 33–35], though not all [e.g. 5, 18], to claim a causal link between risk of lung cancer and exposure to ETS, and there have been recent moves in some countries, e.g. by the US Occupational Safety and Health Administration [32], to regulate workplace smoking.

It is interesting to note that there is no direct evidence that ETS exposure in the workplace causes lung cancer. LeVois and Layard [16] recently reviewed evidence from 14 epidemiological studies demonstrating no excess lung cancer rate in non-smokers working with a smoker. Based on 12 of these studies (two reported no association, but did not cite a relative risk), they estimated a summary relative risk of 1.01, with a 95% confidence interval of 0.92–1.11. This finding is consistent with the conclusion that "marriage to a smoker" is the only index of ETS exposure associated with lung cancer risk; the overall evidence does not suggest any increase associated with childhood or social exposure either [17, 18].

Why are the results of workplace and spousal studies of ETS and lung cancer inconsistent? Some studies

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[e.g. 24] have indicated that "marriage to a smoker" may be associated, on average, with a greater increase in actual ETS exposure that is "working with a smoker". However, even if this were true for all populations, it would hardly seem to explain the observed complete lack of association of lung cancer risk with "working with a smoker". An alternative explanation may be that relative risk estimates based on the index "marriage to a smoker" are particularly prone to bias. This paper describes the results of a study investigating one specific form of bias, that due to smoking habit misclassification.

Because smokers tend to marry smokers, random misclassification of some smokers as non-smokers will cause an apparent increase in risk of lung cancer in self-reported non-smokers married to smokers even if no true effect of ETS exposure exists [17]. Smoking habit misclassification bias is less likely to affect studies of workplace ETS exposure, because there is not the same tendency for smokers to work with smokers. Earlier, I concluded that such misclassification bias can largely explain the weak association between lung cancer and spousal smoking reported in European and American women [19]. Since fewer Asian women smoke, and since active smoking tends to be more weakly associated with lung cancer in Asian than in Western populations, I showed [17] that misclassification rates needed to be much higher than in the West for this bias to be important in Asian studies. Theoretically social pressure against smoking by women in Japan and other Asian countries might increase misclassification. However, although further studies relating lung cancer to "marriage to a smoker" have been conducted in Japan [1, 13, 14, 26, 28], there are no published reports of misclassification rates specific to that country. Results from the IARC multi-country cotinine study [24], which in any case concerned only non-smokers, have not been reported separately for Japan. The first objective of the study, therefore, was to investigate the extent to which Japanese women smokers misclassify themselves as non-smokers on interview, in an attempt to determine the likely magnitude of bias from this source in lung cancer studies conducted in Japan using "marriage to a smoker" as an index of ETS exposure.

Shortly after Hirayama [10] reported the findings from his large Japanese prospective study, Garfinkel [9] reported a much weaker, statistically non-significant, association between lung cancer risk and "marriage to a smoker" based on a large US prospective study. Hirayama [11] suggested husband's smoking may correlate better with ETS exposure in Japan, where homes are smaller [25] and women less frequently have jobs outside the home. This suggestion can be questioned because of the possibility that Japanese men spend less time at home than their United States counterparts and because the IARC multi-country cotinine study did not support this hypothesis [24]. Furthermore, a stronger association between lu cancer and "marriage to a smoker" has not been consi tently demonstrated in Japan [18]. Nevertheless, t second objective was to validate "marriage a smoker" as an index of ETS exposure in lifelo non-smoking Japanese women by comparing levels cotinine according to husband's smoking habits.

Materials and methods

Organisation

In order to carry out the objectives it was necessary to recr expertise from Japan. Dr. E. Yano of Teikyo University assisted the translation of the questionnaire, the design of the sampli regime, and the training of the interview staff from the Tokyo-bas market research company Emu Efu. Dr. Yano also organised t collection of samples from the field.

Sampling

The study involved 400 married female subjects, 200 from the dens ly populated city of Osaka and 200 from the more rural town Shizoka. The subjects were selected semi-randomly, with quot assigned by district within the target areas to provide a represent tive mix by socio-economic conditions and by age (range 20– years). Most subjects were identified through door-to-door canvas ing during the early evening when they could be expected to be home. The subjects were told the study was to identify life-sty factors common to women in their area. Those who agreed t participate (response rate 33%) were questioned for on averag 20 min on their own and their husband's smoking habits, on the exposure to ETS from various sources, and on a variety of life-sty and dietary issues. The subjects then supplied approximately 50 m urine, which was immediately frozen and transported to Teiky University, where all samples were stored at $-20°C$. As incentive to participate, the subjects were offered a token gift and informatio concerning the sugar and protein content of their urine.

Cotinine estimation

Cotinine was measured in each urine sample by an enzyme linke immunoassay (ELISA). The assay was performed according t a modified version [4] of the method of Bjercke et al. [3]. A samples were presented to the laboratory blind for an initial scree After the cotinine concentrations had been estimated, the sample were re-run in triplicate against the appropriate calibration rang Fifty samples were randomly selected and cross-checked again a gas chromatographic (GC) method. Correlation between the tw methods was ELISA $= 1.07GC - 0.974$ ($R = 0.93$). The limit detection (LOD) represents the minimum response which can b distinguished from a response of four replicates of the zero standar assayed on the same plate, by a one-tail students t test ($P < 0.05$) and was found to be 5.6 ng/ml using the ELISA procedure.

Statistical analysis

Results are expressed as cotinine/creatinine ratios, counting zero fo subjects with a cotinine less than the LOD. Because of the zeros an the skewness of the distribution, medians rather than mean level ar

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usually presented. Standard statistical methods were used to test for the significance of differences of proportions. For continuous variables, rank tests stratified for age as appropriate were used [8].

Results

Exclusions

One subject with an inadequately completed questionnaire and three who provided insufficient urine for creatinine determination were excluded, leaving data on 396 women.

Self-reported smoking habits

According to self-report, 78 (19.7%) were current smokers, 32 (8.1%) ex-smokers and 286 (72.2%) lifelong non-smokers. Ever smokers were significantly ($P < 0.001$) younger (mean age 36.7) than lifelong non-smokers (mean age 42.7).

Socio-demographic characteristics

Table 1 shows the distribution of various socio-demographic characteristics by city and self-reported smoking habits. Annual income, the number of rooms in the house and the likelihood of working in the previous week were all significantly ($P < 0.05$) higher in never smokers and in residents of Shizoka. Numbers of people living at home were also significantly higher on average in Shizoka than in Osaka.

Concordance between smoking habits of husband and wife

There was a strong relationship between the smoking habits of husband and wife. The percentage of women reporting having a husband who currently smoked was 89.7% for current smokers, 59.4% for ex-smokers and 51.0% for lifelong non-smokers. Among lifelong non-smokers, age was not associated with husband's smoking.

Detection of misclassified smokers

Table 2 shows the distribution of CCR by self-reported smoking status. CCR and cotinine levels were about 100 times higher ($P < 0.001$) among current smokers than among non-smokers. Creatinine levels were slightly but not significantly higher in smokers. No value clearly discriminates occasional smokers from subjects heavily exposed to ETS, but it seems reasonable from our results to follow the precedent set by IARC [24] and use a cut-off of 100 ng/mg CCR to distinguish misclassified current smokers. Using this cut-off point a total of 28 women who claimed on interview to be

Table 1 Socio-demographic distribution of the sample (%) by city and self-reported smoking status

	Osaka			Shizoka		
	Never smoked	Ever smoked	Total	Never smoked	Ever smoked	Total
Subjects	136	60	196	150	50	200
Age (years)						
22–34	15	48	25	15	40	22
35–44	49	37	45	41	42	42
45–55	36	15	30	43	18	37
Annual income (mn yen)[a]						
–500	27	52	36	27	28	27
500–900	51	37	46	53	38	49
900 +	22	11	18	20	34	24
Worked in preceding week	53	58	55	62	74	65
People living in residence[b]						
–3	29	35	31	28	14	25
4	47	38	44	37	54	32
5	19	25	21	15	16	15
6 +	5	2	4	20	16	19
Rooms in house						
–3	29	63	39	21	28	23
4 or 5	44	28	39	51	40	48
6 +	27	8	21	28	32	29

[a] Numbers of subjects reporting data on income were, respectively, 95, 54, 149, 130, 47 and 177
[b] One Osaka never smoker did not answer the question on people living in residence

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Table 2 CCR (ng/mg) by self-reported smoking status

	Self-reported smoking status			
	Non-smoker	Never smoker[a]	Ex-smoker	Current smo
Number of subjects (%)				
CCR (ng/mg)				
0[b]	84 (26.4)	78 (27.3)	6 (18.8)	1 (1.3)
2	29 (9.1)	23 (8.0)	6 (18.8)	1 (1.3)
10–	95 (29.9)	86 (30.1)	9 (28.1)	2 (2.6)
25–	64 (20.1)	61 (21.3)	3 (9.4)	1 (1.3)
50–	18 (5.7)	16 (5.6)	2 (6.3)	3 (3.8)
100–	3 (0.9)	3 (1.0)	0 (0.0)	4 (5.1)
250–	2 (0.6)	1 (0.3)	1 (3.1)	9 (11.5)
500–	6 (1.9)	4 (1.4)	2 (6.3)	9 (11.5)
1000–	9 (2.8)	8 (2.8)	1 (3.1)	18 (23.1)
2000-	8 (2.5)	6 (2.1)	2 (6.3)	30 (38.5)
Total	318 (100.0)	286 (100.0)	32 (100.0)	78 (100.0
Median CCR (ng/mg)	17.4	17.4	13.6	1482.8
Median cotinine (ng/ml)	14.3	14.0	16.5	1681.8
Median creatinine (ng/ml)	0.91	0.91	1.06	1.05

[a] CCR for the 22 never smokers above 100 ng/mg were 102, 106, 193, 416, 511, 683, 848, 888, 1052, 1 1177, 1639, 1689, 1737, 1773, 1803, 2069, 2504, 2865, 2923, 3045 and 3946 ng/mg
[b] Subjects with cotinine $\leq$ 5.6 ng/ml were assigned a zero CCR

non-smokers (22 lifelong non-smokers and 6 ex-smokers) were considered smokers. Using a 50 ng/mg cut-off, 46 were.

Lack of association of CCR with husband's smoking in lifelong non-smoking women

After excluding misclassified current smokers (with a CCR > 100 ng/mg) there were 264 confirmed lifelong non-smokers. CCR was non-significantly *lower* if the husband smoked and was not significantly associated with any index of husband's smoking (Table 3). This conclusion was unaffected by using means (rather than medians). Assuming nicotine-based indices are adequate markers and our study population is relevant, the findings suggest that the association between lung cancer and husband's smoking reported in some [1, 10, 13], though not all [14, 26, 28], Japanese studies was not due to ETS exposure. Data relevant to one major potential source of bias, smoking misclassification, are now considered.

Table 3 CCR (ng/mg) by husband's smoking[a]

Index of husband's smoking	Level	No. of subjects	Median C (ng/mg)
Current smoker	No	127	17.98[b,c]
	Yes	137	11.51[b,c]
Cigarettes smoked daily (workdays)	1–15	34	13.86
	16–20	53	10.40
	21 +	50	15.24
Cigarettes smoked daily (holidays)	1–15	50	16.40
	16–20	46	10.66
	21 +	39	14.07
Cigarettes smoked daily at home (workdays)	1–5	49	10.93
	6–10	52	16.38
	11 +	28	5.74
Cigarettes smoked daily at home (holidays)	1–10	45	7.83
	11–20	62	11.11
	21 +	22	12.79

[a] Among lifelong non-smokers excluding those with a CCR ng/mg
[b] Means were 19.26 and 16.49 ng/mg. For cotinine, median 14.00 and 12.50 ng/ml and means were 16.97 and 14.39 ng/n
[c] 95% confidence intervals 15.64–22.12 ng/mg and 7.99 ng/mg for current smoker no and yes respectively

Higher misclassification rates than seen in Western populations

The study provided no data on accuracy of statements made about past smoking and it is possible therefore, that an unknown proportion of self-reported lifelong non-smokers smoked in the past. It did, however, provide data on accuracy of statements made about current smoking. Table 4 presents such data for three cut-off points based on CCR. As reported elsewhere [17], misclassified smokers were found more frequently in self-reported ex-smokers than in self-reported long non-smokers. Whether expressed as a propo of current smokers or as a proportion of lifelong smokers, misclassification rates in this study were much higher than reported in the literature, whi comes from Western populations. For exampl estimate of 8.8% for the percentage of non-sm

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with CCR above 100 ng/mg compares with 1.9% in the IARC study [24], and with an estimate of 1.9% (range 0.0%–2.7%) based on ten Western studies for the percentage with cotinine levels consistent with current regular smoking [17]. The estimate of 26.4% for the percentage of current smokers who deny current smoking (using a 100 ng/mg cut-off) can be compared with an estimate of 3.2% based on data for nine Western studies (range 0.0%–0.4%) [17]. Similarly, the estimate of 20.8% for current smokers claiming to be lifelong non-smokers is very much higher than an estimate of 2.2% from the Western studies.

Table 4 Misclassification of current smoking status

Index	Cut-off point[a]	% (*n*/*N*)
Percent of self-reported non-smokers who are above cut-point and assumed to be current smokers	50 ng/mg	14.5 (46/318)
	100 ng/mg	8.8 (28/318)
	250 ng/mg	7.9 (25/318)
Percent of self-reported life-long non-smokers assumed to be current smokers	50 ng/mg	13.3 (38/286)
	100 ng/mg	7.7 (22/286)
	250 ng/mg	6.6 (19/286)
Percent of self-reported ex-smokers assumed to be current smokers	50 ng/mg	25.0 (8/32)
	100 ng/mg	18.8 (6/32)
	250 ng/mg	18.8 (6/32)
Percent of current smokers[b] who deny current smoking	50 ng/mg	37.1 (46/124)
	100 ng/mg	26.4 (28/106)
	250 ng/mg	24.3 (25/103)
Percent of current smokers[b] who deny current smoking and report being lifelong never smokers	50 ng/mg	30.6 (38/124)
	100 ng/mg	20.8 (22/106)
	250 ng/mg	18.4 (19/103)

[a] Based on CCR
[b] For this calculation current smokers include self-reported current smokers and also those who denied current smoking but had a CCR above the cut-off point

CCR and amount smoked

As shown in Table 5, CCR rose markedly with amount smoked by current smokers (trend $P < 0.001$).

CCR and other indices of ETS exposure in non-smokers

Table 5 presents further results relating CCR to various questionnaire indices of ETS exposure among confirmed non-smokers (with a CCR < 100 ng/mg). CCR was not associated with the number of cigarettes smoked at home per day and was not increased in those women who had worked in the previous week. Although there was some tendency (trend $P < 0.05$) for CCR levels to increase in relation to the number of cigarettes smoked close to the subject at work per day, the general pattern of the results in Tables 3 and 5 does not show any convincing evidence of a relationship of CCR to questionnaire indices of ETS exposure. Thus, CCR was no lower in women reporting no ETS exposure than in those reporting any ETS exposure (see Table 4).

CCR and diet

CCR was not associated with recent consumption of tomatoes or aubergines, two dietary sources of nicotine (results not shown).

Discussion

In our study, a major finding was that, among self-reported lifelong non-smokers with a CCR

Table 5 Variation in CCR (ng/mg) by amount smoked and various indices of ETS exposure

Base	Index of exposure	Level	No. of subjects	Median CCR (ng/mg)
Self-reported current smokers	Cigarettes per day	1–5	11	259
		6–10	20	1018
		11–15	21	1433
		16+	26	2647
Confirmed[a] non-smokers	Cigarettes smoked at home per day	0	134	17.64
		1–10	115	10.04
		11–20	19	14.07
	Cigarettes smoked close to subject at work per day[b]	0	62	9.86
		1–10	67	16.14
		11+	41	18.13
	Working in preceding week	No	122	16.72
		Yes	168	14.49
	Any exposure[c]	No	55	17.56
		Yes	235	14.74

[a] Self-reported non-smokers with CCR < 100 ng/mg
[b] Excluding women who did not report working
[c] Women count as exposed if husband current smoker, any smoking by other household members, any cigarettes smoked close by in previous 48 h, or any workplace exposure to ETS

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< 100 ng/mg, "marriage to a smoker" was not associated with an increased CCR. Indeed, those non-smokers with husbands who smoked tended to have rather lower values than those whose husbands did not smoke. The failure to find an association is unlikely to be due to inadequate chemical methods, since the techniques used [3, 4] should be sensitive enough for the purposes of this study. In an earlier Japanese study [21] an increased CCR was reported in relation to number of smokers in the home, but the mean CCR value cited in non-smokers, 680 ng/mg, was implausibly high compared with the literature, suggesting weaknesses in their chemical methods and/or failure to exclude, as in this study, women who clearly are smokers from the analysis. Since many husbands may spend relatively little time with their wives and many women work and are exposed to ETS outside the home, the lack of association between CCR and "marriage to a smoker" is perhaps not entirely surprising. If this is not a phenomenon of recent history – which seems unlikely, but cannot be formally tested – then Japanese epidemiological studies relating marriage to a smoker to risk of lung cancer have compared groups with approximately equivalent exposure to ETS. If so, then presumably the increased relative risks reported in some of these studies must be due to factors other than ETS exposure.

One possible explanation of the reported increased relative risks is misclassification of current smoking status. This study clearly demonstrated, as has often been predicted but never properly tested previously, a very much higher misclassification rate of smokers as non-smokers among Japanese women than has been reported in Western women. Probably this is because smoking by women is not considered socially acceptable in Japan. This study also showed, as reported in numerous populations [17], a strong concordance between husbands' and wives' smoking habits. The question arises as to the extent of bias to the relationship between lung cancer and spouse smoking that is likely to result from this high rate of misclassification of active smoking status.

In this study 22 women claimed to be lifelong non-smokers but had a CCR above 100 ng/mg. These misclassified women can be considered to have the lung cancer risk of typical current smokers, since their median CCR was 1408 ng/mg, very similar to that of the 78 self-reported current smokers, 1483 ng/mg. First bias estimations follow precedent [17, 22, 34, 35] in assuming that misclassification of current smoking is independent of the smoking habits of the spouse. Since 74, i.e. 94.9%, of the 78 self-reported current smokers were married to a husband who had ever smoked, this assumption implies that 94.9%, i.e. 20.87, of the 22 misclassified women would have been, thus forming 10.2% of the 205 self-reported lifelong non-smokers married to an ever smoking husband. Similarly, 1.13 of the misclassified women would have been married to a never smoking husband, forming 1.4% of the 81 self-reported lifelong non-smokers married to a husband who had never smoked. Further assuming there are no true effects of spouse smoking on lung cancer risk and that current smoking increases risk by a factor of 5, one can then readily calculate that one would actually *observe* that spouse smoking increases risk by a factor of 1.33. This passive smoking bias of 1.33 would only be decreased slightly, to 1.29, by increasing the cut-point to 250 ng/mg. Reducing it to 50 ng/mg would increase the bias but only marginally as the risk in women with a CCR of 50–100 ng/mg would be low. Increasing the assumed current smoking risk to 10 would increase the bias to 1.70, while reducing it to 3 would decrease it to 1.17. Using (as some lung cancer studies do) spouse current smoking rather than spouse ever smoking as the index of ETS exposure (and using our main assumptions) would give a bias of 1.45.

However, it is necessary to consider the validity of the assumption that misclassification of smoking habits is independent of the smoking habits of the spouse. In the study, only 5.1% of the 78 self-reported current smokers reported having a never smoking husband. On the independence assumption, it can be calculated that only 1.13 of the 22 misclassified current smokers should have reported having a never smoking husband. In fact seven did so. This significant ($P < 0.01$) discrepancy, not previously reported in Western studies [17], may have arisen for one or both of two reasons. One reason is that the independence assumption is false and that women are much more likely to deny smoking if married to a lifelong non-smoker. The second reason is that data on her husband's smoking given by a woman who has already denied her own smoking may be incorrect. The study cannot distinguish the two possibilities, since cotinine data are not available for the husband, but it is possible to estimate the bias making varying assumptions about the accuracy of statements made by the women about their husband's smoking habits. If it is assumed that all seven of the misclassified current smokers who reported having a never smoking husband actually denied their husband's smoking as well as their own, the bias estimate rises from 1.33, as calculated above using the independence assumption, to 1.43. If it is assumed that three of these seven women denied their husband's smoking, the bias estimate falls to 1.13. If it is assumed that all seven of these women reported their husband's smoking accurately the bias estimate becomes slightly negative, 0.96, though even then the 95% confidence limits, 0.78–1.19, still do not rule out the possibility that a meaningful bias exists.

A number of other issues make any estimation of bias uncertain. These include sampling variation, the possibility that disease status is associated with the tendency to deny smoking, and non-representativeness of the sample. The low response ratio in this study, actually not untypical of Japanese interview studies, clearly leads to the possibility of selection bias, but

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seems unlikely to undermine the conclusions for two reasons. In the first place, it seems likely that women willing to be interviewed are *more* likely to tell the truth about their smoking than women who are unwilling to be interviewed, so that the misclassification rate is underestimated. In the second place, even if the reverse were true in an extreme form, so that *all* the women not interviewed were truthful about their smoking, the misclassification rate of the total population, though 3 times lower than that observed in the respondents, would still be very high.

The age of our sample (range 20–55 years) is markedly lower than that typical of subjects in epidemiological studies of lung cancer. For this reason, and also because estimates of smoking habit misclassification vary markedly from study to study depending on the circumstances under which the questions are asked [17], one should not assume that the actual rates of misclassification observed would apply to all the Japanese studies. However, since the rates reported here are much higher than those seen in comparable Western studies [17], it seems reasonable to believe that a Japanese woman smoker is substantially more likely to deny her smoking than is a Western woman smoker questioned in similar circumstances.

In the EPA report [31], corrections for bias due to smoking misclassification were applied to individual study estimates of lung cancer risk associated with smoking by the husband. These corrections were based on an estimate of the smoking misclassification rate derived from Western studies. Because smoking by women in Japan is much less common than in the West, corrections to Japanese study estimates were much lower than those to estimates for Western studies, and were in fact quite minor. Although there are difficulties in estimating the bias precisely, it is clear the EPA's corrections are invalid, as they are based on the totally false assumption that Japanese misclassification rates are the same as in the West, when in fact they are much higher.

The analyses presented mainly use CCR to index ETS exposure and 100 ng/mg to indicate smoking. Conclusions were unaffected by using alternative indices such as uncorrected continine, or continine corrected by Thompson's method [29], or alternative cut-off points.

Sources of bias other than smoking habit misclassification may affect epidemiological studies of lung cancer and ETS exposure. Confounding by life-style risk factors may be another potential serious source of bias. A number of studies in other countries have shown [15, 20, 27] that ETS-exposed non-smokers have diets with a low intake of β-carotene, one of the dietary factors associated with reduced risk of lung cancer [6], while "marriage to a smoker" has been associated [7] with increased exposure to occupational hazards, higher alcohol consumption and lower education. More generally, a recent large British study [30] confirmed that, for a whole range of unhealthy life-style characteristics, smokers tend to have higher prevalences than lifelong non-smokers, and that lifelong non-smokers living with a smoker (and ex-smokers) tend to have intermediate prevalences, sufficient to cause moderate confounding effects. The results relating to the life-style characteristics measured in the Japanese study have not been reported in detail in this paper, as the sample size proved to be too small to pick up any very clear effects. However, the general pattern of findings was similar to that in the British study. Among lifelong non-smokers (with a CCR < 100 ng/mg), marriage to a smoker was associated inter alia with reduced consumption of dark green vegetables and dietary sources of vitamin A and β-carotene, including carrots and vitamin supplements, lack of exercise, and reduced consumption of green tea. All these factors have been linked to an increased risk of lung cancer [2, 6, 23].

The overall conclusion from the study is that the findings strongly question the reliability of epidemiological studies in Japanese women using "marriage to a smoker" as a marker of ETS exposure. The lack of association of cotinine levels with "marriage to a smoker" suggests the marker is invalid in Japan, and the large proportion of smokers denying smoking gives a substantial potential for bias. While more studies (including some in which cotinine is determined for both the husband *and* wife) are needed to clarify the importance of misclassification and confounding as sources of bias, the evidence reported here urges caution when interpreting studies of spousal smoking and lung cancer in Japan. The findings of this study help to explain why the epidemiological evidence indicates an association with spousal but not with workplace ETS exposure, and suggests that demands for regulation of workplace ETS exposure based on studies using "marriage to a smoker" as an index of ETS exposure may have little scientific basis.

Acknowledgements I gratefully acknowledge financial support from several companies of the tobacco industry.

I am extremely grateful to Dr. Eiji Yano of Teikyo University for assistance provided in Japan, and to Emu Efu Co. Ltd. for help in sample collection and analysis. I also thank Dr. John Fry for assistance in statistical analysis, Dr. Francis Roe for numerous helpful comments, and Mrs. Pauline Wassell and Mrs. Diane Morris for typing the various drafts.

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