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A comparison of lifestyle factors for Japanese non-smoking women married to smokers with those married to nonsmokers

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Abstract

Findings of a study of 400 Japanese women from Osaka or Shizuoka are reported. The objectives were to determine whether certain lifestyle factors correlate with being a smoker or with marriage to a smoker, to investigate the extent to which Japanese women smokers misclassify themselves as non-smokers on interview, and to quantify differences in environmental tobacco smoke (ETS) exposure in relation to marriage to a smoker. Each subject was asked about diet and lifestyle, and supplied urine for cotinine analysis as a marker of smoking status and ETS exposure.

The most significant finding was that there was little correlation between ETS exposure, as determined by urinary cotinine level, and responses to questions on smoking by the husband. The finding that cotinine levels in non-smokers married to smokers were slightly lower than in non-smokers married to non-smokers suggests that epidemiologic studies in Japan which used marriage to a smoker as a surrogate for ETS exposure may in fact have compared groups with similar ETS exposure.

The study also reports that smokers differed significantly from non-smokers in respect of various lifestyle factors considered risk factors for lung cancer. Smaller differences, only a few of which were statistically significant, were also seen among non-smokers in relationship to marriage to a smoker.

As judged by urinary cotinine levels, around 9% of women who were in fact smokers claimed to be non-smokers. However, there was a strong tendency for smokers to marry smokers was observed, but the rate of misclassification was higher among women married to non-smokers. Moreover, around 10% of self-reported smokers had cotinine levels less than 100 ng/ml, suggesting that either there may be some considerable flexibility in female smoking habits or that the questions on smoking habit were not fully understood.

Introduction

Epidemiologic studies have, over the last decade, investigated a possible relationship between exposure to environmental tobacco smoke (ETS) and lung cancer.[1] An early study by Hirayama reported a small but statistically significant increased incidence of lung cancer among non-smoking Japanese women whose husband smoked.[2] Over 30 studies of lung cancer have used husband's smoking as a marker of ETS exposure.[1] While only a few have reported a statistically significant relationship, most have reported relative risks in excess of one, though generally below two. This has led some,[3-5] though not all,[1,6] to claim a causal link between exposure to ETS and lung cancer.

Any epidemiologic study attempting to detect a possible small risk must consider whether confounding or bias is influencing the data. For the ETS studies, a variety of possible confounders and biases have been suggested. Confounding arises if smoking by the husband is associated with a difference in the extent of exposure to other lung cancer risk factors. Studies in Hong Kong[7] and in the US[8,9] have reported that non-smokers exposed to ETS have diets (in particular a lower intake of dietary beta-carotene) that are likely to leave them at higher risk of lung cancer than non-exposed non-smokers. Friedman[10] reported that marriage to a smoker is correlated with higher exposure to occupational hazards, higher alcohol consumption and a lower level of education. Such

differences in lifestyle could falsely elevate the risk attributed to ETS. One objective of this study was to investigate the possible importance of confounding factors in studies of Japanese women.

Misclassification of smoking status arises if subjects deny smoking on interview. Since active smoking is a risk factor for lung cancer, inclusion of misclassified smokers may increase the risk among the group classified as non-smokers. Some studies have suggested that women married to smokers are more likely to be smokers than women married to non-smokers.[1] It follows that, for any given misclassification rate, a self-reported non-smoking woman is more likely actually to be a smoker if she is married to a smoker than if she is married to a non-smoker. This differential misclassification (with more misclassified smokers in the exposed than in the non-exposed group) may falsely elevate the relative risk associated with ETS exposure in epidemiologic studies. In a review of available evidence, all from Western populations, on misclassification rates, Lee[1] estimated bias from this source can largely and perhaps completely explain a weak positive association between lung cancer and husband's smoking found in European and American women.[1] Because fewer Asian women smoke, and because the reported association between active smoking and lung cancer is weaker in Asia, Lee noted that misclassification would not cause a significant bias in Asian studies unless rates of misclassification were much higher than in the West. Higher rates might exist in Japan, though to date misclassification has hardly been investigated, even though a number of studies of ETS and lung cancer have been conducted here.[2,11-15] A second objective of this study was to assess the extent of misclassification of smoking status.

Shortly after Hirayama[2] reported the findings of his large Japanese prospective study, Garfinkel[16] 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[17] suggested marriage to a smoker may be associated with a higher ETS exposure in Japan than in the US for two reasons. First, Japanese homes are smaller on average than US homes.[18] Second, Japanese women tend to work less frequently outside the home, and therefore have less background (i.e., non home-related) ETS exposure, than do US women. The suggestion that Japanese women are more exposed to ETS from their spouse smoking than are US women can be questioned because Japanese men who work tend to spend less time at home than do their US counterparts, so reducing the time when the spouse could be exposed at home. Moreover, the findings in a ten country study of cotinine levels in non-smokers conducted by the International Agency for Research on Cancer (IARC) did not provide support for this suggestion.[19] A third objective of this study was to measure ETS exposure in non-smoking women according to their husband's smoking habits.

Materials and Methods

The study involved 400 married female subjects, 200 from the densely populated city of Osaka and 200 from the more rural town of Shizuoka. The subjects were selected semi-randomly, with quotas assigned by district within the target areas to provide a representative mix by socio-economic conditions and by age (range 20-55). Most subjects were identified through door-to-door canvassing during the early evening when they could be expected to be at home. The subjects were told the study was to identify lifestyle factors common to women in their area. Those who agreed to participate (response rate 33%) were questioned for on average 20 minutes on their own and their husband's smoking habits, on their exposure to ETS from various sources, and on a variety of lifestyle and dietary issues. The subjects then supplied approximately 50 ml urine, which was immediately frozen and transported to Teikyo University, where all samples were stored at -20°C. The subjects were offered a token gift and information

concerning the sugar and protein content of their urine as incentives to participate.

Cotinine was measured in each urine sample by an enzyme linked-immunoassay (ELISA). The assay was performed according to a modified version[20] of the method of Bjercke et al.[21] All samples were presented to the laboratory blind for an initial screen. After the magnitude of the cotinine concentrations had been estimated, the samples were re-run in triplicate against the appropriate calibration range. Fifty samples were randomly selected and cross-checked against a gas chromatographic method. Correlation between the two methods was ELISA = 1.07GC - 0.974 ($R = 0.93$). The limit of detection (LOD) represents the minimum response which can be distinguished from a response of four replicates of the zero standard, assayed on the same plate, by a one tail student t-test ($p<0.05$), and was found to be 5.6 ng/ml using the ELISA procedure. In this paper results are expressed as cotinine/creatinine ratios, counting zero for subjects with a cotinine less than the LOD. Because of the zeros and the skewness of the distribution, medians rather than mean levels are 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.[22]

Results

After excluding one subject with an inadequately completed questionnaire and three who provided insufficient urine for creatinine determination, we had data on 396 women. According to self-report 78 (19.7%) were current smokers, 32 (8.1%) ex-smokers, and 286 (72.2%) lifelong never smokers. A higher proportion of ever smokers (80.4%) than never smokers (51.0%) were married to a current smoker ($p<0.001$). Ever smokers were significantly ($p<0.001$) younger (mean age 36.7) than never smokers (42.7), but among never smokers age was not associated with husband's smoking.

Exclusion of misclassified smokers

Table I shows the distribution of cotinine/creatinine ratio by self-reported smoking status. Median levels of the ratio and of cotinine were about two orders of magnitude higher ($p<0.001$) among current smokers than among nonsmokers. Creatinine levels were slightly, but not significantly, higher in smokers. No value clearly discriminates occasional smokers from subjects heavily exposed to ETS, but it seemed reasonable from our results to follow in the path of a study recently reported by IARC,[19] and use a cut-off of 100 ng cotinine per mg creatinine to distinguish between smokers and non-smokers. Using this cut-off point a total of 28 (8.8%) women who claimed on interview to be non-smokers were in fact smokers. If a 50 ng/mg cut-off point is used then the misclassification rate is 14.5%.

It should be noted that at a cut-off of 100 ng/mg 8 of 78 self-reported current smokers (10%) would be misclassified by cotinine/creatinine. At a cut-off of 50 ng/mg, this reduces to 6.4%. This suggests that it is possible that the women in this study were either somewhat flexible in their smoking, or that there was some misunderstanding of the questions on their smoking habit.

Lack of association of cotinine with spouse smoking

After excluding ex-smokers and misclassified current smokers, there were 264 lifelong never smokers. Among those married to smokers, cotinine/creatinine ratio was non-significantly lower than among those married to nonsmokers (11.5 ng/mg as compared to 18 ng/mg). Moreover, no significant relationship was seen with any index of smoking by the husband (Table II). This conclusion was not affected by the exclusion criteria used, by the index of nicotine uptake used, or by the use of means rather than medians.

The indices used included the reported number of cigarettes

smoked per day by the husband either in total or just at home corresponding either to a weekday or to a non-working weekend day (holiday). It is notable that nearly 40% of the smoking husbands smoked 5 or less cigarettes at home per day on week days, and only around 20% were reported as smoking more than 11 cigarettes per day at home.

Misclassification of smoking status

This study provided no data on the accuracy of statements made about past smoking and it is possible therefore that an unknown proportion of self-reported lifelong never smokers smoked in the past. The study did, however, provide data on accuracy of statements made about current smoking. Table III presents such data for three cut-off points based on cotinine/creatinine ratio. Consistent with data from other studies,[1] misclassified smokers were found more frequently in self-reported ex-smokers than in self-reported never smokers.

The rate of misclassification varies with the value selected for the cut-off point. The percentage of self-reported non-smokers with cotinine to creatinine ratios equivalent to current smokers was 14.5 at at cut point of 50 ng/mg, 8.8 at 100 ng/mg and 7.9 at 250 ng/mg.

As is detailed in Table I, many of the misclassified non-smokers had relatively high cotinine levels, indicating frequent smoking. 23 subjects reporting to be non-smokers had urinary cotinine to creatinine levels in excess of 500 ng/mg. 8 subjects had levels greater than 2000 ng/mg.

Confounding variables as a potential source of bias of the spouse smoking/lung cancer relationship

Never smokers married to non-smokers, never smokers married to

current smokers, and ever smokers were compared in respect of a range of lifestyle variables. As ever smokers were younger than never smokers, comparisons were age adjusted by direct standardization to the overall age distribution (in three groups, 0-34, 35-44, 45+.) Women with a cotinine/creatinine ratio above 100 ng/mg were classified under ever smokers in these analyses. No significant differences were seen in respect of having children, age of children, family income, or the type or size of the house lived in and the number of inhabitants in it and the period of living there. As shown in Table IV, however, a number of significant differences were seen, principally in terms of frequency of consuming various dietary items, but also in terms of taking physical exercise, contact with traffic fumes and some aspects of heating the home and of working. Examining the results from this table, three general conclusions can be reached. First, most differences between ever and never smokers were in the direction of ever smokers having a less healthy lifestyle. Thus, for example, ever smokers clearly took less exercise, drank more alcohol and coffee, and ate less dark green vegetables and carrots than never smokers. Second, differences in relation to marriage to a smoker were usually in the same direction as differences in relation to ever having smoked, though there were exceptions, notably for alcohol and coffee consumption. Third, differences in relation to marriage to a smoker were generally smaller than differences in relation to ever having smoked, and were usually not statistically significant at the 95% confidence level. The only significant differences seen were that those married to a smoker drank green tea and took vitamin supplements less often than those married to a non-smoker.

Sources of cotinine

Among current smokers cotinine/creatinine ratio rose markedly with amount smoked, with median values 259, 1018, 1433 and 2647

ng/mg for smokers of 1-5, 6-10, 11-15 and 16+ cigarettes/day (trend $p<0.001$).

Among confirmed non-smokers (i.e. with a cotinine/creatinine ratio less than 100 ng/mg) we have demonstrated (Table II) that various indices of spouse smoking were not associated with an increased ratio. Cotinine/creatinine ratio was also not associated with the number of cigarettes smoked at home, nor was it higher in women who had eaten tomatoes or eggplants (two dietary sources of nicotine) during the 48 hours before interview. There was, however, some indication that women more exposed to tobacco smoke at work had a higher ratio. Thus the median ratios for working women with 0, 1-10 and 11+ cigarettes per day smoked close by at work were 9.86, 16.14 and 18.13 ng/mg (trend $p<0.05$). However, median ratios for women who had worked in the preceding week were slightly, but not significantly, lower at 14.49 than for those who had not, 16.72.

Discussion

Assuming nicotine based indices are adequate markers of ETS exposure, and assuming our study population is relevant to the populations of women in the Japanese epidemiological studies of ETS and lung cancer, our findings suggest that the association between lung cancer and spouse smoking reported in some,[2,11,12] though not all,[13-15] of these studies did not arise as a result of ETS exposure. The finding that spousal smoke exposure is an inadequate marker of ETS exposure in Japan is perhaps not surprizing since men tend to work long hours, limiting the time that spousal exposure could occur. However, if it were to be the case that the epidemiologic findings on ETS and lung cancer in Japan were not associated with ETS exposure, then there should be an explanation for the excess relative risks found in several of the studies. There are two obvious possible sources of bias that might be influencing the data -- differential misclassification of smoking status and a

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differential bias in lifestyle factors associated with lung cancer risk.

The misclassification rates in this study are somewhat higher than those reported in similar studies of Western populations. For example, the estimate of 8.8% for the percentage of nonsmokers with cotinine levels above 100 ng/mg compares with 1.9% in the IARC study[19] and 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[1].

The study also suggests, as reported in numerous populations[1], a strong concordance between husbands' and wives' smoking habits. Assuming misclassification rates are random, this concordance would produce a much greater proportion of misclassified smokers among self-reported never smokers married to a smoker than among those married to a non-smoker, and in consequence a markedly higher lung cancer rate in the former group in the absence of any effect of ETS exposure. However, the results of our study casts some doubt upon the hypothesis that misclassification rates are random; smoking women who denied smoking were much more likely than expected to claim their husband was a non-smoker, an observation not previously reported in Western studies.[1] Whether this observation actually indicates non-randomness is unclear; it could also be explained if women who deny they smoke themselves also deny their husband does. Resolution of this issue is only possible in a study in which cotinine (or other markers) is determined for both husband and wife. Although considerable uncertainty remains about the actual extent of bias, the misclassification rates seen in this population suggest that bias is possible. Because smoking is not very common in Japanese women it has been argued[28] that misclassification could not cause material bias to results of studies conducted there. This argument may not stand up to scrutiny, but more data is needed in order to resolve this issue.

For many lifestyle characteristics listed in Table IV there is published evidence of an association with lung cancer risk after adjustment for smoking habits. These characteristics include failure to take physical exercise[24], drinking green tea[25], drinking alcohol[26], and reduced consumption of dark green vegetables and of dietary sources of vitamin A and beta-carotene, including carrots and vitamin supplements[27]. Relative risks reported for these associations are typically about two. While our study provides no direct information on risk, it is of interest to gain some idea of the extent of the order of magnitude of potential bias that might occur from confounding by these lifestyle characteristics. If, for example, one assumes that eating dark green vegetables less than once a day doubles risk of lung cancer (compared with eating them once a day or more), and if one interpolates so that risk increases steadily with decreasing level of consumption, one can calculate that never smokers married to a smoker would be expected to have a lung cancer risk that is 1.056 times higher than never smokers married to a non-smoker simply because the former group eats dark green vegetables less often. Similarly, assuming subjects more exposed to the risk factor had twice (or half for a protective factor) the risk of subjects who were less exposed, one could calculate biases for other lifestyle characteristics. A number of lifestyle characteristics in Table IV produced biases calculated in this way that exceeded 1.05, including physical exercise (1.062), dark green vegetables (1.056), carrots (1.075) and vitamin supplements (1.068). Although the assumptions concerning risk in these calculations are to some extent arbitrary, they do serve to illustrate that confounding by these lifestyle characteristics may create biases that are important when viewed against the magnitude of association of spouse smoking with lung cancer, a recent estimate of which is 1.18.1

Conclusions

In this study of Japanese women, a major finding was that,

among non-smokers, marriage to a smoker was not associated with an increased level of urinary cotinine. Indeed, non-smokers married to a smoker had rather lower cotinine values than non-smokers married to non-smokers. These findings contradict an earlier study[28] which reported an increased cotinine/creatinine ratio in relation to smokers in the home with a mean ratio of 680 ng/mg, which seems somewhat high compared with the literature. Since many husbands spend relatively little time with their spouses and many women work and are exposed to ETS outside the home, the lack of association between cotinine and marriage to a smoker is perhaps not entirely surprising. If this is not a phenomenon of recent history Japanese epidemiologic studies relating marriage to a smoker to risk of lung cancer have compared groups with approximately equivalent exposures to ETS. If this is so, then presumably the increased relative risks reported in some of these studies must be due to factors other than ETS exposure.

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One possible explanation of this is misclassification of current smoking status. The data in this report does suggest the possibility of relatively high rate of misclassification compared with Western studies. However, the misclassification was not differential and there were significant numbers of non-smokers misclassified by self-report as smokers. Whether misclassification plays a major role in Japanese epidemiologic studies can only be resolved by further study.

Another potential source of bias occurs if non-smokers living with smokers are more exposed to various risk factors for lung cancer than are non-smokers living with non-smokers. This study showed that smokers differ significantly from non-smokers in exposure to many risk factors and that for most of these marriage to a smoker is associated with a smaller difference in the same direction. Although most of the differences in risk factor exposure associated with marriage to a smoker were not statistically significant, it is possible that this is because the

sample size (of 400 women) was inadequate. A British study of over 9000 subjects, which demonstrated[30] that, for a wide range of risk factors, if exposure is associated with the smoking habits of the subject, it is also associated with the smoking habits of the spouse, lends credence to this assumption. Although differences in risk factor exposure in relation to spouse smoking are modest, they could cause bias to the spouse smoking/lung cancer relationship, especially when one considers biases from multiple individual risk factors will combine to cause a larger bias.

Most of this work has been presented using cotinine/creatinine ratio as an index of ETS exposure and using 100 ng/mg as a marker of misclassified current smoking. However, the general conclusions of the study were not affected when using alternative indices (cotinine uncorrected for creatinine, or cotinine corrected for creatinine according to the method of Thompson et al[31]) or when alternative cut-points were used. It is also believed that the relatively low response rate in this study is unlikely to have influenced the main findings.

The findings of this study provide sufficient doubt about the use of spousal smoking as a surrogate for ETS exposure in epidemiologic studies performed in Japan to suggest that more research is needed to clearly resolve the possibility of confounding and bias having a significant effect on these studies.

TABLE I - URINARY COTININE/CREATININE RATIO (ng/mg) BY SELF-REPORTED SMOKING STATUS

	Number of subjects (%)	
Range (ng/mg)	Nonsmoker (n=318)	Current smoker (n=78)
0*	84 (26.4)	1 (1.3)
2-	29 (9.1)	1 (1.3)
10-	95 (29.9)	2 (2.6)
25-	64 (20.1)	1 (1.3)
50-	18 (5.7)	3 (3.8)
100-	3 (0.9)	4 (5.1)
250-	2 (0.6)	9 (11.5)
500-	6 (1.9)	9 (11.5)
1000-	9 (2.8)	18 (23.1)
2000-	8 (2.5)	30 (38.5)
Median ratio (ng/mg)	17.4	1482.8
Median cotinine (ng/ml)	14.3	1681.8
Median creatinine (mg/ml)	0.91	1.05

*Subjects with cotinine ≤5.6 ng/ml were assigned a zero ratio.

TABLE II - COTININE/CREATININE RATIO (ng/mg)

BY HUSBAND'S SMOKING*

Index of husband's smoking	Level	No. of subjects	Median ratio (ng/mg)
Spouse current smoker	No	127	17.98'
	Yes	137	11.51'
Cigarettes smoked by husband (weekdays)	1-15	34	13.86
	16-20	53	10.40
	21+	50	15.24
Cigarettes smoked by husband (holidays)	1-15	50	16.40
	16-20	46	10.66
	21+	39	14.07
Cigarettes smoked by husband at home (weekdays)	1-5	49	10.93
	6-10	52	16.38
	11+	28	5.74
Cigarettes smoked by husband at home (holidays)	1-10	55	7.83
	11-20	62	11.11
	21+	22	12.79

*Among lifelong never smokers excluding those with a ratio >100 ng/mg.

'Means were 19.26 and 16.49 ng/mg. For cotinine, medians were 14.00 and 12.50 ng/ml and means were 16.97 and 14.39 ng/ml.

TABLE III - MISCLASSIFICATION OF CURRENT SMOKING STATUS

Index	Cut-point[1]	% (n/N)
Percentage 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)
Percentage of self-reported never 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)
Percentage 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)

[1]Based on cotinine/creatinine ratio

TABLE IV - RELATIONSHIP OF SMOKING AND SPOUSE SMOKING TO VARIOUS LIFESTYLE CHARACTERISTICS

Variable (Level)	Age-adjusted percentage					
	Never* smoked	Ever* smoked	p	Married to non-smoker**	Married to smoker**	p
Use oil/gas/coke stove	36.5	21.4	<0.01	38.9	34.4	NS
Physical exercise (1+/month)	29.3	17.8	<0.05	34.6	24.3	NS
In contact with traffic fumes (>15 mins/day)	51.2	60.0	<0.05	54.9	47.7	NS
Work outdoors	9.8	19.6	<0.05	7.2	12.0	NS
Green tea (>1/day)	79.1	70.7	NS	84.6	74.0	<0.05
Beer	45.5	55.1	<0.01	48.4	42.7	NS
Other alcohol (than beer)	23.8	38.7	<0.01	24.7	23.1	NS
Salad (>1/wk)	71.8	79.7	<0.05	73.5	70.3	NS
Dark green veg (1+/day)	61.4	41.2	<0.001	63.6	59.5	NS
Carrots (1+/day)	30.1	21.2	<0.05	32.5	28.2	NS
Raw fish (1+/wk)	59.4	67.7	<0.05	58.8	59.7	NS
Smoked fish	38.0	46.0	<0.05	40.6	35.5	NS
Beef (>1/wk)	41.4	51.4	<0.01	36.8	45.8	NS
Vitamin supplements	26.5	23.0	NS	33.7	23.4	<0.05
Coffee (1+/day)	49.3	78.4	<0.001	52.0	46.6	NS
Cheese	62.8	50.6	<0.05	68.8	59.0	<0.1
Cook with salt (less than average)	34.1	19.1	<0.01	38.4	30.1	NS

* Reclassifying women with cotinine/creatinine over 100 ng/mg as ever smoked.

**Analyses restricted to never smokers (excluding reclassified subjects).

' Based on age-adjusted rank test.

N.B. Questions re diet refer to frequency of consumption, not quantity.

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