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RESEARCH PAPER

Cigarette nicotine yields and nicotine intake among Japanese male workers

K Ueda, I Kawachi, M Nakamura, H Nogami, N Shirokawa, S Masui, A Okayama, A Oshima

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Objectives: To analyse brand nicotine yield including "ultra low" brands (that is, cigarettes yielding \leq 0.1 mg of nicotine by Federal Trade Commission (FTC) methods) in relation to nicotine intake (urinary nicotine, cotinine and trans-3'-hydroxycotinine) among 246 Japanese male smokers.

Design: Cross sectional study.

Setting: Two companies in Osaka, Japan.

Subjects: 130 Japanese male workers selected randomly during their annual regular health check up and 116 Japanese male volunteers taking part in a smoking cessation programme.

Main outcome measurements: Subjects answered a questionnaire about smoking habits. Following the interview, each participant was asked to smoke his own cigarette and, after extinguishing it, to blow expired air into an apparatus for measuring carbon monoxide concentration. Urine was also collected for the assays of nicotine metabolites.

Results: We found wide variation in urinary nicotine metabolite concentrations at any given nicotine yield. Based on one way analysis of variance (ANOVA), the urinary nicotine metabolite concentrations of ultra low yield cigarette smokers were significantly lower compared to smokers of high ($p = 0.002$) and medium yield cigarettes ($p = 0.017$). On the other hand, the estimated nicotine intake per ultra low yield cigarette smoked (0.59 mg) was much higher than the 0.1 mg indicated by machine.

Conclusions: In this study of Japanese male smokers, actual levels of nicotine intake bore little relation to advertised nicotine yield levels. Our study reinforces the need to warn consumers of inappropriate advertisements of nicotine yields, especially low yield brands.

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Many smokers interpret the information on tar and nicotine yields as shown on cigarette packs as representing the relative harmfulness of the cigarette.^{1,2} However, because of the well documented effects of compensatory behaviour among users of "low yield" brands, researchers have pointed out that labelling of nicotine/tar yields provides misleading consumer information.^{3,4} According to the Federal Trade Commission (FTC) method, the nicotine yield of a cigarette is measured by a smoking machine with a mechanical mouth, drawing a fixed number of standard puffs—a 35 ml volume drawn over 2 seconds repeated every 60 seconds until the cigarette burns down to a predetermined butt length. However, real smokers are not machines, and they respond to the "ultra low" and "low" nicotine yield cigarette by altering their smoking patterns. Studies have shown that smokers who switch from higher to lower yield brands regulate their nicotine intake, by inhaling more deeply, taking more puffs per cigarette, or simply blocking the ventilation holes with their fingers and lips.^{1,5-12}

Not surprisingly, then, studies have shown little correlation between the advertised nicotine yield of cigarettes and the actual concentrations of nicotine or nicotine metabolites in biological samples of users.^{3,4,13-22} Recently, Jarvis and colleagues²³ reported in a representative British sample of smokers that the nicotine yield of self selected cigarette brands showed little relation with salivary cotinine concentrations. As the authors noted, few of the existing studies included smokers of "ultra low" brands (that is, cigarettes yielding \leq 0.1 mg of nicotine by FTC methods). Data are also sparse in countries outside Britain and the USA, which may differ in their historical pattern of the introduction of "low yield" brands, as well as patterns of smoking habit (for example, depth of inhalation, or the length of the cigarette smoked). Accordingly, we carried out an analysis of brand

nicotine yield (including ultra low cigarettes) in relation to nicotine intake among a sample of Japanese male smokers in worksites.

METHODS

Study population

We recruited 130 male smokers from a chemical company, and 116 male smokers from a clothing wholesales company, in Osaka, Japan in 1997. In the former site, 130 males were selected from 334 smokers (out of a total 629 male workers) during their annual regular health check up. The subjects were selected through systematic random sampling from a master list of smokers. At the second site (employing 475 male workers), we offered a smoking cessation programme to 135 smokers out of 270 smokers, based on their residential proximity to our clinic. One hundred and sixteen smokers responded to our offer, representing an 85.9% response rate.

We defined smokers as those who smoked at least 10 cigarettes per day for more than a year. The average (SD) age of participants was 39.7 (9.4) years. The subjects answered a questionnaire about smoking habits. Following the interview, each participant was asked to smoke his own cigarette and, after extinguishing it, to blow expired air into the apparatus for measuring carbon monoxide concentration. Urine was also collected for the assays of nicotine metabolites. These biochemical markers can be regarded as representing usual steady state carbon monoxide and nicotine intake because

Abbreviations: ANOVA, analysis of variance; FTC, Federal Trade Commission; HPLC, high performance liquid chromatography; JT, Japan Tobacco

Table 1 Selected characteristics of smokers and smoking behaviours according to cigarette nicotine yield

Variables	Nicotine yield (mg/cigarette)				χ^2
	Ultra low yield (0–0.1) n=19	Low yield (0.1–<0.6) n=88	Medium yield (0.6–<1.0) n=102	High yield (\geq 1.0) n=37	
Age, mean (SD)	44.7 (7.5)	39.1 (8.6)	39.3 (10.0)	40.0 (9.8)	39.7 (9.4) (all)
Number of years smoked, mean (SD)	24.4 (9.0)	20.0 (8.0)	19.6 (9.4)	20.7 (9.2)	20.3 (8.9) (all)
Inhalation pattern					
Light	15.8	5.7	7.9	2.7	p=0.031
Medium	63.2	35.2	33.7	27.0	
Deep	21.0	59.1	58.4	70.3	
Time to first morning cigarette (%)					
\leq 5 mins	15.8	26.1	33.7	48.6	p=0.053
5 mins to \leq 30 mins	47.4	43.2	43.6	35.2	
30 mins to < 60 mins	21.0	17.1	5.9	13.5	
\geq 60 mins	15.8	13.6	16.8	2.7	
Stage of change					
Precontemplation	78.9	95.5	93.1	94.6	p=0.260
Contemplation	15.8	3.4	5.9	5.4	
Preparation	5.3	1.1	1	0	
Quit attempts in the past (%)					
Yes	78.9	54.6	43.6	29.7	p=0.002
No	21.1	45.4	56.4	70.3	

χ^2 tests of the relation between smoking behaviours and cigarette nicotine yield were conducted.

these were measured on a day of normal smoking. Informed consent was obtained from each subject.

Ascertainment of smoking habits

Subjects were asked about their smoking habits using a self administered questionnaire. The questionnaire inquired about the brand and nicotine yield of currently smoked cigarettes, the number of years smoked, the number of cigarettes smoked per day, inhalation pattern, stage of change, time to the first morning cigarette, and quit attempts in the past. The cigarette nicotine yield was obtained by FTC methods, as advertised on the cigarette packet. Nicotine yields were defined according to the following categories: ultra low (0–0.1 mg), low (>0.1 and < 0.6 mg), medium (\geq 0.6 to < 1.0 mg), and high yield (\geq 1.0 mg). The subjects' stage of change was categorised based on Prochaska's transtheoretical stage of change model (precontemplation, contemplation, or preparation).^{24–26} Inhalation pattern was categorised as light/medium/deep, while time to the first morning cigarette was categorised as five minutes or less, > 5 minutes but \leq 30 minutes, > 30 minutes but \leq 1 hour, and more than 1 hour. Past quit attempts were dichotomised (yes/no).

Biochemical markers

Physicians, nurses, and counsellors trained in the use of the EC 50 Micro Smokerlyzer (Bedford Instruments, UK) examined the subjects' expired carbon monoxide concentrations. The subjects provided a forced, end expiratory breath sample after a 15 second breath holding procedure. Spot samples of urine were obtained and frozen at -30°C until the time of laboratory analyses. We measured urinary nicotine, cotinine, and trans-3'-hydroxycotinine concentrations with high performance liquid chromatography (HPLC, Waters Corporation, USA). These markers were free forms not including glucuronic acid conjugates. HPLC is the preferred technique to measure cotinine and nicotine in urine.^{27–29} Urinary creatinine concentration was measured by the Jaffe method in a microplate.

All metabolites in a 24 hour urine excretion reflect the amount of nicotine that a person takes in each day.³⁰ Trans-3'-hydroxycotinine is the major urinary metabolite of nicotine, accounting for an average of 39.1% of all nicotine metabolites.³⁰ Nicotine and cotinine additionally account for an estimated 10.4% and 13.3% of urine nicotine metabolites.³⁰ Therefore the total concentrations of measured metabolites amount to 62.8% of the nicotine that a person takes in each

day. Our urine samples are from a spot collection. However, since the pattern of metabolism is consistent for an individual over time,³⁰ our samples reflect the nicotine daily intake.

Statistical analyses

We used one way analysis of variance (ANOVA) to test differences in urinary nicotine metabolite concentrations summing up urinary nicotine, cotinine and trans-3'-hydroxycotinine concentrations, urinary cotinine concentrations, expired carbon monoxide concentrations, as well as the daily number of cigarettes, across categories of nicotine yield. Bonferroni multiple comparison tests were carried out. We used χ^2 tests to test differences between nicotine yield and categorical smoking variables, including stage of change, inhalation pattern, time to first morning cigarette, and quit attempts in the past. Smokers of cigarette brands with lower nicotine yields are likely to differ from those choosing cigarettes with higher nicotine yields. Accordingly, we also carried out multiple regression analyses to examine the associations between cigarette nicotine yields and urinary nicotine metabolite concentrations, controlling for potential confounding factors such as

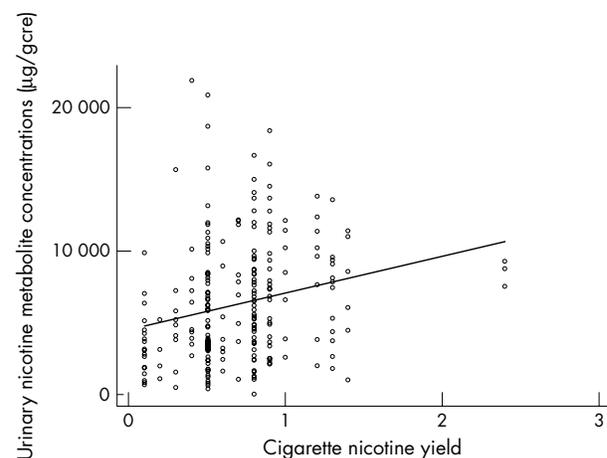


Figure 1 Scatterplot relating cigarette nicotine yields and urinary nicotine metabolite concentrations. Urinary nicotine metabolite concentrations = $4503.2 + 2557.05$ (nicotine yield); $r = 0.23$, $p < 0.001$. gcrea, g creatinine.

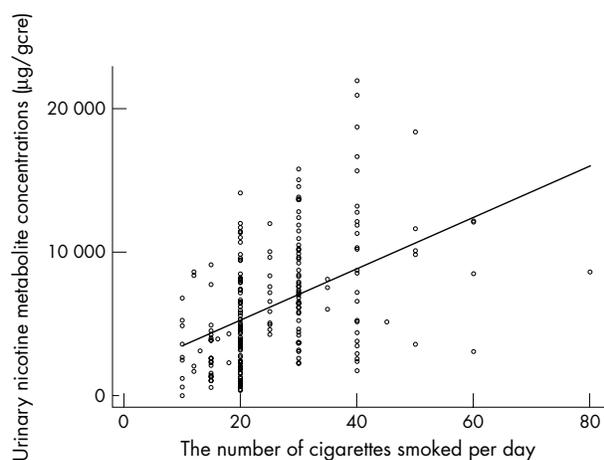


Figure 2 Scatterplot relating the number of cigarettes smoked per day and urinary nicotine metabolite concentrations. Urinary nicotine metabolite concentrations = $1698.99 + 179.74$ (the number of cigarettes per day); $r = 0.46$, $p < 0.001$.

the number of cigarettes smoked per day and inhalation pattern. Statistical significance was determined by two tailed $p \leq 0.05$.

RESULTS

Our study population included 19 ultra low yield cigarette smokers, 88 low yield cigarette smokers, 102 medium yield cigarette smokers, and 37 high yield cigarette smokers (table

1). In other words, 43.5% of subjects usually smoked ultra low or low yield cigarettes. Although smokers of ultra low yield brands tended to be somewhat older than the others, the differences were not significant ($F = 2.00$, $p = 0.114$), nor were the number of years smoked ($F = 1.62$, $p = 0.185$) (table 1). However, differences were found in the stage of change, inhalation pattern, time to the first morning cigarette, and quit attempts in the past. Smokers of ultra low yield cigarettes were less likely to inhale cigarettes deeply ($p = 0.031$). There was also a significant difference between nicotine yield and quit attempts in the past ($p = 0.002$); 78.9% of ultra low yield cigarette smokers had tried to quit smoking in the past compared to only 29.7% of high yield cigarette smokers. We found no significant differences in the stage of change according to cigarette yield. Consistent with previous reports,^{24, 31, 32} the data in table 1 suggest a lower level of nicotine dependence among users of ultra low and low yield cigarettes, as assessed by longer intervals between waking and smoking the first cigarette of the day, as well as more quit attempts in the past.

As shown in fig 1, we found wide variation in urinary nicotine metabolite concentrations at any given yield of nicotine determined by the FTC method. Although there was a small but significant correlation between brand nicotine yield and urinary nicotine metabolite concentration ($r = 0.23$, $p < 0.001$), the nicotine yield based on the FTC method could account for only 5.3% of the variance in metabolite concentrations. We also reanalysed the data after excluding three subjects who used a brand yielding over 2 mg nicotine, because these subjects may have unduly influenced the regression coefficients. However, we obtained virtually the same result ($r = 0.23$, $p < 0.001$). By contrast, we found a stronger correlation between the number of cigarettes smoked

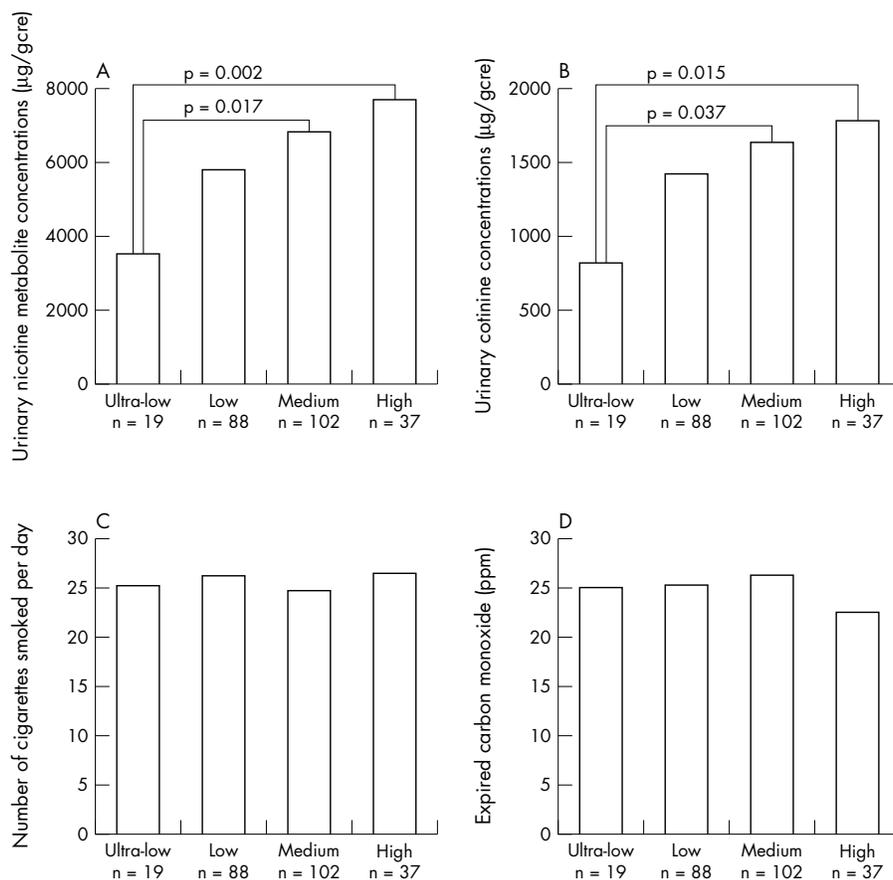


Figure 3 (A) Urinary nicotine metabolite concentrations ($F = 4.87$, $p = 0.0026$); (B) urinary cotinine concentrations ($F = 3.45$, $p = 0.0173$); (C) the number of cigarettes smoked per day ($F = 0.43$, $p = 0.734$); and (D) expired carbon monoxide concentrations ($F = 0.93$, $p = 0.425$) by cigarette nicotine yield groups.

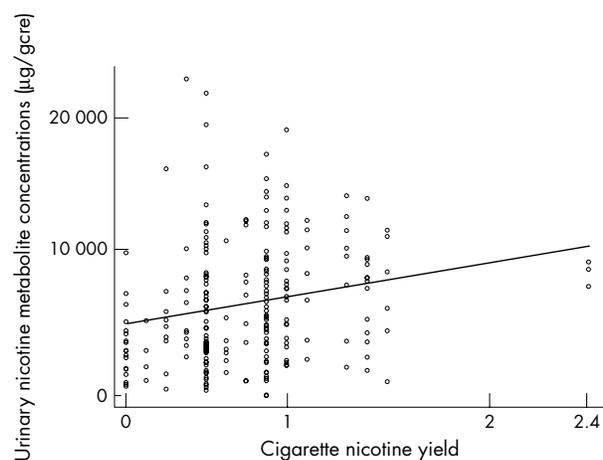


Figure 4 Scatterplot relating cigarette nicotine yields and urinary nicotine metabolite concentrations after control for the number of cigarettes smoked per day and inhalation pattern. Urinary nicotine metabolite concentrations = 4703.51 + 2344.23 (nicotine yield) at mean of the number of cigarettes per day and inhalation patterns; $r = 0.53$, $p < 0.001$.

per day and urinary nicotine metabolite concentrations ($r = 0.46$, $p < 0.001$) (fig 2).

In the one way ANOVA analysis, urinary nicotine metabolite concentrations of ultra low yield cigarette smokers were also significantly different from smokers of high yield cigarettes ($p = 0.002$) and medium yield cigarettes ($p = 0.017$) (fig 3A). Urinary cotinine concentrations of ultra low yield cigarette smokers were significantly different from users of high yield cigarettes ($p = 0.015$) and medium yield cigarettes ($p = 0.037$) (fig 3B). We found no group differences in the number of cigarettes per day and expired carbon monoxide concentrations (fig 3C, D).

Self reported inhalation pattern was positively related to urinary nicotine metabolite concentrations ($r = 0.20$, $p = 0.002$), even though self reported inhalation is poorly correlated with objective inhalation measures.^{33, 34} In multiple regression adjusting for confounders such as the number of cigarettes smoked per day and inhalation pattern, we found that the slope relating brand nicotine yield to urinary nicotine metabolite concentrations was shallower (fig 4), though it remained significant ($p < 0.001$). The incremental proportion of variance explained by the brand nicotine yield after adjustment for confounders was 4.1%.

According to Benowitz and Jacob, every 1000 $\mu\text{g/g}$ creatinine of urinary nicotine and metabolite excretion over 24 hours is equivalent to a daily intake of 3.549 mg of nicotine.³⁰

We estimated the daily nicotine intake and nicotine intake per cigarette smoked using this approximation (table 2). Though the estimated nicotine intake per ultra low yield cigarette was lower than other brands, the estimated nicotine intake (0.59 mg) was much higher than the value of 0.1 mg indicated by the FTC method. Similarly, the estimated nicotine intake per cigarette for other brands bore no relation to cigarette yields advertised. We caution, however, that this part of the analysis is based on the use of an average conversion factor to estimate daily nicotine intake from urinary metabolite profiles. Growing evidence suggests that smokers metabolise, transport, and uptake nicotine at different rates, and furthermore, there may be genetic differences between Japanese smokers and Western populations.

DISCUSSION

Our findings in Japanese male smokers reinforce the point that the nicotine yield advertised on cigarette packets bear little relation with actual nicotine exposure. Low yield nicotine cigarettes were developed for the first time in the USA in 1964 as a "safe" alternative to conventional cigarettes. At the same time, Japan Tobacco Inc (JT) also moved to produce lower nicotine/tar cigarettes. In 1988, JT started to sell ultra low cigarettes. Since 1990, the Japanese Ministry of Finance has required tobacco companies to indicate the nicotine/tar yield on cigarette packets, according to the FTC method. In response, the strategy of cigarette manufacturers has been to shift production to lower nicotine/tar yield cigarettes, and to promote them as cigarettes with lower health risk. JT reported that of all the domestic brands that it produced in 2001, 13% and 27% of cigarettes were, respectively, ultra low (0–0.1 mg) and low (> 0.1 and < 0.6 mg) nicotine yield.³⁵ Domestically produced cigarettes accounted for 75% of the Japanese market share in 2000. The market share of imported cigarettes has risen rapidly from 2.4% in 1985, to 25% in 2001 following market liberalisation.^{36, 37} These imported cigarettes also heavily emphasise low nicotine/tar yield brands. According to the Tobacco Institute of Japan, ultra low and low yield cigarettes accounted for just 0.2% and 1.2%, respectively, of the top 100 popular brands in 1990. On the other hand, the corresponding figures had risen to 12.6% and 32.7% by 2000.

Our study indicated 43.5% of subjects smoked ultra low or low nicotine yield cigarettes. This proportion is considerably higher than that in England (34.2%) or the USA.²³ At the same time, the smoking rate among Japanese males remains relative high (53.5% in 2000)³⁸ compared to England (29%) and the USA (25%).³⁹ It is likely that ultra low and low yield cigarette smokers use these brands as an alternative to quitting altogether.¹ Low yield cigarettes are a threat to public health to the extent that they distort smokers' perceptions of health risks, and reduce their intentions to quit.¹

Table 2 Estimation daily nicotine intake and intake per cigarette smoked by cigarette nicotine yield

Variables	Nicotine yield (mg/cigarette)				ANOVA
	Ultra low yield (0–0.1) n=19	Low yield (0.1–<0.6) n=88	Medium yield (0.6–<1.0) n=102	High yield (≥ 1.0) n=37	
Urinary nicotine metabolite concentrations ($\mu\text{g/g}$ creatinine)*, mean (SD)	3582 (2350)	5931 (4408)	6616 (4093)	7716 (3491)	F=4.87 p=0.0026
Estimated daily nicotine intake (mg), mean (SD)	15.8 (10.7)	26.0 (23.8)	31.8 (27.2)	34.5 (19.4)	F=3.45 p=0.0174
Self reported daily cigarette consumption, mean (SD)	25.3 (9.0)	26.7 (10.8)	25.1 (11.6)	26.5 (8.3)	F=0.43 p=0.734
Estimated intake of nicotine (mg) per cigarette smoked, mean (SD)	0.59 (0.32)	1.01 (0.86)	1.27 (0.82)	1.36 (0.82)	F=5.5 p=0.0011

*Urinary nicotine metabolite concentrations were defined as summing up urinary nicotine, cotinine, and trans-3'-hydroxycotinine concentrations.

It is well known that smokers behaviourally compensate their smoking patterns to regulate their daily nicotine intake.^{8,40-45} Studies of smokers switching to lower yield cigarettes showed that they tend to increase the volume per puff,^{5,7} and the depth of inhalation.⁶ Similar findings have been obtained among stable smokers of lower yield cigarettes.^{9,40} In our study, we found no group differences in expired carbon monoxide concentrations, supporting the presence of compensation. However, in contrast to Jarvis and colleagues,²³ we found significantly lower concentrations of nicotine metabolites among users of ultra low brands. The reasons for the difference between our carbon monoxide and nicotine metabolite findings are not clear. Nor can we say whether the observed association between advertised nicotine yield and intake is wholly due to self selection or to some real (but small) effect of yield on intake.

What we can say is that the yield advertised on the cigarette packs grossly underestimated actual nicotine intakes. The estimated nicotine intake per ultra low yield cigarette was six times higher than that indicated by machine method. Djordjevic and colleagues in the USA also found that the FTC protocol underestimated the exposure not only to nicotine but also to other components of cigarette smoke that affect lung cancer risk such as tar and benzo[a]pyrene and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.⁴⁶ The health benefit of smoking low yield cigarettes is therefore far from established. Indeed, some studies suggest an increase in adenocarcinoma associated with the increased use of these cigarettes.⁴⁷

Urinary cotinine is a widely used measured of nicotine intake.^{5,6,8,13,14,21,48-53} We used spot urine samples to avoid burden on our subjects during working hours. The pattern of nicotine metabolism is consistent for an individual over time,³⁰ so that our spot samples may be reasonably assumed to reflect daily nicotine intake. Nicotine is extensively metabolised and excreted into urine as several nicotine metabolites over a day.³⁰ The percent of cotinine converted to trans-3'-hydroxycotinine varies among individuals.³⁰ However, our measurement of total nicotine metabolite concentrations combined nicotine, cotinine and trans-3'-hydroxycotinine concentrations, and should reflect overall nicotine intake well. On the other hand, we did not take account of individual differences in percent conversion of nicotine (perhaps related to genetic or age differences in metabolic activity),³⁰ or differences in urine pH.⁵⁴

Socioeconomic status might have been a potential confounding factor in our analyses, although we did not measure it. A study in Britain found that smokers of lower nicotine yield cigarettes compared to other types of cigarettes tended to be better educated, own a car, own their homes, and to not have a manual occupation.²³ The socioeconomic status of workers in our two work places (a chemical and clothing wholesales company) could be described as more middle class. Although they were not representative of the Japanese male workforce, they were similar to the overall population of Japanese adult males with respect to their smoking rates. The smoking prevalence at our two work sites (53.1% and 56.8%) was quite comparable to the national figure for Japanese males (53.5%).

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What this paper adds

Previous studies have found little relation between the advertised nicotine yield of cigarettes and concentrations of nicotine metabolites measured in smokers. However, few studies have included smokers of "ultra low" brands (cigarettes yielding ≤ 0.1 mg of nicotine by FTC methods). Data are also sparse in countries outside Britain and the USA.

We conclude that, based on the concentrations of urinary biomarkers, the FTC nicotine yields in cigarette smoke were not equivalent to nicotine exposure at any advertised yield level. Moreover, ultra low and low yield cigarettes may not reduce the risk of ill health.

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