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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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