Smoking and Lung Cancer Risk in American and Japanese Men: An International Case-Control Study[1]

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Abstract

Rates of lung cancer in American men have greatly exceeded those in Japanese men for several decades despite the higher smoking prevalence in Japanese men. It is not known whether the relative risk of lung cancer associated with cigarette smoking is lower in Japanese men than American men and whether these risks vary by the amount and duration of smoking. To estimate smoking-specific relative risks for lung cancer in men, a multicentric case-control study was carried out in New York City, Washington, DC, and Nagoya, Japan from 1992 to 1998. A total of 371 cases and 373 age-matched controls were interviewed in United States hospitals and 410 cases and 252 hospital controls in Japanese hospitals; 411 Japanese age-matched healthy controls were also randomly selected from electoral rolls. The odds ratio (OR) for lung cancer in current United States smokers relative to nonsmokers was 40.4 [95% confidence interval (CI) = 21.8–79.6], which was >10 times higher than the OR of 3.5 for current smokers in Japanese relative to hospital controls (95% CI = 1.6–7.5) and six times higher than in Japanese relative to community controls (OR = 6.3; 95% CI = 3.7–10.9). There were no substantial differences in the mean number of years of smoking or average daily number of cigarettes smoked between United States and Japanese cases or between United States and Japanese controls, but American cases began smoking on average 2.5 years earlier than Japanese cases. The risk of lung cancer associated with cigarette smoking was substantially higher in United States than in Japanese males, consistent with population-based statistics on smoking prevalence and lung cancer incidence. Possible explanations for this difference in risk include a more toxic cigarette formulation of American manufactured cigarettes as evidenced by higher concentrations of tobacco-specific nitrosamines in both tobacco and mainstream smoke, the much wider use of activated charcoal in the filters of Japanese than in American cigarettes, as well as documented differences in genetic susceptibility and lifestyle factors other than smoking.

Introduction

Since the 1950s, lung cancer rates in American men have greatly exceeded those in Japanese men, despite a much lower prevalence of smoking in the United States The mortality rates of lung cancer were two to three times higher in the United States during this period, although both countries experienced a substantial increase from 1955 to 1985 (1, 2). Incidence trends were similar to mortality: the 1988–1992 lung cancer incidence in white males in the United States Surveillance Epidemiology and End Results program of the National Cancer Institute areas was 61.3 per 100,000 compared with 39.6 for males in Miyagi Prefecture (3). During the same 30-year period, there was a decline in the prevalence of smoking from 54% in 1955 to 33% in 1985 in United States men, whereas the percentage of Japanese men who smoked increased from 76% in 1955 to a peak of 82% in 1965 before declining to 60% in 1992 (4, 5).

The rates of lung cancer in Japanese migrants and their offspring in the United States are similar to United States-born whites, which strongly suggests that most of the international variation in lung cancer rates is not attributable to ethnic differences in susceptibility (6). In a comparison of several prospective studies of lung cancer mortality rates, smoking-specific rates were consistently lower in Japanese than in British, Norwegian, Swedish, or American smokers (7, 8). Although there are other risk factors for lung cancer including exogenous factors such as diet (9, 10), occupation (11), and inborn differences in metabolizing enzymes (12), cigarette smoking causes >90% of cases (8). Therefore, attempts to explain this anomaly must begin with a comparison of smoking-specific factors such as the duration of smoking habit, cpd,[4] or age at onset of smoking.

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[3] Deceased.

[4] The abbreviations used are: cpd, cigarettes per day; AC, adenocarcinoma of the lung; CI, confidence interval; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; SCC, squamous cell carcinoma of the lung; OR, odds ratio.

This study took advantage of long-standing collaborations between the American Health Foundation and Japanese researchers. In 1977, Wynder and Hirayama (1) summarized the trends and differences in United States and Japanese cancer rates in relation to lifestyle characteristics. Subsequently, they found that lung cancer rates were rapidly increasing among Japanese men as a consequence of increased numbers of heavy cigarette smokers (2). The United States-Japan lung cancer anomaly has persisted in more recent comparisons (13). Because these ecological comparisons of population data cannot directly establish the risk of smoking, we conducted a multicentric case-control study in the United States and Japan to compare smoking behaviors as risk factors in both countries.

Materials and Methods

Participating Centers. Study subjects were interviewed in a case-control study conducted simultaneously in large urban centers in the United States and Japan. Eight Japanese hospitals in Nagoya and 10 United States hospitals participated (see "Acknowledgments"). The majority of United States patients (80%) were enrolled in hospital cancer centers in New York City (Memorial Sloan-Kettering Cancer Center, Columbia-Presbyterian Medical Center, Tisch Hospital-New York University Medical Center, and Long Island Jewish Medical Center) and Washington, DC (George Washington University Medical Center). Japanese cancer patients were recruited at Aichi Cancer Center in Nagoya (44%), National Nagoya Hospital (24%), First Red Cross Hospital (17%), Aichi Prefectural Hospital, and several smaller hospitals in Aichi Prefecture (15%).

Eligibility. Cases were patients between the ages of 20 and 81 years newly diagnosed with primary lung cancer within 1 year of the interview date and who had no previous history of another tobacco-related cancer. All of the cases were histologically or cytologically confirmed through hospital pathology reports or discharge summaries. United States lung cancer cases were patients admitted to participating hospitals between March 1992 and February 1997; Japanese cases were enrolled between June 1993 and May 1998. Hospital controls were patients ages 20–81 years admitted for a nontobacco related condition and having no history of the following tobacco related diseases: cancer of the esophagus, larynx, oral cavity, nasal sinus, pancreas, liver, kidney, or bladder. Patients hospitalized for other tobacco-related cardiovascular conditions (*i.e.*, myocardial infarction, stroke, or coronary artery disease) and respiratory disorders (*i.e.*, emphysema, chronic bronchitis, or chronic obstructive pulmonary disease) were also excluded as hospital controls. Hospital controls in both countries were frequency matched on age (±5 years), hospital, and date of interview (initially ±2 months, extended in September 1995 to ± 4 months in Japan because of the requirement of obtaining individual physician consents). Hospital controls in both countries included large percentages of patients with digestive, genitourinary, and musculoskeletal diseases, and injury or poisoning. However, a higher percentage of United States controls were admitted for neoplasms (29.0% *versus* 1.2% in Japan), of which 38.9% were cases of malignant neoplasm of prostate, and 25.9% were cases of leukemia and lymphoma; 56.3% of Japan hospital controls were diagnosed with digestive and genitourinary diseases compared with 32.1% of United States hospital controls.

Hospital controls were included in the United States component of the study because we previously showed no differences in smoking prevalence between hospital and community-based controls (14). Because it had not been determined previously whether smoking prevalence was similar in Japanese hospital patients and community members, the Japanese study design included both hospital and community-based controls. Controls were frequency matched by age (±5 years), date of interview (±2 months; ±4 months after September 1995), and neighborhood of residence to cases. Community controls were chosen from residents who lived in the same or neighboring district of the hospital in which matching cases were chosen in a random selection process from a list of names with corresponding addresses and dates of birth, kept as part of the electoral records system in Nagoya and Okazaki City. The United States portion of the study comprised 371 white male cases and 373 white male hospital controls. The total number of male Japanese subjects available for analysis included 410 lung cancer cases, 252 hospital controls, and 411 community controls. The overall response rate among United States patients was 82.8% of those approached and was nearly identical among cases and controls. Response rates in Japanese cases and controls were similar and also exceeded 80%.

Questionnaires and Interview Procedures. The Japanese version of the questionnaire was developed by translating the English version and then back-translating it into English by a different translator to insure comparability. Trained interviewers were given the same instructions in both countries. To assure procedural uniformity in the two countries, three of the Japanese investigators, who are all fluent in English, received intensive training in New York, whereas one of the United States investigators (S. D. S.) made frequent visits to the Japanese sites. The Japanese questionnaire was printed in bilingual form to facilitate data entry by the American keypunchers. All of the subjects signed a consent form, which was approved by the Institutional Review Boards of the collaborating institutions. The questionnaire included detailed items on smoking history such as age at onset, smoking status, years and amount, cigarette brand, history, and years since quitting.

Smoking Categories. Subjects were classified as nonsmokers (never smoked regularly; *i.e.*, at least once a day for 1 year), current smokers (smoked within the past year), or ex-smokers (did not smoke within the past year). Persons who smoked cigars or pipes only were excluded from the analyses except for the descriptions of mean age and years of education. Among United States men, "cigar/pipe only" smokers made up 5.4% and 0.85% of cases and controls, respectively; there were no Japanese subjects who reported smoking either cigars or pipes.

Statistical Methods. OR and 95% CI were calculated by logistic regression, and adjusted for confounding variables such as age at diagnosis, education (three categories: <12, 12, >12 years), and hospital (for analyses using hospital controls). Dummy variables were introduced to code categories of smoking status (non-, current, or ex-smoker), total years of smoking (≤40 or 41+ years), average number of cpd (<20, 20–29, ≥30 cpd), age at onset of smoking (0–14, 15–17, 18–20, >20 years old), and number of years since quit smoking (1–9, 10–15, 16+ years). Wald's χ^2 statistic was used to test statistical significance against the null hypothesis of no association, and 95% CIs were obtained. Differences in mean values were tested for significance with Student's *t*. The χ^2 test for trend was conducted by the Mantel-Haenszel extension method with data stratified into age groups by decade.

Results

Table 1 compares the distributions of age and education in cases and controls in the United States and Japanese study

Table 1 Distribution of age and education levels in years for the United States and Japanese study populations[a]

	United States		Japan		
	Cases (n = 371)	Controls (n = 373)	Cases (n = 410)	Hospital controls (n = 252)	Community controls (n = 411)
Age					
≤39	1.6	1.3	1.7	2.4	1.5
40–49	5.7	8.6	10.0	15.5	10.0
50–59	20.8	18.5	24.2	34.1	22.1
60–69	42.9	42.4	42.2	35.7	41.1
≥70	29.1	29.2	22.0	12.3	25.3
Total	100	100	100	100	100
Education level in years					
<12	17.6	11.5	52.8	43.0	42.4
=12	27.6	22.8	22.6	26.3	19.8
>12	54.9	65.7	24.6	30.7	37.8
Total	100	100	100	100	100

[a] Distribution is by percentage.

Table 2 Smoking status and adjusted ORs for lung cancer

Smoking status	United States			Japan			
	% Cases (n = 371)	% Hospital controls (n = 373)	OR (95% CI)[a]	% Cases (n = 410)	% Hospital controls (n = 252)	% Community controls (n = 411)	OR (95% CI) (HC[a]/CC[b])
Nonsmokers	4.3	41.0	1	4.6	11.5	17.0	1
Ex-smokers	55.8	48.5	10.5 (6.2–19.0)	26.1	42.9	44.0	1.3 (0.6–2.9)/2.2 (1.3–4.0)
Current smokers	39.9	10.5	40.4 (21.8–79.6)	69.3	45.6	38.9	3.5 (1.6–7.5)/6.3 (3.7–10.9)
Total	100	100		100	100	100	

[a] HC, hospital controls. Reference group is nonsmokers; adjusted for age, education, and hospital.
[b] CC, community controls. Reference group is nonsmokers; adjusted for age and education.

populations. As expected, cases in both countries were less educated than controls, but the matching insured that the ages were similar between hospital cases and controls. Japanese community controls were somewhat younger than their corresponding cases.

Table 2 shows the smoking prevalence in the two countries and corresponding ORs for lung cancer. In controls, the percentage of current smokers was greater in Japan than in the United States. In both countries smoking was strongly related to the risk of lung cancer, and the risk for former smokers was about one-third that for current smokers. However, the strength of the association between lung cancer and smoking differed substantially between the two countries. The OR for lung cancer among current smokers relative to nonsmokers in the United States was 40.4 (95% CI = 21.8–79.6), which was >10 times larger than that in Japan when using hospital controls (OR = 3.5; 95% CI = 1.6–7.5) and more than six times as large as that in Japan when using community controls (OR = 6.3; 95% CI = 3.7–10.9). Similarly, the ORs for ex-smokers were five to eight times as great in the United States as in Japan, respectively. The small number of nonsmokers among cases in both countries resulted in wide CIs; however, the 95% CI for lung cancer risks for United States and Japanese subjects do not overlap.

We examined whether specific smoking variables such as smoking duration, cpd, or age at onset accounted for the lower risk in Japan (Table 3). For all three of the variables, the magnitudes of the ORs were much greater in the United States subjects than in the Japanese subjects. There were no significant differences in mean years of smoking between United States and Japanese cases or between the United States controls and either set of Japanese controls. In both countries there was a strong dose-response relationship with years of smoking, but within each duration stratum the adjusted American ORs were from 5 to 12 times as high as the Japanese ORs. For example, the adjusted OR for lung cancer in United States subjects who had smoked for >40 years was 57.8 (95% CI = 27.4–132), whereas for Japanese subjects it was 7.4 (95% CI = 2.9–19.4) using hospital controls and 8.3 (95% CI = 4.5–15.4) using community controls.

Also as expected, there was a strong dose-response relationship between lung cancer risk and cpd in both United States and Japanese subjects. There were no significant differences in the average number of cpd between United States and Japanese controls. The adjusted ORs in the United States study population ranged from 4 to 15 times that of the Japanese within the same cpd stratum. For example, for subjects who currently smoked 20–29 cpd, the OR in United States subjects was 53.4 (95% CI = 23.1–135), whereas in Japanese subjects it was 3.5 (95% CI = 1.5–8.4) when using hospital controls and 4.3 (95% CI = 2.4–7.6) when using community controls.

Table 3 also shows that the average age of smoking onset was 2.5 years later for Japanese cases than American cases ($P < 0.001$) and 2.4 to 2.7 years later for Japanese compared with American controls ($P < 0.01$). Whereas one-fifth of the currently smoking controls in the United States had started smoking before age 15, there were almost no Japanese who reported starting smoking so young. Statistically significant trends of decreasing lung cancer risk with later age of onset of smoking were observed in both countries ($P < 0.01$ in United States and $P < 0.001$ in Japan). The estimated effect of starting to smoke at a later age was more apparent using community controls as a reference than hospital controls.

Table 3 Lung cancer risk in current smokers in relation to smoking duration, cpd, and age at onset of smoking habit

	United States			Japan			
	Cases	Hospital Controls	OR (95% CI)	Cases	Hospital Controls	Community Controls	OR (95% CI) (HC; CC)[a]
n	148	39		284	115	160	
Smoking duration (yr) %							
≤40	38.5	56.4	25.2 (11.9–61.0)[b]	40.5	71.3	45.0	2.2 (1.1–5.2); 4.8 (2.6–8.9)[c]
>40	61.5	43.6	57.8 (27.4–131.9)[b]	59.5	28.7	55.0	7.4 (2.9–19.4); 8.3 (4.5–15.4)[c]
Mean (SD)	42.6 (10.8)	38.7 (12.3)		41.6 (9.8)	35.4 (9.8)	40.6 (10.3)	
cpd %							
<20	10.8	38.5	10.9 (4.4–28.0)[b]	16.8	29.8	30.6	1.6 (0.7–3.9); 2.6 (1.4–4.9)[c]
20–29	35.1	28.2	53.4 (23.1–135.2)[b]	35.0	34.2	41.3	3.5 (1.5–8.4); 4.3 (2.4–7.6)[c]
≥30	54.1	33.3	73.3 (32.5–181.6)[b]	48.2	36.0	28.1	6.2 (2.6–15.0); 9.3 (5.2–16.7)[c,d]
Mean (SD)	30.6 (15.5)	22.9 (16.4)		29.5 (15)	25 (14.8)	22.7 (12.8)	
Age at onset of smoking (yr) %							
<14	30.4	20.5	1.2 (0.4–3.4)[e]	0.7	0.0	0.0	([f])
15–17	38.5	33.3	1 (reference)[e]	21.1	11.3	15.6	1 (reference)[g]
18–20	18.2	25.6	0.6 (0.2–1.7)[e]	61.6	68.7	60.0	0.2 (0.1–0.6); 0.8 (0.5–1.3)[g]
>20	12.8	20.5	0.5 (0.2–1.4)[e]	16.6	20.0	24.4	0.2 (0.1–0.8); 0.5 (0.3–0.9)[g,h]
Mean (SD)	16.8 (5.8)	17.8 (5.0)		19.3 (2.9)	20.2 (4.7)	20.5 (5.8)	

[a] HC, hospital controls; CC, community controls.
[b] Adjusted for age, education, and hospital; reference group is nonsmokers.
[c] Adjusted for age and education; reference group is nonsmokers.
[d] $P < 0.001$, test for linear trend.
[e] Adjusted for age, education and hospital; reference group is 15–17 yrs.
[f] ORs were not computed because no current smokers started smoking before the age of 15 in Japanese controls.
[g] Adjusted for age and education; reference group is 15–17 yrs.
[h] $P < 0.01$, test for linear trend.

Table 4 Adjusted ORs for lung cancer comparing ex-smokers with current smokers according to years since quitting

Time since quitting in years	United States Hospital Controls	Hospital Controls	Japan Community Controls
	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]
Current Smokers	1	1	1
Ex-smokers			
1–4	0.5 (0.3–1.0)	0.9 (0.3–2.9)	0.9 (0.5–1.7)
5–9	0.5 (0.2–0.9)	0.8 (0.3–1.8)	0.8 (0.5–1.4)
10–15	0.4 (0.2–0.8)	0.2 (0.1–0.5)	0.2 (0.1–0.4)
16+	0.1 (0.1–0.2)[c]	0.2 (0.1–0.4)[c]	0.2 (0.1–0.30)[c]

[a] Reference group is current-smokers; adjusted for age, education, and hospital.
[b] Reference group is current-smokers; adjusted for age and education.
[c] $P < 0.001$, test for linear trend.

Table 4 displays the pattern of the reduction in lung cancer risk in ex-smokers according to years since quitting, relative to current smokers. Among United States subjects, the risk was reduced as much as 50% for those who had quit within the last 10 years, whereas among Japanese former smokers, the corresponding reduction was only 10–20%. The relative risk estimates were examined by the two most common histological types of lung cancer: AC and SCC (Table 5). OR estimates for SCC are not shown for the United States study population, because there were no SCC cases among nonsmokers and only 32 among current smokers. ORs for AC in the United States population and for both histological types in Japan increased both with duration and with cpd. ORs for AC in the United States population were all significantly >1 and were greater than those in Japan. Among Japanese current smokers, a steeper increase in ORs was observed for SCC compared with ORs for AC, and ORs calculated from community controls were larger than those obtained by using hospital controls.

Discussion

The risk of lung cancer in the United States study population was at least 10 times higher than in Japanese despite the higher percentage of smokers among the Japanese. These findings are consistent with ecological data on smoking and lung cancer rates in the United States and Japan described previously (13). Our results are also consistent with comparisons of studies of lung cancer risk associated with ever-smoking (4, 15–23). For example, Sobue *et al.* (17) showed that the relative risk for Japanese smokers *versus* nonsmokers had risen over time but was still less than the risks for Western European smokers. The risks for lung cancer in current cigarette smokers ranged from 2.1 to 4.4 in Japanese studies as compared with 9 to 15.8 in United States and Western European studies (15, 18, 19).

An important difference between United States and Japanese smokers was the lower average age at onset of smoking in American men (<15 years), which was associated with an elevated risk of lung cancer. Almost no Japanese smokers began smoking before the age of 15. Nevertheless, earlier age of smoking onset was also a risk factor in Japanese men as shown by the lower ORs associated with smoking onset at age of 18 or older compared with an earlier age at onset of smoking (between 15 and 17 years of age). Sobue *et al.* (17) have noted that smoking has been illegal in Japan for persons under age 20 since 1900. However, this prohibition is clearly flouted by younger Japanese, according to surveys in Japanese high schools that showed rapidly increasing smoking rates during the 1980s (24).

Although some epidemiological studies have suggested that age at onset of smoking is an independent risk factor for lung cancer (25), this relationship remains controversial, since early age at onset of smoking is associated with heavy subsequent cigarette consumption (26). A recent study also showed that the effect of age at onset of smoking is not strong enough to explain the causal relationship between smoking and damage in lung tissues among current smokers, but was a significant

Table 5 Adjusted ORs for SCC and AC comparing current smokers with nonsmokers according to smoking duration and cpd

	United States[a]	Japan			
	AC	AC		SCC	
	Hospital controls OR (95% CI)[b]	Hospital controls OR (95% CI)[b]	Community controls OR (95% CI)[c]	Hospital controls OR (95% CI)[b]	Community controls OR (95% CI)[c]
Smoking duration in years					
Nonsmokers	1	1	1	1	1
≤40	15.1 (5.2–43.9)	1.1 (0.4–2.8)	2.6 (1.3–5.4)	6.3 (1.2–33.4)	13.1 (2.9–58.6)
>40	34.7 (14.1–85.5)	3.9 (1.3–11.5)	4.1 (1.9–8.6)	19.3 (3.8–99.0)	22.8 (5.2–99.4)
cpd					
Nonsmokers	1	1	1	1	1
<20	7.0 (2.2–22.4)	0.6 (0.2–1.8)	1.2 (0.5–29)	7.4 (1.3–42.2)	10.2 (2.2–46.7)
20–29	37.3 (12.7–109.7)	2.2 (0.8–5.9)	2.9 (1.4–5.9)	13.7 (2.5–76.2)	14.1 (3.2–62.1)
≥30	54.6 (18.8–158.4)	3.3 (1.2–8.8)	5.5 (2.7–11.3)	31.8 (5.4–185.8)	35.7 (8.1–156.5)

[a] ORs for SCC were highly unstable in the United States study population; there were no cases observed among nonsmokers and only 32 among current smokers.
[b] Reference group is current-smokers; adjusted for age, education, and hospital.
[c] Reference group is current-smokers; adjusted for age and education.

Table 6 Comparison of ORs for lung cancer in recent Japanese and Western studies

	SCC[a]		AC[a]		All types[a]	
	Ex	Current	Ex	Current	Ex	Current
Japan						
Present study[b]	5.7	18.5	1.5	3.2	2.2	6.3
Nakamura[22]	3.7	6.0	1.7	2.8		
Ohno[20]					2.5	4.1
Gao[4]					3.6	6.6
Shimizu[21]		12.8[c]		1.5[c]		3.1[c,d]
Sobue[17]	13.1	18.1	1.5	1.9	2.8	4.1
Western Europe						
Lubin[18]	8.4–23.0	20.9	1.8–3.5	3.5		
United States						
Present Study	[e]	[e]	6.4	25.6	10.5	40.4
Thun[23]		[f]		19.2		

[a] Reference group is nonsmokers.
[b] Risks estimated using community controls.
[c] Ex-smokers were included with current smokers.
[d] Estimated from published data.
[e] Could not be estimated because of the lack of nonsmoking cases.
[f] Not reported because of too few nonsmoking cases.

factor among ex-smokers (27). Hence, although it is possible that the higher risk of lung cancer in the United States might partly result from earlier age at onset of smoking among current smokers, it is unlikely to account for the large difference in OR between United States and Japan.

Numerous studies have found that lung cancer risk decreases with increasing years since quitting in the United States (8, 28, 29) and Japan (17, 30). In the present study, it was observed that American former smokers experienced a more dramatic reduction in lung cancer risk during the first decade after cessation than the Japanese ex-smokers did. After 16 years of cessation, lung cancer risks for ex-smokers in both countries were slightly lower for the United States group. Given the higher overall risk among United States current cigarette smokers, this additionally emphasizes the importance of smoking cessation as an essential risk reduction step for all smokers.

The dose-response for SCC was considerably steeper than for AC in the Japanese population whether duration or cpd was the dosage variable (Table 5). This disparity in histology-specific risks is consistent with reports from case-control studies reported from both the United States and Japan over the past 2 decades (Refs. 17, 31, 32; Table 6). The risk for SCC in the United States group would undoubtedly have been much greater than for AC had there been sufficient cases to permit computation; however, the steady decline in the prevalence of current smokers among American men in the lung cancer age group along with the continuing clinical shift from SCC to AC (33) has greatly reduced the available number of cases with SCC that are either current smokers or nonsmokers. The relative proportions of SCC and AC were similar in both countries.

There are several possible explanations for higher smoking-related risks in the United States than in Japan, beginning with the observation that mainstream smoke from American cigarettes may contain higher concentrations of toxic and carcinogenic compounds than that of Japanese cigarettes (34). Measurements made in our laboratories have found that the leading brands of United States cigarettes deliver 35% more benzo(*a*)pyrene and 170% more NNK than do the leading Japanese brands when measured in mainstream smoke under standardized experimental conditions (*i.e.*, the United States Federal Trade Commission machine-smoking protocol; Ref. 35) despite similar deliveries of nicotine (34). This marked difference in delivery of two major classes of lung carcinogens is probably partly attributable to differences in the tobacco

blends used in the manufacture of American and Japanese cigarettes and partly to the much wider use of charcoal filters in Japanese cigarettes. Samples of American blended tobacco contain 2.6 times the concentration of NNK and 1.4 times the concentration of nitrate as do samples of Japanese blended tobacco (36). Furthermore, for the past two decades, more than two-thirds of cigarettes purchased in Japan have had charcoal filters, compared with <1% of cigarettes purchased in the United States (34). Charcoal filter tips selectively remove certain gaseous/volatile compounds (*e.g.*, hydrogen cyanide, formaldehyde, acetaldehyde, and acrolein) in mainstream smoke that are known inhibitors of lung clearance; charcoal filters also have a tendency to selectively retain benzene and toluene (37, 38). Doses of carcinogens "presented" to Japanese and American smokers may also differ because of differences in smoking topography (inhalation, puff volume, and so forth). We have found that American smokers of low- and medium-yield cigarettes (≤1.2 mg nicotine) inhale more than twice as much nicotine, "tar," and NNK as predicted by the United States Federal Trade Commission protocol (35); such measurements have yet to be made for Japanese smokers.

Both genetic and lifestyle factors may modify smoking-related lung cancer risk. A higher prevalence has been reported in Japanese of genetic polymorphisms in some P450 enzymes that catalyze activation of carcinogenic polycyclic aromatic hydrocarbons such as those found in cigarette smoke (39, 40). Tyndale *et al.* (41) recently found the prevalence of the (protective) *2 and *4 null alleles of CYP2A6 to be 21.2% in Japanese compared with 2.6% in Caucasians; this enzyme is one of several that metabolically activate *N*-alkylnitrosamines such as NNK (42). Polymorphisms such as these may be associated with as much as a 2-fold risk of lung cancer in both white and Japanese populations (12), but many other factors may also be needed to explain the 10-fold differential in relative risk observed by us. Marmot and Smith (43) have pointed out that Japanese in general have a longer life expectancy than people in England, and possible explanations for the lower mortality in Japan could be the effects of different aspects of Japanese lifestyle. Wynder *et al.* (13) have suggested previously that differences in diet, particularly dietary fat, may also contribute to the differences in lung cancer rates. Gao *et al.* (4), using data obtained earlier from a Nagoya hospital population, reported a protective effect of fruit and vegetable consumption on risk of lung cancer. Ohno *et al.* (20) also reported a protective effect of tea consumption against lung cancer in residents of Okinawa. All of these factors may be considered as candidate effect modifiers of smoking-related lung cancer risks in future studies.

Potential biases from misclassification of ex-smokers as nonsmokers in some Japanese case-control studies could result in an underestimate of OR (17). However, it is unlikely that a substantial nonrandom misclassification would occur in only one of the two countries unless Japanese ex-smokers and United States ex-smokers differ greatly in the variety of self-reports of smoking status. Comparison of the distribution of smoking prevalence from this study with population statistics suggests that this is not the case. Because lung cancer in young patients differs from lung cancer in older patients (44), all of the OR calculations were adjusted for age in this study. Also, because smoking behaviors vary by social class (45, 46), education level was controlled in the analyses.

Lung cancer cases from hospitals may not be representative of all of the lung cancer cases in the underlying population. The smoking prevalence in the control groups was reduced after excluding hospital patients with diseases related to smoking. However, the exclusion of smoking related diseases from hospital controls was an important element of the study design and has been shown to be a successful strategy for reducing selection bias in case-control studies of tobacco-related diseases in United States studies (14). In the Japanese study population, all of the ORs calculated using community controls were higher than those estimated using hospital controls, but these differences were small in comparison with United States-Japan differences for all of the major dosage variables.

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