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Impact of smoking on lung cancer risk is stronger in those with the homozygous aldehyde dehydrogenase 2 null allele in a Japanese population

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The main lifestyle contributor to acetaldehyde exposure is the drinking of alcoholic beverages, but tobacco smoke also makes some contribution. Although acetaldehyde is associated with upper aerodigestive tract cancer risk, in accordance with genetically determined acetaldehyde metabolism, it is unclear whether lung cancer, a representative smoking-related cancer, is associated with acetaldehyde or genes impacting its metabolism. We conducted a case–control study to examine possible interaction between smoking and aldehyde dehydrogenase 2 (*ALDH2*) Glu504Lys polymorphism (rs671) on the risk of lung cancer in Japanese. Subjects were 718 lung cancer cases and 1416 non-cancer controls enrolled in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center. Lifestyle factors, including smoking, were determined by self-administered questionnaire. We applied pack-years (PY; categorized into five levels: never, <15, <30, <45 and ≥45) as a marker of cumulative exposure to smoking. The impact of smoking, *ALDH2* genotype, and their interaction on lung cancer risk were assessed by odds ratio (OR) and 95% confidence interval adjusted for potential confounders. Adjusted ORs for PY <15, <30, <45 and ≥45 relative to never smokers among those with Glu/Glu or Glu/Lys were 1.39, 1.80, 3.44 and 6.25, respectively (P-trend = 1.4×10^{-30}). In contrast, ORs among Lys/Lys were 1.01, 10.2, 11.4 and 23.2, respectively (P-trend = 2.6×10^{-7}). Interaction between *ALDH2* genotype (Glu/Glu + Glu/Lys versus Lys/Lys) and cumulative smoking dose was statistically significant ($P = 0.036$) and was consistently observed in the analysis among never-drinkers (interaction $P = 0.041$). These results suggest that *ALDH2* Lys/Lys, a null enzyme activity genotype, modifies the impact of smoking on the risk of lung cancer.

Introduction

Alcohol consumption is an established risk factor for cancers of the head and neck, esophagus, colon and breast (1), an effect for which several biological mechanisms have been proposed (2,3). Interestingly, several recent reviews of epidemiologic studies have suggested a potential role for alcohol in carcinogenesis in the lung (4–6). Acetaldehyde, the first oxidative metabolite of ethanol, strongly impacts upper aerodigestive tract cancer via multiple mutagenic effects on DNA, suggesting that it may also play a role in carcinogenesis in the lung (7,8).

Acetaldehyde, which is also an ingredient in tobacco smoke (9–11), is oxidized into acetate by the aldehyde dehydrogenase (ALDH) enzymes. This oxidation is largely dependent on ALDH2 enzyme. The presence of a functional polymorphic site in *ALDH2* is known, namely 504Glu (*1: active)/504Lys (*2: null) (rs671: G>A). The *ALDH2* 504Lys allele is an inactive subunit, and thus, enzyme activity in individuals with the *ALDH2* Lys/Lys genotype is markedly limited compared with that of those homozygous for *ALDH2* 504Glu. Given that the *ALDH2* 504Lys alleles are clustered in East Asian populations, including Japanese, and their well-established impact on alcohol drinking behavior (12), we speculated that this polymorphism may affect lung cancer risk in Japanese in combination with drinking or smoking behavior. We were particularly interested in the possible interaction between this polymorphism and smoking-related acetaldehyde exposure.

Here, we evaluated the association between the *ALDH2* Glu504Lys polymorphism and the lung cancer risk in a case–control study in a Japanese population.

Materials and methods

Study population

The present subjects were aged 20–79 years and were enrolled between January 2001 and November 2005 in the framework of the second version of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). Details of the study design and subject characteristics have been described elsewhere (13,14). In brief, the second version of HERPACC was initiated at Aichi Cancer Center Hospital, Nagoya, Japan, in 2001. Information on lifestyle factors as well as a 7 ml blood sample was requested from all first-visit outpatients at our hospital, including cancer and non-cancer patients. Before first examination at our hospital, patients were asked about their lifestyle when healthy or before the current symptoms developed. Responses were systematically collected and checked by trained interviewers. Completed responses were obtained from 96.7% of 29 538 eligible subjects, of whom 50.7% donated a blood sample. Questionnaire data were loaded into the HERPACC database and periodically linked with the hospital cancer registry system to update cancer incidence. All participants gave written informed consent and the study was approved by the Ethics Committee of Aichi Cancer Center.

Cases and controls

Cases were 718 patients (423 adenocarcinomas, 127 squamous cell carcinomas, 66 small cell carcinomas, 49 large cell carcinomas, 14 others and 2 unknown) histologically diagnosed with lung cancer between January 2001 and 2005 at Aichi Cancer Center Hospital with no prior history of any cancer. Control subjects were randomly selected from first-visit outpatients who visited our hospital during the same period. A total of 7054 individuals who completed the questionnaire and provided blood samples and were confirmed not to have cancer according to the cancer registry, medical record and self-report were deemed potential controls. Eventually, 1416 controls were frequency matched with case, age and sex. In previous studies, we assessed the clinical diagnosis among non-cancer outpatients and confirmed that there were almost no abnormal findings or non-specific diseases among them (15). We also confirmed the feasibility of using non-cancer outpatients at our hospital as controls in epidemiological studies on the basis that their general lifestyles were accordant with those of a general population randomly selected from the electoral roll in Nagoya City, Aichi Prefecture (16).

Genotyping of ALDH2

DNA of each subject was extracted from the buffy coat fraction using BioRobot EZ1 and an EZ1 DNA Blood 350 ml kit (Qiagen, Tokyo, Japan) or DNA Blood mini kit (Qiagen). Genotyping for the *ALDH2* Glu504Lys

Abbreviations: ALDH2, aldehyde dehydrogenase 2; HERPACC, Hospital-based Epidemiologic Research Program at Aichi Cancer Center; OR, odds ratio; PY, pack-years.

Table I. Characteristics of cases and controls

	Cases (n = 718), n (%)	Controls (n = 1416), n (%)	OR (95% CI)	P[a]
Age				
<40	20 (2.8)	40 (2.8)	—	
40–49	54 (7.5)	106 (7.5)	—	
50–59	196 (27.3)	390 (27.5)	—	
60–69	277 (38.6)	544 (38.4)	—	
70–79	171 (23.8)	336 (23.7)	—	1.000
Mean age ± SD	61.3 ± 10.0	61.8 ± 9.9		0.262
Sex				
Male	533 (74.2)	1054 (146.8)	—	
Female	185 (25.8)	362 (50.4)	—	0.920
Cumulative exposure to smoking (PY)				
0	176 (24.5)	575 (40.6)	1 (reference)	
<15	45 (6.3)	162 (11.4)	1.36 (0.91–2.04)	0.131
<30	75 (10.4)	204 (14.4)	2.07 (1.44–2.98)	8.6×10^{-5}
<45	131 (18.2)	205 (14.5)	3.82 (2.72–5.37)	1.36×10^{-14}
≥45	286 (39.8)	258 (18.2)	6.83 (4.98–9.36)	7.6×10^{-33}
Unknown	5 (0.7)	12 (0.8)		
Drinking habit				
Never	278 (38.7)	501 (35.4)	1 (reference)	
Former[b]	26 (3.6)	64 (4.5)	0.73 (0.45–1.19)	0.209
Current				
<5 g/day	60 (8.4)	174 (12.3)	0.63 (0.46–0.88)	0.007
<23 g/day	113 (15.7)	272 (19.2)	0.77 (0.58–1.01)	0.057
<46 g/day	94 (13.1)	192 (13.6)	0.91 (0.67–1.23)	0.528
≥46 g/day	132 (18.4)	191 (13.5)	1.29 (0.97–1.72)	0.080
Unknown	15 (2.1)	22 (1.6)		
Family history of lung cancer				
No	640 (89.1)	1289 (91.0)	1 (reference)	
Yes	78 (10.9)	127 (9.0)	1.23 (0.92–1.66)	0.169

CI, confidence interval.
[a]P-values were by chi-squared test or Mann–Whitney test for age and sex. Those for ORs were by Wald test.
[b]Former smokers and drinkers were defined as subjects who had quit smoking and drinking at least 1 year previously.

polymorphism (rs671) was based on TaqMan Assays (Applied Biosystems, Foster City, CA). In our laboratory, the quality of genotyping is routinely assessed statistically using the Hardy–Weinberg test and by retyping of a random sampling of 5% of subjects.

Assessment of alcohol intake and smoking exposure

Consumption of each type of beverage (Japanese 'sake', beer, 'shochu', whiskey and wine) was determined as the average number of drinks per day, which was then converted into a Japanese sake (rice wine) equivalent. One drink equates to one 'go' (180 ml) of Japanese sake, which contains 23 g of ethanol, equivalent to one large bottle (633 ml) of beer, two shots (57 ml) of whiskey and two and a half glasses of wine (200 ml). One drink of shochu (distilled spirit), which contains 25% ethanol, was rated as 108 ml. Total alcohol consumption was estimated as the summarized amount of pure alcohol consumption (g/day) of Japanese sake, beer, shochu, whiskey and wine among current regular drinkers. Cumulative smoking dose was evaluated as pack-years (PY), the product of the number of packs consumed per day and years of smoking.

Statistical analysis

To assess the strength of association between an *ALDH2* polymorphism and risk of lung cancer, odds ratios (ORs) with 95% confidence intervals were estimated using unconditional logistic models adjusted for potential confounders. Potential confounders considered in multivariate analysis were age, sex, smoking, drinking and family history of lung cancer with mutual adjustment of *ALDH2*. Smoking status was divided into five categories considering cumulative exposure to tobacco: 0, <15, <30, <45 or ≥45 PY. Alcohol exposure was also categorized into six levels: never-drinkers, former drinkers and current drinkers of <5, <23, <46 or ≥ 46 g/day. Differences in categorized demographic variables between cases and controls were tested by the chi-squared test. Mean values for age between cases and controls were compared by Student's t-test. Accordance with the Hardy–Weinberg equilibrium was checked for controls using the chi-squared test, and the exact P-value was used to assess any discrepancies between genotype and allele frequency. A P-value <0.05 was considered statistically significant. All analyses were performed using STATA version 10 (Stata Corp., College Station, TX).

Table II. Genotype distributions of *ALDH2* polymorphisms and their impact on the risk of lung cancer in recessive model

	ALDH2			P-value
	Glu/Glu	Glu/Lys	Lys/Lys	
Overall				
n (case–control)	322/688	326/605	70/123	
Model1[a]	1.00 (reference)		1.31 (0.95–1.81)	0.104
Model2[b]	1.00 (reference)		1.10 (0.77–1.57)	0.611

[a]Model 1 adjusted for age, sex and smoking (PY: 0, <15, <30, <45, ≥45 and unknown).
[b]Model 2 adjusted for model 1 with family history of lung cancer and drinking (never, former, current <5 g/d, current <23 g/d, current <46 g/d, current ≥46 g/d and unknown).

Results

Table I shows the distribution of cases and controls by background characteristics. Age and sex were balanced between cases and controls. Heavy smokers in terms of PY were significantly more prevalent among cases than controls (P < 0.001). ORs increased in dose-dependent manner and each of them showed high statistical significance. Drinking habit showed fluctuated association. Those who drank ≥46 g ethanol/day showed marginally increased risk of lung cancer, whereas those who drank <46 g ethanol per day or former drinker showed inverse association with variable statistical significance. No significant association was observed between positive family history and lung cancer risk.

Table II shows genotype distributions for *ALDH2* and its ORs and 95% confidence intervals for lung cancer risk. The frequencies of

Table III. Adjusted OR[a] and 95% CI for cumulative exposure to smoking according to *ALDH2* genotype

	PY										
	Ca/co	0	Ca/co	<15	Ca/co	<30	Ca/co	<45	Ca/co	≥45	*P*-trend
ALDH2											
Glu/Glu	81/285	1.00 (reference)	23/85	1.31 (0.74–2.32)	31/100	1.78 (1.03–3.08)	64/102	3.89 (2.35–6.46)	110/119	6.72 (4.16–10.8)	1.6×10^{-16}
Glu/Lys	80/226	1.00 (reference)	20/62	1.41 (0.76–2.63)	34/93	1.66 (0.97–2.85)	49/84	2.83 (1.67–4.78)	142/134	5.36 (3.35–8.59)	4.5×10^{-14}
Lys/Lys	15/64	1.00 (reference)	2/15	1.01 (0.18–5.64)	10/11	10.2 (2.42–43.1)	18/19	11.4 (3.09–42.0)	25/14	23.2 (6.23–86.5)	2.6×10^{-7}

Ca/co, cases/controls; CI, confidence interval.
[a]ORs adjusted for age, sex, family history of lung cancer, smoking (PY: 0, <15, <30, <45, ≥45 and unknown) and drinking (never, former, current <5 g/d, current <23 g/d, current <46 g/d, current ≥46 g/d and unknown).

polymorphisms were in accordance with the Hardy–Weinberg equilibrium. On analysis of lung cancer overall, no significant elevation of risk was observed by *ALDH2* genotype in per allele model. As shown in Table II, although the association was rather clear between *ALDH2* polymorphism and lung cancer, it was not statistically significant in model 1 adjusted for smoking and matching factors. Association between *ALDH2* Lys/Lys became far from significant if drinking habit was included in the model, indicating strong confounding by drinking and Lys/Lys genotype. Among controls, 117 of 123 (95.1%) were never-drinkers in those with Lys/Lys, whereas 29.5% were never-drinkers among Glu/Glu or Glu/Lys subjects. In addition, heavier smokers were significantly common in those with *ALDH2* Glu/Glu or Glu/Lys subjects (19.1%) compared with Lys/Lys subjects (11.4%).

Table III shows the effects of cumulative exposure to smoking on lung cancer risk by *ALDH2* genotype as adjusted ORs. For *ALDH2*, adjusted ORs showed a marked difference by genotype. The ORs for Glu/Glu and Glu/Lys showed similar point estimates, at 6.72 and 5.36 for PY ≥ 45 compared with PY = 0, respectively, with statistical significance. Interestingly, individuals with *ALDH2* Lys/Lys showed a significantly greater risk of lung cancer with increased exposure to smoking. The ORs for those with PY ≤ 45 in *ALDH2* Lys/Lys was 23.2 compared with PY = 0 ($P = 2.8 \times 10^{-6}$), indicating possible interaction between cumulative exposure to smoking and the *ALDH2* Lys/Lys genotype. In contrast, we did not see any interaction between alcohol drinking and *ALDH2* genotype (data not shown). We explored effect of *ALDH2* Lys/Lys according to cumulative exposure, duration and intensity as shown in Table IV. It also supports that *ALDH2* Lys/Lys has greater impact in those with heavier exposure.

Table V shows stratified analyses according to histology and drinking status. Based on the results in Tables II, III and IV, we dichotomized the *ALDH2* genotype as Glu/Glu + Glu/Lys and Lys/Lys. Overall, adjusted ORs among those with Glu/Glu or Glu/Lys for PY <15, <30, <45 and ≥45 relative to never smokers were 1.39, 1.80, 3.44 and 6.25, respectively (*P*-trend = 1.4×10^{-30}), versus 1.01, 10.2, 11.4 and 23.2, respectively, for those with Lys/Lys (*P*-trend = 2.6×10^{-7}). We observed a statistically significant interaction between *ALDH2* genotype (Glu/Glu + Glu/Lys versus Lys/Lys) and cumulative dose of smoking (interaction $P = 0.036$). By histologic type, significant interaction was observed in adenocarcinoma (interaction $P = 0.009$), but others were not evaluable owing to the limited number of low-exposure subjects. Interestingly, a significant interaction between the *ALDH2* Lys/Lys genotype and cumulative smoking dose was consistently observed in never-drinkers (interaction $P = 0.041$), indicating that the interaction might exist independent of drinking (Table V).

Table IV. Adjusted OR and 95% CI for *ALDH2* Lys/Lys relative to *ALDH2* Glu/Glu and Glu/Lys according to smoking exposure[a]

Cumulative exposure to smoking	Ca/co Glu/Glu + Glu/Lys	Ca/co Lys/Lys	Odds ratio[b]	*P*-value
Cumulative exposure to smoking				
0	161/511	15/64	0.73 (0.40–1.35)	0.316
<15	43/147	2/15	0.41 (0.09–1.91)	0.258
<30	65/193	10/11	3.51 (1.37–8.97)	0.009
<45	113/186	18/19	1.77 (0.87–3.60)	0.113
≥45	261/244	25/14	1.82 (0.91–3.64)	0.09
Years of smoking				
0	161/11	15/64	0.73 (0.40–1.35)	0.316
<20	37/150	3/18	0.77 (0.21–2.84)	0.699
<40	198/381	28/21	2.81 (1.51–5.20)	0.001
≥40	247/242	24/20	1.29 (0.69–2.44)	0.427
Intensity of smoking (pieces per day)				
0	162/511	15/64	0.73 (0.40–1.35)	0.316
<20	99/233	10/18	1.33 (0.58–3.03)	0.498
<40	278/393	38/33	2.06 (1.23–3.45)	0.006
≥40	107/147	7/8	1.02 (0.33–3.14)	0.966

Ca/co, cases/controls; CI, confidence interval.
[a]Subjects who were unknown for cumulative smoking were excluded from analyses.
[b]ORs adjusted for age, sex, family history of lung cancer, smoking (PY: 0, <15, <30, <45, ≥45 and unknown) and drinking (never, former, current <5 g/d, current <23 g/d, current <46 g/d, current ≥ 46 g/d and unknown).

Discussion

In this study, we found a significant gene–environment interaction between cumulative exposure to smoking and *ALDH2* Lys/Lys for the risk of lung cancer among a Japanese population. A significant interaction among never-drinkers only strongly suggests that this interaction was independent of drinking behavior. In contrast, we did not find an association between lung cancer and *ALDH2* polymorphism alone.

Given the strong evidence for gene–environment interaction between alcohol drinking and *ALDH2* polymorphism in aerodigestive tract cancers in Japanese populations (17–19), we were interested to examine the possible role of the functional genetic polymorphisms involved in acetaldehyde metabolism, *ALDH2* Glu504Lys, in lung cancer. To our knowledge, only a few studies have investigated the association between lung cancer and *ALDH2* polymorphism (20,21). Yokoyama *et al.* (20) reported that the *ALDH2* Lys allele was associated with an increased risk of lung cancer among Japanese alcoholics, albeit in a study population of only seven cases. Minegishi *et al.* examined the impact of *ALDH2* in combination with drinking habit in 505 cases and 256 unmatched controls, who were extensively screened as non-cancer by chest computed tomography, bronchofibroscopy and video-assisted thoracoscopic biopsy under suspicion of lung cancer. Results showed a highly significant increase in the risk of lung cancer by alcohol consumption in those with the *ALDH2* Lys allele. When adjusted for age, sex and alcohol consumption, however, risk for individuals with the *ALDH2* Lys allele in these studies was not further increased by smoking. In contrast, we saw no evidence of interaction between *ALDH2* genotype and drinking behavior, which does not support the previous studies. Interaction between alcohol drinking and *ALDH2* polymorphism in the risk of lung cancer therefore remains to be determined.

Table V. Adjusted OR[a] and 95% CI for the impact of smoking, *ALDH2* genotype and their interaction on lung cancer risk according to histrogical subtype and drinking status

	PY										
ALDH2	Ca/co	0	Ca/co	<15	Ca/co	<30	Ca/co	<45	Ca/co	≥45	*P*-interaction
Overall[b]											
Glu/Glu + Glu/Lys	161/511	1.00 (reference)	43/147	1.39 (0.92–1.05)	65/193	1.80 (1.23–2.12)	113/186	3.44 (2.41–4.97)	261/244	6.25 (4.49–8.70)	
Lys/Lys	15/64	1.00 (reference)	2/15	1.01 (0.18–5.64)	10/11	10.2 (2.42–43.1)	18/19	11.4 (3.09–42.0)	25/14	23.2 (6.23–86.5)	0.036
Histology											
Adenocarcinoma											
Glu/Glu + Glu/Lys	143/511	1.00 (reference)	27/147	0.95 (0.58–1.54)	42/193	1.36 (0.88–2.10)	55/186	1.95 (1.28–2.97)	107/244	3.04 (2.08–4.45)	
Lys/Lys	13/64	1.00 (reference)	2/15	1.19 (0.21–6.75)	7/11	7.71 (1.68–35.4)	10/19	7.00 (1.69–26.6)	13/14	13.6 (3.31–55.6)	0.009
Squamous/small cell carcinoma											
Glu/Glu + Glu/Lys	2/511	1.00 (reference)	7/147	14.9 (2.93–75.5)	18/193	27.5 (6.01–126.3)	40/186	63.9 (14.3–285.4)	111/244	129.8 (29.5–571.9)	
Lys/Lys	0/64	1.00 (reference)	0/15	NE	1/11	NE	4/19	NE	9/14	NE	NE
Drinking											
Never											
Glu/Glu + Glu/Lys	98/246	1.00 (reference)	13/17	2.77 (1.22–6.29)	19/39	2.14 (1.07–4.27)	21/31	3.15 (1.53–6.47)	57/47	6.00 (3.23–11.2)	
Lys/Lys	15/61	1.00 (reference)	2/14	0.96 (0.17–5.43)	10/11	9.17 (2.17–38.7)	18/19	10.1 (2.75–37.3)	23/12	22.2 (5.80–84.9)	0.041
Ever											
Glu/Glu + Glu/Lys	63/266	1.00 (reference)	30/130	1.21 (0.73–2.00)	46/154	1.71 (1.07–2.73)	92/155	3.44 (2.24–5.29)	204/197	6.20 (4.16–9.26)	
Lys/Lys	0/3	1.00 (reference)	0/1	NE	0/0	NE	0/0	NE	2/2	NE	NE

Ca/co, cases/controls; CI, confidence interval; NE, not estimated.

[a]Adjusted for age, sex and smoking (PY: 0, <15, <30, <45, ≥45 and unknown), family history of lung cancer and drinking (never, former, current <5 g/d, current <23 g/d, current <46 g/d, current ≥46 g/d and unknown).

[b]Five cases and 12 controls were excluded from analysis because of unknown PY status.

In addition to being a metabolite of alcohol, acetaldehyde is also a constituent of tobacco smoke (10,11,22). Our present results show that the influence of exposure to acetaldehyde in cigarettes on lung cancer risk, which might be surrogated by cumulative smoking exposure, is remarkably stronger in individuals with Lys/Lys, who cannot metabolize acetaldehyde well. The possibility that this finding was confounded by alcohol consumption can be excluded since statistical significance was adequately reflected on the interaction in never-drinkers. The hypothesis that increased acetaldehyde concentrations contribute to the development of lung cancer is possible because the *ALDH2* Lys/Lys genotype almost completely lacks acetaldehyde oxidation activity. Nevertheless, we cannot deny the possible presence of an unknown gene that is both linked to *ALDH2* polymorphism and at the same time relevant to the metabolism and detoxification of carcinogens in tobacco smoke, albeit that no such gene has been reported to date. It is thought that *ALDH2* itself has no power to directly detoxify carcinogenic compounds in tobacco other than acetaldehyde and that detoxification ability in Lys/Lys individuals might be poor. In any case, confirmation of this association and clarification of its background mechanism are essential.

We note that distribution of histology was different between *ALDH2* Lys/Lys and others. Among ever smokers without history of drinking, adenocarcinoma was significantly more prevalent in those with *ALDH2* Lys/Lys (70.5%) compared with other genotypes (51.7%). This may suggest that possible involvement of acetaldehyde from either sources, smoking or drinking, in adenocarcinoma.

Our study had several methodological strengths and weaknesses. One strength is that it was conducted in a single region in central Japan with a substantial number of subjects and a high response rate. Although controls were selected from non-cancer patients at Aichi Cancer Center Hospital, it is reasonable to assume the same base population as that from which the cases were selected, warranting internal validity. In terms of controls, we previously confirmed that questionnaire-based lifestyle characteristics in this population were similar to those of the general population in Nagoya City in terms of a range of exposures of interest in HERPACC-I (16) and HERPACC-II (H. Ito, K. Matsuo, M. Inoue, K. Tajima, unpublished data), warranting the study's external validity. In addition, the equivalence of genotype distribution for the *ALDH2* polymorphism between our controls and those in public databases and former studies (21,23) for Japanese indicates a lack of bias in the selection of controls, justifying the external validity of our observation. A second strength was that potential confounding by age and sex was addressed by matching of these factors in cases and controls, and smoking and drinking were adjusted in the models.

One weakness of our study was that it was unclear whether the cumulative dose of smoking reflected cumulative exposure to acetaldehyde. A second potential weakness was residual confounding by known or unknown risk factors; in particular, the limited number of cases, particularly in stratified analyses by genotype, indicates the need to replicate our findings in a larger study. A third potential weakness was the information bias intrinsic to case–control studies. The HERPACC system is less prone to this bias than typical hospital-based studies, however, as the data for most if not all patients were collected before diagnosis. In particular, subjects and investigators had no information about *ALDH2* genotype, limiting the impact of information bias in the analysis.

In conclusion, our case–control study showed that the *ALDH2* Lys/Lys genotype, which results in null enzyme activity, modified the impact of smoking on the risk of lung cancer in a Japanese population. This result suggests the possible contribution of acetaldehyde to the pathogenesis of lung cancer. Further replication study is warranted.

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Nonfilter and filter cigarette consumption and the incidence of lung cancer by histological type in Japan and the United States: analysis of 30-year data from population-based cancer registries

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Shifts in the histologic type of lung cancer accompanying changes in lung cancer incidence have been observed in Japan and the United States. We examined the association between the shift in tobacco design from nonfilter to filter cigarettes with changes in the incidence of adenocarcinoma (AD) and squamous cell carcinoma (SQ) of the lung. We compiled population-based incidence data from the Surveillance, Epidemiology and End Results in the United States (1973–2005) and from selected Japanese cancer registries (1975–2003). Trends in age-standardized rates of lung cancer incidence by histologic type were characterized using joinpoint analyses. A multiple regression framework was used to examine the relationship between tobacco use and incidence by histologic type. We observed that AD has replaced SQ as the most frequent histologic type in males and females in both Japan and the United States. Filter cigarette consumption was positively associated with the incidence of AD, with time lags of 25 and 15 years in Japan and the United States, respectively ($\hat{\beta}_2^{AD}$: 1.946×10^{-3}, $p < 0.001$ and 3.142×10^{-3}, $p < 0.001$). In contrast, nonfilter cigarette consumption was positively associated with the incidence of SQ, with time lags of 30 and 20 years in Japan and the United States, respectively ($\hat{\beta}_2^{SQ}$: 0.464×10^{-3}, $p = 0.006$ and 0.364×10^{-3}, $p = 0.008$). In conclusion, the shift from nonfilter to filter cigarettes appears to have merely altered the most frequent type of lung cancer, from SQ to AD.

Epidemiology

The association between cigarette smoking and lung cancer was firmly established in the 1950s.[1] The rapid increase in incidence rates in the 20th century has led to an epidemic of lung cancer, particularly among men in industrialized countries.[2,3] In the United States, where serious smoking control efforts were instituted almost 50 years ago, the incidence of lung cancer among men peaked in 1982 and began to decline thereafter,[4] but it continues to rise in countries where smoking control efforts have been less aggressive. In Japan, despite a continuous decline in smoking rates over the last 50 years, lung cancer incidence continues to rise.[4,5]

Lung cancer incidence patterns and trends vary by histological type[6] and have been shown to be related to smoking patterns and exposures to other lung risk factors.[3] Shifts in histologic type have been reported to accompany changes in lung cancer incidence. Relative and absolute increases in adenocarcinoma (AD) of the lung were first recognized in the 1970s[7] and continued to be observed in the United States[8,9] and European countries.[10] Although this trend has now peaked in the United States,[11,12] incidence appears to be still increasing in certain areas of Japan.[13–15]

Trends in the incidence of lung cancer by histologic type are of interest in the evaluation of the impact of changes in cigarette manufacture. In particular, although low-tar, low-nicotine, filtered cigarettes appear to have contributed to the overall decline in lung cancer, and most notably in squamous

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cell carcinoma (SQ),[16] they may have simultaneously increased the risk of certain peripheral tumors, such as AD,[17–20] and it has been hypothesized that the upward trend in the incidence of AD is mainly due to the dissemination of low-tar filtered cigarettes.[18–20] Smoke from low-yield filter-tipped cigarettes is inhaled more deeply than that from earlier unfiltered cigarettes.[21,22] Inhalation transports tobacco-specific carcinogens more distally toward the bronchioalveolar junction, where ADs often arise. The change in cigarette consumption from nonfiltered to filtered cigarettes also reduces the yield of carcinogenic polycyclic aromatic hydrocarbons, which are inducers of SQs, while simultaneously increasing that of carcinogenic tobacco-specific N-nitrosamines, which are inducers of ADs.[19]

Here, we investigated differences in the effects of nonfilter and filter cigarette consumption on changes in the incidence of SQ and AD in Japan and the United States.

Material and Methods

Lung cancer incidence data in Japan were obtained from nine of the 36 regional registries used to estimate nationwide incidence, namely Yamagata, Niigata, Fukui, Shiga, Osaka, Okayama, Saga, Nagasaki and Hiroshima City, which together account for about 18% of the Japanese population. For the United States, lung cancer incidence data were obtained from the Surveillance and End Results (SEER) program of the US National Cancer Institute, which makes aggregate data available to the public. The data cover about 10% of the US population in nine geographical regions, namely the states of Connecticut, Hawaii, Iowa, New Mexico and Utah, as well as the metropolitan areas of Atlanta (GA), Detroit (MI), San Francisco-Oakland (CA) and Seattle-Puget Sound (WA). We selected cases diagnosed with lung or bronchus cancer from 1973 through 2005 for the US data and from 1975 through 2003 for the Japanese data. Morphology codes indicating lung cancer cell type were grouped into eight major categories according to the WHO scheme[23]: (*i*) SQ (International Classification of Disease for Oncology version 3 (ICD-O-3) codes 8050–8078, 8083–8084); (*ii*) AD (8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8551, 8570–8574, 8576); (*iii*) small cell carcinoma (8041–8045, 8246); (*iv*) large cell carcinoma (including giant cell, clear cell and large cell undifferentiated carcinoma 8010–8012, 8014–8031, 8035, 8310); (*v*) other specified carcinoma; (*vi*) sarcoma (8800–8811, 8830, 8840–8921, 8990–8991, 9040–9044, 9120–9133, 9150, 9540–9581); (*vii*) other specified malignant neoplasm and (*viii*) unspecified malignant neoplasm (8000–8005). The percentages of cases with unspecified morphology in the United States and Japan differed by an order of magnitude: only 3.9% of the US cases had morphology codes of 8000–8005, indicating "unspecified malignant neoplasm," whereas 33.6% of case reports in Japan were coded 8000–8005. In accordance with Devesa *et al.*,[10] we proportionally allocated the cases with unspecified morphology 8 to the other seven categories on a registry-, year at diagnosis-, sex- and age-specific basis.

US age-standardized incidence rates (ASR) were calculated for the years 1973–2005 and Japanese ASR for the years 1975–2003, by major morphological type, namely SQ, AD and small cell carcinoma. Age standardization incorporated the Segi world standard.[24] All incidence rates were expressed as newly diagnosed cases of malignant neoplasm per 100,000 person-years.

The trends in ASR were also characterized by the widely used joinpoint regression analysis, as described in detail elsewhere.[25] Briefly, joinpoint regression is a statistical technique that describes changing trends over successive segments of time and the magnitude of an increase or decrease within each segment after identifying the best fitting model. Essentially, within each time segment, the log of the ASR is modeled as a linear function of time (calendar year), thereby yielding annual exponential rates of change in ASR. The technique identifies the timepoint(s), also referred to as joinpoint(s), at which there is a statistically significant change in the incidence trend. A maximum of three joinpoints in the model was allowed in the model fitting. The resulting trend segments, as delimited in time by joinpoints, were described by the annual percentage change (APC), that is, the slope of the line segment.[25] The calculation assumes that rates increase or decrease at a constant rate over time, although the validity of this assumption has not been tested. APC is calculated based on the following regression model:

$$\log(R_y) = b_0 + b_1 y$$

where $\log(R_y)$ is the natural log of the rate in year y

The APC from year y to $y+1$

$$= \left(\frac{R_{y+1} - R_y}{R_y}\right) \times 100$$

$$= \left(\frac{e^{b_0+b_1(y+1)} - e^{b_0+b_1(y)}}{e^{b_0+b_1(y)}}\right) \times 100$$

$$= \left(e^{b_1} - 1\right) \times 100$$

In describing the trends, the terms "increase" or "decrease" were used when the slope (APC) of the trend was statistically significant ($p < 0.05$); otherwise, the terms "stable" or "level" were used.

Data on cigarette consumption were based on the market share of nonfilter and filter cigarettes sale in each year. These data were obtained from the US Federal Trade Commission,[26] the Ministry of Health, Labour and Welfare, Japan,[27] the Ministry of Finance, Policy Research Institute, Japan,[28] Japan Tobacco and Salt Co. and the Tobacco Institute of Japan.

To assess whether the incidence rates of SQ and AD of the lung were correlated to annual nonfilter and filter cigarette consumption per capita, we used a multiple regression framework.[29] For a specific subpopulation (*i.e.*, Japanese), we let $Y^{AD}(t)$ represent the ASR (per 100,000 person-years) of AD at time t, and $Y^{AD}(t^+)$ represent the ASR of AD at one time point ahead of time t. For example:

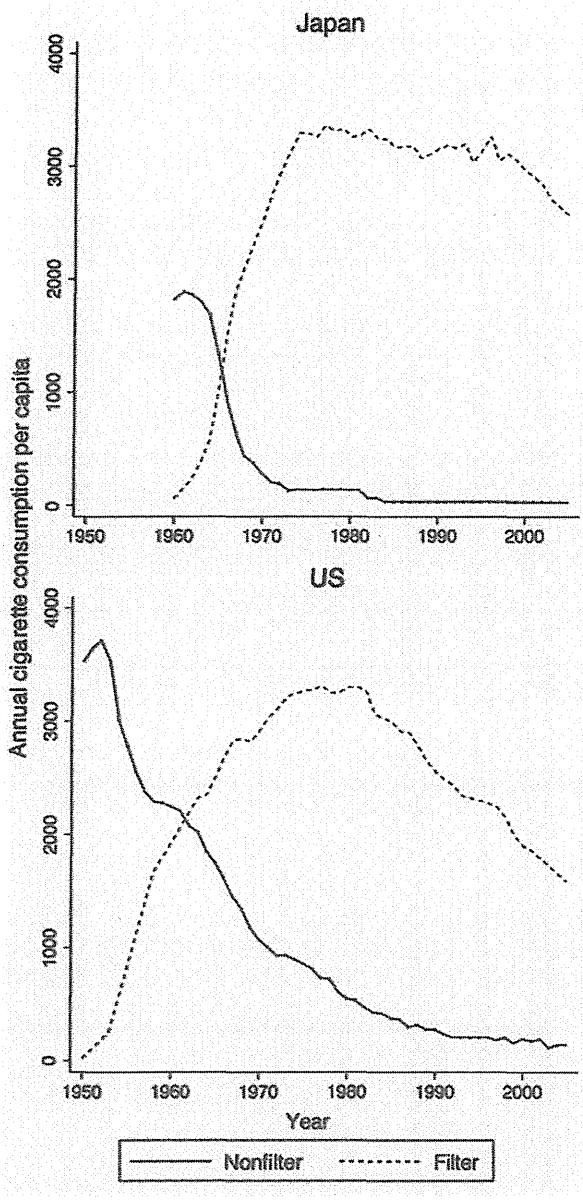

Figure 1. Japan and US nonfilter and filter cigarette consumption. Data for annual consumptions of nonfilter (solid line) and filter (dashed line) cigarettes per capita are presented. The shift from nonfilter to filter cigarettes occurred in the 1960s and the 1950s in Japan and the United States, respectively.

$$Y^{AD}(t) = [Y^{AD}(1), Y^{AD}(2), \ldots, Y^{AD}(T-1)]$$
$$Y^{AD}(t^{+}) = [Y^{AD}(2), Y^{AD}(3), \ldots, Y^{AD}(T)]$$

Likewise, we let $Y^{SQ}(t)$ represent the ASR (per 100,000 person-years) of SQ at time t and $Y^{SQ}(t^{+})$ represent the ASR of SQ at one time point ahead of time t. Additionally, we let

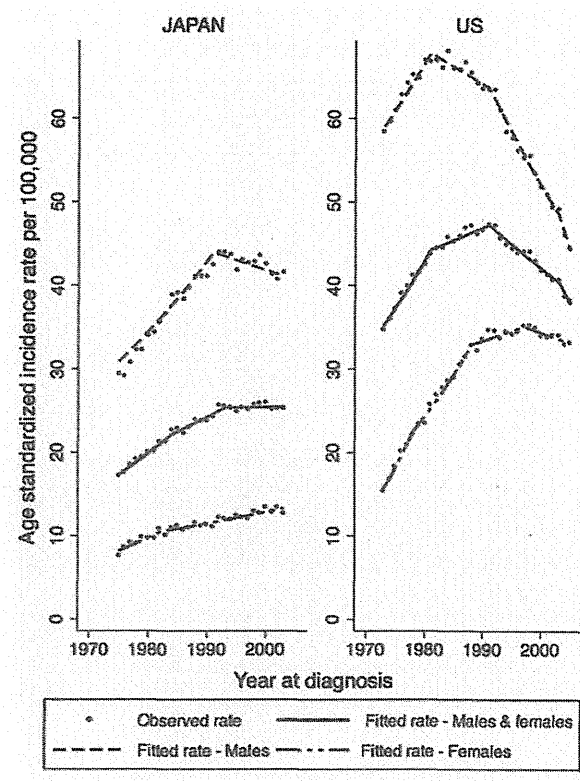

Figure 2. Joinpoint analysis of the overall age-standardized incidence rates (ASR) of lung cancer among individuals in Japan and the United States.

$X(t^{+} - \tau)$ represent the nonfilter or filter cigarette consumption at time $t^{+} - \tau$, where τ is the appropriate time lag. Thus, for each subpopulation, we have the following models:

$$Y^{SQ}(t^{+}) = \beta_0^{SQ} + \beta_1^{SQ} Y^{SQ}(t) + \beta_2^{SQ} X(t^{+} - \tau) + \varepsilon^{SQ} \quad (1)$$
$$Y^{AD}(t^{+}) = \beta_0^{AD} + \beta_1^{AD} Y^{AD}(t) + \beta_2^{AD} X(t^{+} - \tau) + \varepsilon^{AD} \quad (2)$$

We set τ from 5 to 30 years according to the epidemiological evidence: in this regard, because the incidence of lung cancer does not appear to be lower among ex-smokers who quit smoking within 5 years than current smokers,[30,31] the sum of the induction period and latent period of lung cancer caused by tobacco smoking is likely longer than 5 years.

We then examined the adjusted R^2 in the model with different time lags τ among subpopulations and cigarette designs to find the best fitting models (1) and (2) for nonfilter and filter cigarettes among Japanese and Americans. R^2 value was interpreted to mean that for every unit increase in annual nonfilter or filter consumption per capita, we expect a β_2 point increase in the ASR of AD or SQ, holding all other variables constant.

Table 1. Trends of overall age-standardized incidence rates of lung cancer with joinpoint analyses in Japan and the United States

	Trend 1		Trend 2			Trend 3		Trend 4
	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
Japan (1975–2003)								
Males & females	1975–1984	2.8† (2.0, 3.6)	1984–1993	1.5† (1.0–2.1)	1993–2003	0.0 (−0.3, 0.3)		
Males	1975–1992	2.2† (1.9, 2.5)	1992–2003	−0.6† (−0.9, −0.2)				
Females	1975–1982	3.6† (1.5, 5.8)	1982–2003	1.1† (0.9, 1.4)				
USA (1973–2005)								
Males & females	1973–1981	2.9† (2.4, 3.4)	1981–1991	0.7† (0.3, 1.0)	1991–2003	−1.3† (−1.5, −1.1)	2003–2005	−3.1† (−6.2, 0.0)
Males	1973–1981	1.8† (1.3, 2.2)	1981–1991	−0.6† (−1.0, -0.3)	1991–2003	−2.2† (−2.5, −2.0)	2003–2005	−4.5† (−8.0, 0.9)
Females	1973–1978	7.5† (5.6, 9.5)	1978–1988	3.9† (3.3, 4.4)	1988–1997	0.7† (0.2, 1.2)	1997–2005	−0.7† (−1.2, −0.3)

Source: SEER-9 areas covering about 10% of the US population (States of Connecticut, Hawaii, Iowa, Utah, and New Mexico, and the metropolitan areas of San Fransisco-Oakland, Detroit, Atlanta, and Seattle-Puget Sound), and Japanese nine areas covering about 10% of the Japanese population (Prefectures of Yamagata, Niigata, Fukui, Shiga, Osaka, Okayama, Saga and Nagasaki, Hiroshima City and Nagasaki City).

Joinpoint analyses with up to three joinpoints were based on rates (per 100,000 persons) and were age adjusted to the world population. Joinpoint analysis used the Joinpoint Regression Program, version 3.3. April 1, 2008, National Cancer Institute.

APC is based on rates that were age standardized to the world population.

†APC is statistically significantly different from zero (two-sided $p < 0.05$, calculated using a *t*-test.)Abbreviations: APC: annual percent change; CI: confidence interval.

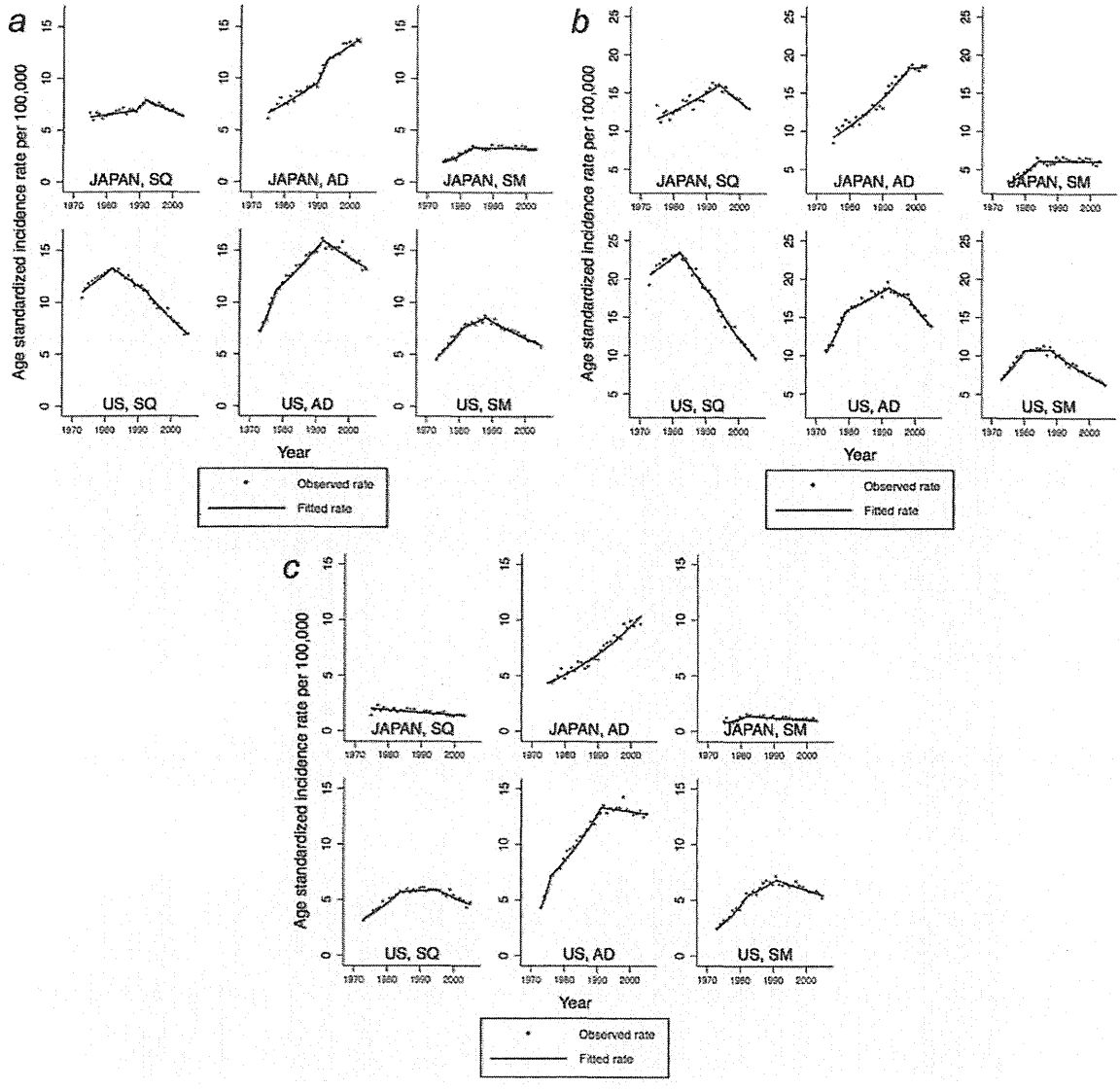

Figure 3. Joinpoint analysis of the age-standardized incidence rates (ASR) of lung cancer by histologic type among individuals in Japan and the United States. (*a*) Males and females combined Joinpoint analyses of the histology-specific ASR of lung cancer among individuals in Japan and in the United States are presented for (*a*) males and females combined, (*b*) males, (*c*) females. SQ, AD and SM indicate squamous cell carcinoma, adenocarcinoma and small cell carcinoma, respectively.

We used STATA version 10.1 (STATA Corporation, College Station, TX) for all analyses except the joinpoint regression analysis, for which we used the Joinpoint Regression Program version 3.3 (US National Cancer Institute, Bethesda, MD).

The Brown University Research Protections Office ruled that this study did not involve human subjects.

Results

Figure 1 illustrates temporal trends in annual nonfilter and filter cigarette consumption per capita in Japan and the United States. The sharp increase in filter cigarette consumption and sharp decrease in nonfilter consumption began in the 1960s and 1950s in the United States and Japan, respectively. Compared with the United States, the shift in consumption from nonfilter to filter cigarettes occurred more rapidly in Japan, with the share of filter cigarettes during this period rapidly reaching 99%. Further, the sharp increase in total consumption owed largely to increasing filter cigarette consumption. Filter cigarette consumption then generally continued to be flat until the late 1990s, when it began to

Table 2. Trends of age-standardized rates of lung cancer with joinpoint analyses by sex and histological group in Japan and the United States

	Trend 1		Trend 2		Trend 3		Trend 4	
Histology	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
Males & Females combined								
Japan (1975–2003)								
Squamous cell carcinoma	1975–1989	0.7† (0.2, 1.2)	1989–1992	4.4 (−3.3, 12.7)	1992–2003	−1.9† (−2.3, −1.4)		
Adenocarcinoma	1975–1990	2.4† (1.8, 3.0)	1990–1993	7.1 (−1.1, 15.9)	1993–2003	1.7† (1.1, 2.2)		
Small cell carcinoma	1975–1984	6.7† (4.2, 9.2)	1984–2003	0.2 (−0.6, 0.2)				
USA (1975–2003)								
Squamous cell carcinoma	1973–1982	2.1† (1.4, 2.8)	1982–1992	−1.7† (−2.4, −1.1)	1992–2005	−3.6† (−4.0, −3.2)		
Adenocarcinoma	1973–1978	9.4† (6.6, 12.3)	1978–1992	2.5† (2.4, 3.0)	1992–2005	−1.4† (−1.8, −1.0)		
Small cell carcinoma	1973–1981	6.4† (5.3, 7.6)	1981–1988	1.8† (0.4, 3.1)	1988–2005	−2.2† (−2.4, −1.9)		
Males								
Japan (1975–2003)								
Squamous cell carcinoma	1975–1994	1.7† (1.3, 2.1)	1994–2003	−2.4† (−3.1, −1.6)				
Adenocarcinoma	1975–1998	3.0† (2.7, 3.4)	1998–2003	0.2 (−1.6, 1.9)				
Small cell carcinoma	1975–1984	7.4† (4.4, 10.6)	1984–2003	−0.0 (−0.5, 0.5)				
USA (1973–2005)								
Squamous cell carcinoma	1973–1982	1.5† (0.7, 2.3)	1982–1992	−2.8† (−3.5, −2.1)	1992–2005	−4.5† (−4.9, −4.0)		
Adenocarcinoma	1973–1979	7.2† (5.7, 8.8)	1979–1992	1.4† (1.0, 1.8)	1992–1998	−1.3† (−2.6 – −0.0)	1998–2005	−3.3† (−4.1, −2.6)
Small cell carcinoma	1973–1980	6.2† (4.7, 7.7)	1980–1988	0.2 (−0.9, 1.3)	1988–2005	−3.1† (−3.4, −2.8)		
Females								
Japan (1975–2003)								
Squamous cell carcinoma	1975–2003	−1.4† (−1.8, −1.0)						
Adenocarcinoma	1975–2003	3.2† (2.9, 3.5)						

decrease. In the United States, filter cigarette consumption peaked in the late 1970s.

Figure 2 and Table 1 provide the long-term trends in overall lung cancer incidence in Japan and the United States using the joinpoint regression analyses. For males and females combined, while the peak incidence has already occurred in the United States, with a downward trend beginning in 1991, the incidence for Japanese continues to be flat, followed by an upward trend until 1993. While the peak incidence for Japanese males occurred in 1992, the incidence for Japanese females continues to increase. Rates among Japanese males decreased by 0.6% per year from 1992 to 2003, after increasing by 2.2% annually from 1975 to 1992, and rates among Japanese females increased by 3.6% annually from 1975 to 1982 and by 1.1% after 1982. In the United States, peak incidence has already occurred in females in 1988, 7 years later than that in males. Among American males, rates decreased by 0.6% per year from 1981 to 1991 and by 2.2% per year from 1991 to 2005, after increasing by 1.8% annually from 1973 to 1978.

Figure 3 illustrates temporal patterns in ASR for selected histological types of lung cancer in Japan and the United States. For males and females combined (Fig. 3*a*), the peak incidence of SQ in Japanese occurred in 1992, 10 years later than that in the United States. In the United States, the rate of decline in SQ incidence significantly increased after 1992. While the incidence of AD continues to increase in Japan, peak incidence has already occurred in Americans, with a downward trend beginning in 1992. The incidence of AD in Japanese and Americans overtook the incidence of SQ in 1984 and 1976, respectively. For males (Fig. 3*b*), the peak incidence of SQs has already occurred in Japanese, with a downward trend beginning in 1994, 12 years later than that in the United States. While the incidence of AD for Japanese males leveled in 1998 after an upward trend, the peak incidence occurred in the US males, with a downward trend beginning in 1992. For females, the trends of SQ and AD in Japanese are different to those in Americans (Fig. 3*c*). In Japanese, the incidence for SQ continues to decrease and that for AD continues to increase. In contract, the peak incidences of SQ and AD have already occurred in 1982 and 1991 in the United States, respectively.

Table 2 provides the long-term trends in different histological groups of lung cancer incidence using the joinpoint regression analyses. For SQ, rates among Japanese increased by 0.7% annually from 1975 to 1989, were stable from 1989 to 1992, and then decreased by 1.9% from 1992 to 2003. Among Americans, rates increased by 2.1% annually from 1973 to 1982, then decreased by 1.7% from 1982 to 1992 and by 3.6% from 1992 to 2005. For AD, rates among Japanese increased by 2.4% annually from 1975 to 1990, were stable from 1990 to 1993 and then increased by 1.7% from 1993 to 2003. In contrast, rates among Americans increased by 9.4% annually from 1973 to 1978 and by 2.5% from 1978 to 1992 and then decreased by 2.2% from 1992 to 2005. In Japan,

Table 2. Trends of age-standardized rates of lung cancer with joinpoint analyses by sex and histological group in Japan and the United States (Continued)

	Trend 1		Trend 2		Trend 3		Trend 4	
Histology	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
Small cell carcinoma	1975–1982	8.7† (2.0, 15.7)	1982–2003	−1.6† (−2.3, −0.9)				
USA (1973–2005)								
Suamous cell carcinoma	1973–1984	5.3† (4.2, 6.3)	1984–1995	0.2 (−0.6, 1.1)	1995–2005	−2.5† (−3.3, −1.7)		
Adenocarcinoma	1973–1976	19.1† (9.5, 29.5)	1976–1991	4.2† (3.7, 4.7)	1991–2005	−0.3 (−0.7, 0.1)		
Small cell carcinoma	1973–1982	9.0† (7.2, 10.9)	1982–1991	2.7† (1.3, 4.1)	1991–2005	−1.6† (−2.1, 1.1)		

Source: SEER-9 areas covering about 10% of the US population (States of Connecticut, Hawaii, Iowa, Utah, and New Mexico, and the metropolitan areas of San Fransisco-Oakland, Detroit, Atlanta, and Seattle-Puget Sound), and Japanese nine areas covering about 10% of the Japanese population (Prefectures of Yamagata, Niigata, Fukui, Shiga, Osaka, Okayama, Saga and Nagasaki, Hiroshima City and Nagasaki City).
Joinpoint analyses with up to three joinpoints were based on rates (per 100,000 persons) and were age adjusted to the world population. Joinpoint analysis used the Joinpoint Regression Program, version 3.3.April 1, 2008, National Cancer Institute.
APC is based on rates that were age standardized to the world population.
†APC is statistically significantly different from zero (two-sided $p < 0.05$, calculated using a *t*-test.)
Abbreviations: APC: annual percent change; CI: confidence interval.

Table 3. The relationship between cigarette consumption and lung cancer incidence by histologic type in Japan and the United States

	SQ			AD		
Type of cigarette	Lag time τ*	$\hat{\beta}_2^{SQ}$ ($\times 10^{-3}$)†	95% CI ($\times 10^{-3}$)	Lag time τ*	$\hat{\beta}_2^{AD}$ ($\times 10^{-3}$)†	95% CI ($\times 10^{-3}$)
Japan						
Nonfilter	30	0.464‡	(0.164, 0.764)	24	−1.099‡	(−1.767 to −0.431)
Filter	30	−0.340‡	(−0.518, −0.162)	25	1.946‡	(1.297–2.594)
United States						
Nonfilter	20	0.455‡	(0.319, 0.591)	17	0.353	(−0.020 to 0.757)
Filter	25	−0.268‡	(−0.383–0.152)	15	3.183‡	(1.955–4.411)

*τ is defined as the lag between lung cancer incidence and cigarette consumption; CI, confidence interval. †β_2 is the coefficient for cigarette consumption in the model of $Y(t^+) = \beta_0 + \beta_1 Y(t) + \beta_2 X(t^+ - \tau) + \varepsilon$ ‡Statistically significantly different from zero (two-sided $p < 0.05$, calculated using a *t*-test).

rates for small cell carcinoma increased by 6.7% annually from 1975 to 1984, then leveled off thereafter. In contrast, rates in the United States increased by 6.4% annually from 1973 to 1981 and by 1.8% from 1981 to 1988, and then began to decrease thereafter.

Because sex-specific data on cigarette consumption by cigarette design were not available on public, we examined the relationship between cigarette consumption and lung cancer incidence by histologic type in males and females combined. Table 3 summarizes the statistical relationship between them using multiple regression analyses. The models in Table 3 did not violate assumptions of normality and uncorrelatedness. Among Japanese, the trend in nonfilter consumption was positively associated with the incidence of SQ ($\hat{\beta}_2^{SQ}$, 0.464×10^{-3}, 95% confidence interval (CI), [0.164×10^{-3}, 0.764×10^{-3}], $p = 0.006$) with the appropriate time lag of 30 years, and the trend in filter cigarette consumption was positively associated with AD incidence ($\hat{\beta}_2^{AD}$, 1.946×10^{-3}, 95%CI, [1.297×10^{-3}, 2.594×10^{-3}], $p < 0.001$) with the appropriate time lag of 25 years. Similarly, among Americans, the trend in nonfilter consumption was positively associated with SQ incidence ($\hat{\beta}_2^{SQ}$, 0.364×10^{-3}, 95%CI, [0.109×10^{-3}, 0.619×10^{-3}], $p = 0.008$) with the appropriate time lag of 20 years, while the trend in filter consumption was positively associated with AD incidence ($\hat{\beta}_2^{AD}$, 3.142×10^{-3}, 95%CI, [1.923×10^{-3}, 4.361×10^{-3}], $p < 0.001$) with the appropriate time lag of 15 years. The negative association between trends in nonfilter cigarette consumption and AD and between trends in filter consumption and SQ among Japanese and Americans reflect the shift in market share from nonfilter to filter cigarettes.

Discussion

AD has replaced SQ as the most frequent histologic type of lung cancer in both Japan and the United States. This increase in AD incidence in both the countries is also associated with the introduction of filtered cigarettes and the substantial increase in filter cigarette consumption. The decrease in nonfilter cigarette consumption due to the shift in market share from nonfilter to filter cigarette is associated with the decrease in the incidence of SQ. To our knowledge, these empirical observations, using population-based data from two distinct countries, are the first to support the long-held hypothesis that smoking filtered *vs.* nonfiltered cigarettes leads to separate presentations of lung cancer. These results are consistent with previous epidemiological study obtained using data at the individual level.[32–34]

Another possible explanation for the change in trends for AD of the lung is changes in exposure to air pollution. Long-term exposure to some components of polluted air, particularly NO*x*, might play a role in the development of AD.[12] Given that air pollution can be considered a general phenomenon, this possibility is not contradicted by the similarity in trends in AD incidence in US males and females but is contradicted by the difference in gender-specific trends in Japanese males and females. In addition, compared with current smokers, the lung cancer rate is very low among never smokers.[35] A prospective cohort study in Norway suggested that although air pollution is one of the causes of lung cancer, it may still much less than cigarette smoking that causes lung cancer.[36,37] A second possible explanation for this AD trend might be related to underlying trends in exposure to environmental tobacco smoke (ETS). Recent regulations have strictly reduced ETS exposure in the United States.[38] The consequent decrease in exposure to ETS might explain the recent decrease in incidence of ADs of the lung in the United States, at least, in part. Although this point should be examined in the future with more detailed exposure and outcome evaluation, it is clear that ETS has much less impact on the risk than active smoking.

Reflecting the wide-scale adoption of filter cigarettes beginning in the 1960s, the United States observed a sharp increase in ADs in the early 1970s, with 9.4% increases annually from 1973 to 1979. Interestingly, although filter cigarettes penetrated the Japanese market more rapidly in the 1970s, the increase in ADs in Japan has not been as sharp as in the United States. There are two explanations for this. First, the greater use of charcoal-containing cigarette filters in Japan (70 *vs.* 1% in the United States) may have had a beneficial effect, perhaps by trapping a greater load of fine particulates

than other filters or by removing a greater load of volatile toxic agents, such as hydrogen cyanide, N-nitrosamines and volatile aldehydes known to act as inhibitors of lung clearance.[19] In this regard, Muscat *et al.* found no association between charcoal filters and an attenuated risk of lung cancer in a Japanese population.[39] Second, it is of course also possible that the differences between the Japanese and US experience may have been affected by the assumptions used in allocating specific morphologies to cases of unknown morphology. Additional analyses focused on this issue may clarify the observed differences.

It is considered paradoxical that a proportion of Japanese who smoke is higher than American males but have a lower incidence of lung cancer.[19] Several factors acting either alone or in combination may explain this lower rate in Japan,[19,40] including age at onset of cigarette smoking, specific personal smoking (*i.e.*, manner of smoking, particularly shallow inhalation), and the contents and construction of cigarettes. Despite the higher smoking prevalence in Japan, total cigarette consumption per capita was lower than in the United States until 1987, suggesting that Japanese smokers smoked fewer cigarettes per day than their American counterparts. Other differences may explain the lower lung cancer rates in Japan: *e.g.*, because consumption of filter cigarettes increased rapidly around the same time that smoking became popular in Japan, Japanese smokers were less exposed to unfiltered cigarettes. Additionally, the Japanese diet may have a protective effect against lung cancer, owing to its relatively high consumption of soybeans,[41,42] which contain the strong tumor inhibitor genistein, and fish[41] and relatively low intake of dietary fat.[43] Frequent consumption of green tea[44] may also have a protective effect. Finally, Americans may have a greater genetic susceptibility to tobacco carcinogens than Japanese. In this regard, the lower relative risks by smoking in epidemiological studies conducted in Japan *versus* the United States is well known.[19,45] In this study, we found a shorter lag time of τ in Americans than in Japanese, which represents the shorter sum of induction and latent period in Americans than in Japanese (*e.g.*, lag times for AD after the advent of filter cigarettes were 25 years in Japan *vs.* 15 years in the United States). This might be a reflection of a difference in patterns of smoking behavior, life styles and susceptibility to lung cancer between Japan and the United States.

Our findings suggest that the trends of incidence of lung cancer by histologic type differ in males and females as well as the associations between changes in the incidences and in filter/nonfilter cigarettes differ among males and females, in both Japan and in the United States. That may be due to the differences in patterns of smoking behavior and the susceptibility to lung cancer in cigarette smokers among males and females. Smoking rate is significantly lower for females than for males in both the countries (11.0 and 39.4% in males and females in Japan, respectively, and 17.4 and 23.4% in the United States).[27,46] Females were more likely than men to smoke filter cigarettes (89.0–90.6% *vs.* 75.0–79.3% in the 1970s,[47,48] and 92.9–94.6% *vs.* 87.0–90% in the 1980s). Females with lung cancer are more likely to be never smokers or less intense smoking history, and have AD subtypes.[49] Therefore, the sex-specific analysis for cigarette types and incidence patterns by histology subtype would sharpen the findings. However, unfortunately, the data on filter/nonfilter cigarette consumption are not available both in Japan and the United States so that we could not analyze the sex specific relationships between the trend in lung cancer incidence by histologic type and consumptions of filter or nonfilter cigarettes. Therefore, the analyses in males and females combined may weaken a true relationship between the increased trend in AD and filter cigarette consumption. Nevertheless, we could obtain the statistically significant relationship between them using the data for males and females combined.

Molecular examinations of lung cancer might give us an insight to interpret different patterns of change in histology-specific incidence by sex and ethnicities discussed above. It has been reported that epidermal growth factor receptor (*EGFR*) mutations commonly present in female, never-smoker and Asian ethnicity.[50] Potential differences in several risk factors including smoking by *EGFR* mutational status have been reported to date.[51,52]

Several limitations of this study warrant mention. First, as an ecological study, it possesses all the limitations inherent to ecological analyses. Aggregate data on exposure and disease—data obtained from population aggregates—cannot be linked to individuals. Although estimated consumption of cigarettes was based on nationally averaged levels for the respective countries, consumption may in fact vary by area (rural *vs.* metropolitan), race/ethnicity, sex, age and education. The increased consumption of filter cigarettes may have played different roles in the increase in AD incidence in males and females, but the present data lacked the sensitivity to detect changes at this level. Second, the data collected from Japanese prefectural population-based cancer registries have major quality issues and fail to meet international data quality standards for the proportion of death-certificate-only cases, incidence-to-mortality ratio and proportion of histologically verified cases.[53] Based on mathematical modeling, true incidence may be underestimated by as much as 20%.[54] Moreover, because one-third of the Japanese cases in this study were of unknown morphology, the data may not adequately reflect the true changes in lung cancer incidence by histologic type. Nevertheless, we do not consider that our allocation methodology biased the results, and reanalysis of the data without the proportional reallocation of cases with unspecified morphology returned virtually identical results. Finally, another limitation may be change over time in the definition of AD[55] or in diagnostic practice,[56] although we consider that these themselves cannot account for the increase in AD incidence. For example, major diagnostic advances such as bronchoscopy, thin-needle aspiration, computed tomography scans

and improved stains for mucin were all introduced in the 1980s,[56] after the increases in the incidence of AD were observed.

While the decreased incidence of SQ among Japanese and Americans is encouraging in terms of cancer prevention and control, it is counterbalanced by the increases in AD, especially among Japanese. As realization of the detrimental health effects of cigarette smoking initially grew, the tobacco industry strove to develop filtered cigarettes as less harmful cigarettes, but subsequent scientific evidence has failed to demonstrate any benefit from changes in cigarette design or manufacturing.[57] Despite the tobacco industry became well aware of the fact that filtered cigarettes were not less harmful, it has been advertised filtered or low-tar cigarettes to intend to reassure smokers and were meant to prevent smokers form quitting since the early 1950s in the United States[58] and later in Japan.[59] The false reassurances provided by marketing strategies of filtered/low-tar cigarettes might be related to the rising incidence of ADs of the lung.

The present results suggest that the shift from nonfilter to filter cigarettes may have had the result of replacing one cancer type with another. These findings emphasize the importance of tobacco control programs, namely programs that prevent the initiation of smoking, hasten the rate of smoking cessation or limit exposure to ETS, have been associated with a decrease in both cigarette consumption and smoking rates, and subsequently with a decrease in lung cancer incidence.[4,60]

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