Cancer Causes and Control **12**: 289–300, 2001.

The heterogeneity in risk factors of lung cancer and the difference of histologic distribution between genders in Taiwan

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Received 6 September 2000; accepted in revised form 12 January 2001

Key words: fume extractor, histologic type, lung neoplasm, risk factors, tobacco smoke pollution.

Abstract

Objective: The difference in histologic patterns of lung cancer between men and women in Taiwan may be associated with the heterogeneity in causal factors of lung cancer between the sexes. A sex- and age-matched case–control study was designed to investigate such a relationship.
Methods: Cases consisted of 236 male and 291 female incident cases with newly diagnosed and histologically confirmed primary carcinoma of the lung, and were compared to one or two individually matched controls.
Results: Cigarette smoking, occupations, and previous tuberculosis history were found to independently correlate with an elevated risk of squamous/small cell carcinoma and adenocarcinoma for male patients. However, there was little difference in the effect of these risk factors except smoking. The use of fume extractors in the kitchen, and the habit of waiting to fry after the fumes were emitted, separately explained the majority of the attributable fraction of female squamous/small cell carcinoma (28.2%) and adenocarcinoma (47.7%). With the exception of a kitchen with fume extractors and a clinical history of tuberculosis, the environmental causal factors of lung cancer were heterogeneous between these two histologic cell groups.
Conclusions: Our results suggested that the causal factors of lung cancer might be specific for the type of tumor concerned. The gender-specific risk factors of lung cancer could partly explain the difference in cell-type distribution between men and women.

Introduction

Lung cancer has been the leading cause of cancer mortality for females, and the second leading cause for males, in Taiwan since 1986. From 1992 to 1996, the age-adjusted average mortality rate of lung cancer in Taiwan was 30.3 and 13.0 per 100,000 among men and women, respectively [1]. Although the age-adjusted mortality rate in men was not particularly high, the comparable rate in women ranked among the highest in the world [2]. Smoking is well established as the major causal risk factor in lung cancer occurrence. While studies in Taiwan have shown that 86% of the male lung cancer patients had a history of cigarette smoking, the proportion of smoking history, however, is about 9–10% among female patients [3]. Smoking behavior cannot fully explain the differences in epidemiologic characteristics of lung cancer between men and women in Taiwan.

Recent epidemiologic studies demonstrated that risk factors of lung cancer differ according to histologic

types [4–13]. Of the major risk factors for lung cancer, cigarette smoking was found to be strongly associated with squamous cell and small cell carcinoma, but less strongly with adenocarcinoma [4, 5]. Some studies indicated that saturated fat intake [6, 7], familial tumor history [8], previous lung diseases [9], specific occupational exposure [10], cooking practices [11], and genetic susceptibility [12, 13] are correlated with an elevated risk of adenocarcinoma of the lung. For lung cancer patients with strong smoking-related cell types, cigarette smoking accounted for a major proportion of lung cancer. In contrast, for patients with weak smoking-related histologic types of lung cancer, factors other than smoking were important. Therefore, the analytical studies should take histologic types into account when exploring and assessing risk factors of lung cancer.

In the general population in Taiwan, the prevalence rate of smoking for women aged over 16 years (3–4%) was significantly lower than that for men (55–62%) [14, 15], and the cell type distribution of lung cancer differed notably across genders. According to annual reports from the national cancer registry in Taiwan, squamous cell carcinoma was the most common type of lung cancer in men (42–45%), but for women the most common type was adenocarcinoma (54–63%) [16]. We suspected that the risk factors of lung cancer between the genders, as well as between histologic types, were heterogeneous. To test our hypothesis, we conducted a hospital-based case–control study to evaluate the heterogeneity of lung cancer among Taiwanese male and female patients.

Materials and methods

Cases and controls

The study population consisted of residents of the greater Kaohsiung area in tropical southern Taiwan, which includes a city and some suburban and rural communities. Kaohsiung is a highly industrialized city covering approximately 153 km^2 with a population density as high as 9185 persons/km^2 in 1996.

The cases in the original study were collected from Kaohsiung Medical University Hospital, which is a highly regarded teaching hospital in southern Taiwan, and is accessible to patients from all socioeconomic groups. Patients who were eligible for the case group included those aged 18–83 years, newly hospitalized in the chest or oncology department for primary carcinoma of the lung (*International Classification of Disease*, Ninth Revision code 162), and histologically confirmed by pathologists during 1993 and 1999 (the recruitment of male patients was stopped in 1996, due to insufficient research funding). All cancer diagnoses were reviewed by pathologists according to the World Health Organization lung carcinoma classification [17]. Of the 574 lung cancer patients, 527 (91.8%; 236 male and 291 female patients) with complete information were selected for our study case group. Among male cases, 87 (36.9%) were adenocarcinoma, 75 (31.8%) were squamous cell carcinoma, 32 (13.6%) were small cell carcinoma, seven (3.0%) were large cell carcinoma, eight (3.4%) were bronchioloalveolar cell carcinoma, and 27 (11.4%) were microscopically verified but not classified carcinoma. For female patients, the distribution was 162 (55.7%), 59 (20.3%), 25 (8.6%), six (2.1%), 16 (5.5%), and 23 (7.9%), respectively.

The controls were ascertained from the same geographic areas as the cases. They were selected from hospitalized patients at the same hospital with conditions unrelated to tobacco use, including patients with eye problems (cataract and glaucoma), bone fractures, and those undergoing physical checkups. The first and/or second eligible controls were selected within 3 weeks after a case was identified and matched on sex and age (within 2 years). Of the 883 matched controls, 805 (91.2%) agreed to be interviewed. Among them, 61.6% had eye problems, 23.1% had bone fractures, and 15.3% were having physical checkups.

Interviews

A structured questionnaire was completed for each case and control patient in a face-to-face interview by two trained interviewers. The questionnaire was designed to collect information on demographic characteristics, smoking history, environmental tobacco smoke, occupations, lifetime residence, history of lung diseases, dietary factors, air pollution inside the home, cooking practice and conditions, and other risk factors. A field supervisor checked all completed questionnaires and relevant medical abstracts, which were then transferred to coding sheets for computer analyses.

Data specification

Ever-smokers were defined as patients who had smoked one cigarette or more per day for at least 1 year. Among them, current smokers were those who had smoked within the past year, and ex-smokers were those who had stopped smoking at least 1 year before diagnosis. For all ever-smokers a detailed history of smoking habit was recorded, including daily consumption, age of commencement, duration of smoking, depth of inhalation, and, for ex-smokers, years since giving up the habit.

To assess passive smoking, the interviewers asked each patient about lifetime exposure to environmental tobacco smoke generated by parents, spouse, cohabitants, or coworkers. Anyone who lived or worked with a smoker and was near-distantly exposed to tobacco smoke (measured by identifying smokers whether habitually smoked in the subject's presence), was considered to be a passive smoker. Previous contractions of lung diseases including chronic bronchitis, tuberculosis, emphysema, and asthma were separately collected. The history of each lung disease was confirmed by a chest physician at least 3 years prior to the diagnosis of lung cancer. Occupational history involved a lifetime list of jobs that were held for at least 1 year at a time, and a person's lifetime occupation was taken to be the job that person held the longest. According to occupational exposure to airborne contaminants, each main job was classified into one of six categories: administration, hazardous industrial, transportation, farmer, chef, and others. Of those, the hazardous industries, including asbestos processing industries, iron foundries, and petrochemical industries, were combined due to the small numbers of industry-specific samples. Daily dietary habits were assessed by measuring the frequency and quantity of consumption of 12 food items, among which meat, vegetables, fruits, smoked food, pickles, and various items were separately recorded. The longest residence area where the subject had lived for at least 5 years was considered the main residence. If this was within 1 km of a major industrial complex, the interviewee was classified as living adjacent to an industrial district. Information on other air pollution factors inside the house, such as Taiwanese incense and mosquito coils, was also collected. Detailed information included the type of materials used, duration and frequency of burning incense and mosquito coils, and the patient's age at the time of exposure. Furthermore, information was collected through each subject who had to cook for his/her family regarding the types of cooking practices, cooking fuels, cooking oils, personal cooking preferences, size of window opening to the outside, and the use of fume extractors in the home kitchen. According to Taiwanese traditional cooking concepts, quick frying, when cooking oils have been heated up to reach high temperatures, could keep food as fresh as possible. Hence, for each cooking practice (stir frying, frying, and deep frying), we also measured the cooking frequencies and identified cooking habits that subjects regularly practiced, such as whether or not they waited to cook the food until the fumes were emitted from cooking oils. All information on cooking practices or conditions was collected according to the subject's main cooking period (20–40 years of age), when he/she spent the longest time in the kitchen.

Statistical analyses

Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for lung cancer risk of various factors by using conditional logistic regression analyses. Dose–response ORs were calculated by categorizing exposure variables and treating scored variables as continuous. All analyses were separately conducted for male and female patients who were diagnosed squamous cell or small cell carcinoma (strongly smoking-related tumors), and adenocarcinoma (weakly smoking-related tumors). The excluded tumor types (large cell, bronchioloalveolar cell, and unclassified carcinoma) were small samples and hence could not provide any meaningful information. In order to enhance the validity of risk estimation, all calculations of ORs for men and for women were adjusted for residence area (urban, suburban, rural), educational levels (no formal education, 1–9 years, ≥10 years), socioeconomic status (high, medium, low) and smoking (cumulative pack-years). On the other hand, the exposure effect across tumor types and gender was examined by the Mantel–Haenszel χ^2-test for homogeneity of ORs, and the strength of heterogeneity in ORs between squamous/small cell carcinoma and adenocarcinoma for both sex groups was expressed as ORs [18, 19]. In this analytical procedure, age (the matched variable) was classified as five levels of categorical variable and was considered as a controlling variable because this test was designed for unmatched data. We also evaluated interactive effects of any suspected risk factors by assuming an additive interaction relationship. The synergism index (SI) proposed by Rothman and its 95% CI were computed to assess the empirical deviation from the additive interaction relationship [20]. Otherwise, the proportion of lung cancer cases attributable to one or all risk factors considered (population-attributable risk percent; PAR%) was calculated according to Bruzzi *et al.*'s method [21].

Results

The average age of male lung cancer patients (62.3 ± 9.6 years) was somewhat higher than that of female lung cancer patients (60.6 ± 13.3 years), yet the age patterns of the two case groups were similar. Although most of the male and female patients suffered from adenocarcinoma (36.9% and 55.7% for male and female patients, respectively), the tumor type distribution of squamous/small cell carcinoma and adenocarcinoma of the lung between genders was significantly different ($p < 0.05$).

The demographic distributions of cases and controls were compared by six characteristics (residential area, marital status, religion, ethnicity, years of education, and socioeconomic status) for two tumor groups (squamous/small cell carcinoma and adenocarcinoma) of lung cancer in both sex groups. There was no statistical difference in demographic data between cases and controls. The demographic similarity of the three sources of controls (*i.e.*, patients with eye problems, bone fractures and having a physical checkup) was also examined both for male and female patients, but no substantial differences were detected.

Characteristics of smoking history were examined in male case–control pairs because of the suggestive differences between the patterns for squamous/small cell carcinoma and adenocarcinoma in the literature. Risk for squamous/small cell carcinoma in current smokers was 5.8-fold (OR = 5.6 and OR = 6.5 for squamous and small cell carcinoma, respectively) higher than that for nonsmokers, but only a 2.2-fold increase was observed in adenocarcinoma (Table 1). Smoking patients with squamous/small cell carcinoma consistently had a higher cancer risk (OR = 2.4–5.6) at each exposure level of smoking duration and intensity measures than those who

Table 1. Odds ratios of squamous/small cell carcinoma and adenocarcinoma of the lung associated with cigarette smoking among men, Taiwan

Smoking factors	SQ + SC[a]		AD[a]		OR ratio[c]
	Cases/controls	OR[b] (95% CI)	Cases/controls	OR[b] (95% CI)	
Never-smoked[d]	17/65	1.0	25/54	1.0	
Ex-smoker	20/32	2.1 (0.9–5.0)	19/24	1.9 (0.8–4.5)	
Current smoker	70/51	5.8 (2.8–12.1)	43/43	2.2 (1.1–4.3)	
Dose–response		2.4 (1.7–3.5)		1.5 (1.0–2.1)	1.6[e]
Age first smoked (years)					
≥21	34/33	4.0 (1.8–8.8)	22/30	1.6 (0.7–3.3)	
12–20	56/50	4.3 (2.1–8.8)	40/37	2.8 (1.3–5.9)	
Dose–response		2.0 (1.4–2.8)		1.7 (1.1–2.4)	1.2
Duration of smoking (years)					
1–30	16/23	2.8 (1.1–7.1)	14/16	1.7 (0.7–4.2)	
31–40	29/27	4.3 (1.9–9.9)	19/24	1.8 (0.8–4.2)	
≥41	45/33	5.0 (2.3–10.9)	29/27	3.0 (1.3–7.3)	
Dose–response		1.7 (1.3–2.2)		1.4 (1.1–1.9)	1.2
Quantity of smoking (cigarettes/day)					
1–10	14/19	2.9 (1.1–7.4)	19/27	1.6 (0.7–3.8)	
11–20	28/30	3.1 (1.3–7.2)	20/24	2.0 (0.9–4.5)	
≥21	48/34	5.6 (2.6–11.9)	23/16	2.9 (1.2–6.9)	
Dose–response		1.7 (1.4–2.2)		1.4 (1.1–1.9)	1.2
Cumulative lifetime pack-years					
1–20	12/19	2.4 (0.9–6.5)	16/22	1.8 (0.7–4.2)	
21–40	20/24	3.4 (1.4–8.3)	16/18	2.0 (0.9–4.5)	
≥41	58/40	5.1 (2.5–10.3)	30/27	2.5 (1.1–5.4)	
Dose–response		1.7 (1.3–2.1)		1.3 (1.0–1.7)	1.3
Depth of inhalation of smoking					
Uncertain but light more	11/19	1.6 (0.6–4.2)	8/10	1.6 (0.5–5.1)	1.0
Uncertain but deep more	3/2	5.0 (0.7–37.6)	1/4	0.7 (0.1–7.2)	7.1
Light	15/20	3.4 (1.3–8.9)	19/21	1.9 (0.8–4.5)	1.8
Deep	61/42	6.8 (3.0–15.0)	34/32	2.5 (1.2–5.3)	2.7
Years since cessation of smoking					
≥6	8/15	0.9 (0.2–3.6)	10/14	2.8 (0.6–13.2)	
1–5	12/17	3.5 (0.6–19.9)	9/10	2.0 (0.5–8.0)	
Dose–response		1.6 (0.8–3.4)		1.5 (0.8–2.9)	1.1

[a] SQ: squamous cell carcinoma, SC: small cell carcinoma, AD: adenocarcinoma.

[b] SQ + SC and AD cell types had independent reference groups; odds ratios were adjusted for residential area, education, and socioeconomic status.

[c] The heterogeneity in ORs between SQ + SC and AD cell types was expressed as ORs ratio.

[d] Never-smokers were reference category.

[e] $p < 0.05$ for tests of homogeneity of the ORs by SQ + SC and AD cell types.

had adenocarcinoma (OR = 1.6–3.0). These differences were strengthened especially when comparing current smokers with nonsmokers (2.7–12.2-fold *vs.* 1.2–4.9-fold). Dose–response relationships were also detected for such smoking habits and lung cancer in these two histologic cell groups. Although the biologic gradient relationship among squamous/small tumor patients was stronger than that among adenocarcinoma patients (OR > 1), only the OR of smoking status was significantly heterogeneous across these two cell types of lung cancer (OR = 1.6; $p < 0.05$). On the other hand, depth of smoke inhalation was a significant factor in both squamous/small cell carcinoma and adenocarcinoma and this type of smoker displayed the highest lung cancer risk compared with other types of smoker.

The effect of cigarette smoking associated with female lung cancer was also assessed by the two groups of histologic type. Most of the adenocarcinoma patients were nonsmokers (96.9%), but 19.4% of squamous/small tumor patients had a history of cigarette smoking. After adjusting for area of residence, education level, and socioeconomic status, smokers were found to have a 6.9-fold (95% CI = 1.9–24.6) higher risk of squamous/small cell carcinoma than nonsmokers. However, due to limited sample sizes no sufficient statistical evidence supported the relationship between cigarette smoking and the development of adenocarcinoma (OR = 1.1; 95% CI = 0.4–3.6) (data not shown).

Table 2 displays the risks of contracting lung cancer for passive smoking generated from four exposure sources. A woman whose husband smoked in her presence had a 2.1-fold higher risk of adenocarcinoma than a woman whose husband never smoked ($p < 0.05$). In contrast, a husband whose wife smoked in his presence only had a 40% excess risk of the same tumor type of lung cancer than a husband whose wife never smoked ($p > 0.05$). There was no evidence of significantly elevated risks of lung cancer in squamous/small cell carcinoma patients due to exposure to passive smoke produced by parents, other family members, or environmental tobacco smoke in the workplace. While most of the ORs between squamous/small carcinoma and adenocarcinoma were larger than one, no statistical heterogeneity was detected in either sex group (Table 2).

Table 3 shows the assessment of previous lung diseases and other environmental factors. The risks of squamous/small cell carcinoma and adenocarcinoma were both significantly elevated for men and women who had a pulmonary tuberculosis history, but not for those who had chronic bronchitis (Table 3), emphysema, or asthma (data not shown). The proportion of occupational exposure to hazardous industries was apparently elevated in male squamous/small cell carcinoma and adenocarcinoma patients. However, the increased risks were not significant in female patients. Among these occupation categories, restaurant cook

Table 2. Odds ratios of squamous/small cell carcinoma and adenocarcinoma of the lung associated with passive smoking among men and women, Taiwan

Sources	Males					Females				
	SQ + SC[a]		AD[a]		OR ratio[c]	SQ + SC[a]		AD[a]		OR ratio[c]
	Cases/ controls	OR[b] (95% CI)	Cases/ controls	OR[b] (95% CI)		Cases/ controls	OR[b] (95% CI)	Cases/ controls	OR[b] (95% CI)	
Parent										
No	87/125	1.0	71/102	1.0		59/106	1.0	124/213	1.0	
Yes	20/23	1.4 (0.6–2.9)	16/19	1.1 (0.5–2.4)	1.3	25/28	1.6 (0.8–3.2)	38/60	1.2 (0.7–2.0)	1.3
Spouse										
No	102/144	1.0	81/117	1.0		40/80	1.0	70/165	1.0	
Yes	5/4	1.8 (0.4–7.7)	6/4	1.4 (0.4–5.4)	1.3	44/54	1.7 (0.9–3.2)	92/108	2.1 (1.3–3.2)	0.8
Cohabitant										
No	95/130	1.0	76/99	1.0		72/113	1.0	138/245	1.0	
Yes	12/18	1.2 (0.5–3.1)	11/22	0.7 (0.3–1.5)	1.7	12/21	1.2 (0.5–2.8)	24/28	1.5 (0.8–2.7)	0.8
Workplace										
No	57/85	1.0	56/70	1.0		72/125	1.0	146/256	1.0	
Yes	50/63	1.2 (0.6–2.4)	31/51	0.7 (0.4–1.4)	1.7	12/9	3.1 (0.9–10.2)	16/17	1.6 (0.8–3.4)	1.9

[a] SQ: squamous cell carcinoma, SC: small cell carcinoma, AD: adenocarcinoma.

[b] SQ + SC and AD cell types had independent reference groups; odds ratios were adjusted for smoking, residential area, education, and socioeconomic status.

[c] The heterogeneity in ORs between SQ + SC and AD cell types was expressed as ORs ratio.

Table 3. Odds ratios of squamous/small cell carcinoma and adenocarcinoma of the lung associated with previous lung diseases and occupations among men and women, Taiwan

Factors	Males					Females				
	SQ + SC[a]		AD[a]		OR ratio[c]	SQ + SC[a]		AD[a]		OR ratio[c]
	Cases/ controls	OR[b] (95% CI)	Cases/ controls	OR[b] (95% CI)		Cases/ controls	OR[b] (95% CI)	Cases/ controls	OR[b] (95% CI)	
Tuberculosis										
No	94/146	1.0	77/119	1.0		74/132	1.0	148/271	1.0	
Yes	13/2	11.9 (1.4–101.5)	10/2	5.3 (1.1–24.9)	2.2	10/2	5.9 (1.3–27.8)	12/2	7.8 (1.7–35.7)	0.8
Chronic bronchitis										
No	97/141	1.0	83/116	1.0		77/128	1.0	152/263	1.0	
Yes	10/7	1.7 (0.6–5.5)	4/5	0.9 (0.2–4.5)	1.9	7/6	1.6 (0.5–5.5)	10/10	1.6 (0.6–4.2)	1.0
Occupation										
Administration	35/59	1.0	34/50	1.0		46/72	1.0	80/143	1.0	
Hazardous industry	11/5	5.6 (1.3–23.2)	10/5	5.1 (1.2–21.6)	1.1	1/3	0.7 (0.1–6.9)	5/7	0.7 (0.2–2.8)	1.0
Transportation	7/16	1.0 (0.3–3.3)	3/10	0.5 (0.1–2.3)	2.0	11/8	2.4 (0.7–7.7)	14/16	0.9 (0.4–2.1)	2.7
Farmer	30/36	1.7 (0.7–4.2)	19/24	1.6 (0.6–3.8)	1.1	13/31	0.6 (0.2–1.6)	30/66	0.6 (0.3–1.2)	1.0
Chef	1/1	1.2 (0.1–83.6)	1/1	4.3 (0.2–79.3)	0.3	3/2	3.2 (0.5–20.0)	7/4	4.1 (1.2–14.4)	0.8
Others	23/31	1.5 (0.5–4.2)	20/31	1.4 (0.6–3.2)	1.1	10/18	1.2 (0.4–3.1)	26/37	1.6 (0.8–3.0)	0.8
Living near industrial district (years)										
No	89/131	1.0	68/104	1.0		63/123	1.0	132/240	1.0	
1–20	9/10	1.6 (0.5–5.0)	7/7	1.9 (0.6–6.1)		4/4	1.6 (0.4–7.1)	9/9	1.7 (0.6–4.6)	
≥21	9/7	2.3 (0.7–7.9)	12/10	2.7 (0.9–7.4)		17/7	4.8 (1.8–12.8)	21/24	1.7 (0.9–3.2)	
Dose–response		1.5 (0.9–2.7)		1.7 (0.9–2.7)	0.9		2.1 (1.3–3.4)		1.3 (0.9–1.8)	1.6[d]

[a] SQ: squamous cell carcinoma, SC: small cell carcinoma, AD: adenocarcinoma.
[b] SQ + SC and AD cell types had independent reference groups; odds ratios were adjusted for smoking, residential area, education, and socioeconomic status.
[c] The heterogeneity in ORs between SQ + SC and AD cell types was expressed as ORs ratio.
[d] $p < 0.05$ for tests of homogeneity of the ORs by SQ + SC and AD cell types.

was significantly correlated to the higher risk of adenocarcinoma in women. The risk was also significantly elevated for female squamous/small cell carcinoma patients who had resided near industrial districts (within 1 km) for more than 20 years. Furthermore, a significant tumor type difference in dose–response ORs was found in duration of residence adjacent to a major industrial complex (OR = 1.8; $p < 0.05$). Tests for homogeneity of ORs across tumor types and gender were also performed in occupation and previous lung diseases, but no substantial heterogeneity was identified. Otherwise, all other collected factors, including dietary factors, incense, and mosquito coil burning, were not significant in the two histologic cell groups of lung cancer in both sexes.

Over 96% of female participants stated that they regularly cooked family meals, in accordance with tradition. In contrast, less than 7% of men participants reported cooking for the family. There was no significant difference for cooking practices and habits in these male subjects who cook, although the assessment was based on limited information (data not shown). The risks of squamous/small cell carcinoma and adenocarcinoma for women who used wood or charcoal as cooking fuels were separately raised 3.1- and 3.0-fold compared with those who cooked using gas or did no cooking. No significant difference was observed between cases and controls in use of lard or vegetable oil (mainly peanut or soybean oil) for frying (Table 4). After adjusting for demographic factors, housewives who did not use a fume extractor in the home kitchen were 3.0-fold (95% CI = 1.3–7.1) and 3.9-fold (95% CI = 2.3–6.6) more likely to develop squamous/small cell carcinoma and adenocarcinoma as compared to those who did use a fume extractor. Housewives who usually waited until the moment when fumes were emitted from the oil and then stir fried, fried, or deep fried had a significantly higher risk of adenocarcinoma, but not squamous/small cell carcinoma of the lung. In the study, such cooking habits were used to identify whether the temperature of cooking oils was higher at the moment housewives placed the food into the frying pan. The tests for homogeneity of ORs further indicated that the exposure effect of frying food after the fumes were emitted on

Table 4. Odds ratios of squamous/small cell carcinoma and adenocarcinoma of the lung associated with cooking practices and habits among women, Taiwan

Factors[c]	SQ + SC[a]		AD[a]		OR ratio[d]
	Cases/controls	OR[b] (95% CI)	Cases/ controls	OR[b] (95% CI)	
Age first cooked (years)					
>20	27/50	1.0	65/121	1.0	
≤20	55/79	1.5 (0.7–3.1)	93/141	1.1 (0.7–1.7)	1.4
Cooking fuels					
No cooking or gas	48/93	1.0	73/166	1.0	
Coal or anthracite	14/26	1.2 (0.5–3.0)	49/72	2.1 (1.2–3.7)	0.6
Wood or charcoal	22/15	3.1 (1.0–9.2)	40/35	3.0 (1.4–6.4)	1.0
Cooking oils					
Lard	28/33	1.0	50/81	1.0	
Vegetable oil	54/96	0.7 (0.3–1.4)	108/181	1.2 (0.7–1.9)	0.6
Kitchen with fume extractor					
Yes	51/110	1.0	84/214	1.0	
No	31/19	3.0 (1.3–7.1)	74/48	3.9 (2.3–6.6)	0.8
Stir frying after fumes emitted					
No	23/39	1.0	29/85	1.0	
Yes	59/90	0.9 (0.4–1.9)	129/177	2.0 (1.2–3.3)	0.5
Frying after fumes emitted					
No	24/34	1.0	20/71	1.0	
Yes	58/95	0.8 (0.4–1.5)	138/191	2.6 (1.5–4.5)	0.3[e]
Deep frying after fumes emitted					
No	44/59	1.0	68/129	1.0	
Yes	38/70	1.0 (0.5–2.0)	90/133	1.6 (1.0–2.6)	0.6

[a] SQ: squamous cell carcinoma, SC: small cell carcinoma, AD: adenocarcinoma.
[b] SQ + SC and AD cell types had independent reference groups; odds ratios were adjusted for smoking, residential area, education, and socioeconomic status.
[c] No-cooking housewives were excluded in the analyses.
[d] The heterogeneity in ORs between SQ + SC and AD cell types was expressed as ORs ratio.
[e] $p < 0.05$ for tests of homogeneity of the ORs by SQ + SC and AD cell types.

adenocarcinoma was significantly larger than that on squamous/small cell carcinoma.

Table 5 shows a detailed assessment of cooking habits and the equipment of fume extractors. The interaction effects of these two factors on squamous/small cell carcinoma and adenocarcinoma of the lung among women were evaluated by stratifying cooking habits across the use of a fume extractor in the home kitchen. The risks of adenocarcinoma for housewives who wait to cook (stir fried, fried, and deep fried) the food until the cooking oil has reached a high temperature, and use a fume extractor, were elevated 1.6–2.1-fold compared with those who start to cook before oil fumes are emitted. However, for women who prepared meals without a fume extractor the risks were largely elevated when they wait for the oil to reach a high temperature (5.4–8.1-fold). The risk remains significant even when cooking practices were performed prior to the emission of oil fumes when no fume extractor was used (3.7–4.8-fold). Moreover, the risk patterns of adenocarcinoma in stir frying, frying, and deep frying separately appeared higher than the additive interaction effect, although the synergism indices were not significant. No significant combining effects between cooking habits and the use of fume extractors were observed in patients with squamous/small cell carcinoma besides stir frying.

Multivariate logistic regression analyses were separately conducted for male and female patients who had squamous/small cell carcinoma and adenocarcinoma. The potential risk factors which were found to have a significant effect on lung cancer in univariate analyses were simultaneously assessed. In the analyses we adjusted these estimates for residential area, education, socioeconomic status, and occupations. Because of the high correlation between stir frying, frying, and deep frying after the fumes are emitted, in female adenocarcinoma patients, we found it sufficient to include only the method of frying in the regression models. All significant risk factors remained in regression models for both tumor groups and both sexes, except for the types of cooking

Table 5. Interaction effects of squamous/small cell carcinoma and adenocarcinoma of the lung between cooking habits and kitchen with fume extractor among women, Taiwan

Cooking after fumes emitted/using fume extractor	SQ + SC[a]			AD[a]		
	Cases/controls	OR[b] (95% CI)	SI[c] (95% CI)	Cases/controls	OR[b] (95% CI)	SI[c] (95% CI)
Stir frying						
No/Yes	18/36	1.0		18/75	1.0	
Yes/Yes	33/75	1.0 (0.4–2.4)		66/139	1.9 (1.0–3.6)	
No/No	5/4	2.4 (0.3–17.4)		11/10	4.8 (1.5–14.8)	
Yes/No	26/15	4.6 (1.1–19.5)	2.5 (0.1–77.9)	63/38	6.9 (3.1–15.5)	1.3 (0.4–3.9)
Frying						
No/Yes	19/32	1.0		11/61	1.0	
Yes/Yes	32/78	0.8 (0.3–1.8)		73/153	2.1 (0.9–4.6)	
No/No	5/2	3.8 (0.5–26.9)		9/10	3.7 (1.1–13.0)	
Yes/No	26/17	2.8 (0.8–9.5)	0.7 (0.1–14.4)	65/38	8.1 (3.3–19.7)	1.8 (0.6–5.7)
Deep frying						
No/Yes	23/52	1.0		30/100	1.0	
Yes/Yes	28/58	1.2 (0.5–2.6)		50/104	1.6 (0.9–2.8)	
No/No	21/7	6.8 (1.7–26.6)		35/21	4.4 (2.0–9.9)	
Yes/No	10/12	1.9 (0.4–8.1)	0.1 (0.0–3.0)	36/23	5.4 (2.5–11.5)	1.1 (0.4–2.9)

[a] SQ: squamous cell carcinoma, SC: small cell carcinoma, AD: adenocarcinoma.
[b] SQ + SC and AD cell types had independent reference groups; odds ratios in SQ + SC cell types were adjusted for smoking, tuberculosis, living adjacent to industrial district, occupation, residential area, education, and socioeconomic status; odds ratios in AD cell type were adjusted for spouse smoking, tuberculosis, cooking fuels used, occupation, residential area, education, and socioeconomic status.
[c] Synergism index based on an additive model.

fuels in female squamous/small cell carcinoma patients (Tables 6 and 7). Among these risk factors, cigarette smoking was the main cause of squamous/small cell carcinoma and adenocarcinoma of the lung in men. Combining with occupations and previous tuberculosis these risk factors separately accounted for 74.2% and 59.6% of summary population-attributable risks of contracting the two tumor groups of lung cancer. For female lung cancer patients, preparing meals in a kitchen not equipped with a fume extractor, and waiting to fry until the cooking oil has reached a high temperature, separately explained the majority of the attributable fractions of squamous/small cell carcinoma (28.2%) and adenocarcinoma (47.7%). With the exception of a kitchen with fume extractors, and a clinical history of tuberculosis, the environmental causal factors of lung cancer were heterogeneous between these two histologic cell groups.

Discussion

This study presented evidence that the strength of association between cigarette smoking and lung cancer in both sexes differed by histologic types. Similar evidence was shown in studies conducted in Europe, North America, and Japan [5, 22, 23]. Squamous cell and small cell carcinoma in men had a greater magnitude of risk than that for adenocarcinoma. However, all three histologic types of lung cancer were significantly related to cigarette smoking. Recent epidemiologic studies indicated that the difference in lung cancer risk between histologic types may be partly explained by the manner of cigarette smoking [5, 23]. Indeed, male patients who suffered from squamous/small cell carcinoma of the lung initiated smoking at a younger age, had a longer duration of smoking, and smoked more cigarettes per day than patients who contracted adenocarcinoma in this population. We also estimated that the risks of lung cancer increased 27.8% and 21.4% per 10 pack-years among male squamous and small cell carcinoma patients, respectively. On the contrary, only a 7.6% increase in risk was detected for patients with adenocarcinoma. These findings suggested that squamous cell carcinoma was more sensitive to smoking effect than the other two histologic types of lung cancer.

Our study showed that passive smoke produced by a husband was a risk factor for a wife who had adenocarcinoma of the lung, whereas, passive smoke generated by a wife was not correlated with an elevated risk of lung cancer for a husband who had squamous/small cell carcinoma or adenocarcinoma. Although some large-scale case–control studies indicated that women may be more susceptible to tobacco carcinogens than are men [14, 24], insufficient evidence supported the theory that women were more susceptible to carcinogens produced by passive smoke than were men. The reason for passive

Table 6. Adjusted odds ratios and population-attributable risk proportions (PAR%) of squamous/small cell carcinoma and adenocarcinoma of the lung associated with independent factors among men, Taiwan

Factor/category	SQ + SC[a]		AD[a]	
	OR[b] (95% CI)	PAR%	OR[b] (95% CI)	PAR%
Cumulative lifetime smoking, pack-years				
No	1.0	61.8	1.0	38.2
1–20	2.3 (0.8–6.3)		1.8 (0.7–4.6)	
21–40	3.1 (1.2–7.8)		1.8 (0.7–4.4)	
≥41	4.7 (2.2–10.1)		2.7 (1.2–6.5)	
Tuberculosis				
No	1.0	11.0	1.0	9.3
Yes	10.3 (1.2–90.0)		5.1 (1.0–25.7)	
Occupation				
Administration	1.0	22.1	1.0	27.9
Hazardous industry	4.0 (1.1–15.1)		5.3 (1.2–23.0)	
Transportation	0.9 (0.3–3.2)		0.7 (0.2–3.2)	
Farmer	1.3 (0.5–3.2)		1.7 (0.7–4.2)	
Chef	1.4 (0.1–69.9)		4.0 (0.2–76.8)	
Others	1.6 (0.6–4.6)		1.8 (0.7–4.2)	
Summary population-attributable risk proportion (%)		74.2		59.6

[a] SQ: squamous cell carcinoma, SC: small cell carcinoma, AD: adenocarcinoma.
[b] SQ + SC and AD cell types had independent reference groups; odds ratios were derived from a multivariate logistic regression model adjusted for the table's covariates, as well as residential area, education, and socioeconomic status.

smoking being difficult to assess in male lung cancer is that most male lung cancer patients worldwide also smoke (over 81%) [25]. Smoking has accounted for the majority of attributable fractions of lung cancer. The significant association of female adenocarcinoma with passive smoking has been noticed in several analytic epidemiologic investigations [2, 26]. However, some studies tended to support the relationship between passive smoking and squamous cell and small cell carcinoma [27, 28]. From the viewpoint that the components produced by sidestream smoke were likely to penetrate into the peripheral parts of the lung [29], adenocarcinoma seems more likely to be affected by environmental tobacco smoke.

Certain lung diseases may have an etiologic role in lung cancer development [9]. Such an association, especially for pulmonary tuberculosis, is particularly important in Taiwan, where the prevalence of tuberculosis is now increasing. Recent studies in other countries, including America and Mainland China, empirically propounded evidence to support the hypothesis of an association between tuberculosis and lung cancer [30, 31]. Some of the studies even emphasized the association with tuberculosis diagnosed 4–10 years prior to lung cancer [11].

Jöckel *et al.* reported that occupational exposure to certain substances was associated with an increased risk of developing lung cancer [32]. Because this study had only a small number of industry-specific samples, patients who worked in asbestos-processing industries, iron foundries, and petrochemical industries were combined as a broad occupational category (hazardous industry), and this was used to investigate the relationship between occupation and lung cancer. Just as observed by studies conducted in several countries [33, 34], male workers who were employed in the above industries, and reported exposure to airborne contaminants in the workplace, were found to be a high-risk group as regards contracting lung cancer.

Kaohsiung is the heartland of heavy industry in southern Taiwan; there are over 1850 factories registered in this city with a density as high as 12 factories/km^2 in 1996. Heavy air pollution in the area is mainly caused by emission from industry and city traffic. Because industrial factories in Kaohsiung city are commonly situated in the middle of residential areas (79% of petrochemical factories are adjacent to the residence at a distance of less than 500 m) [35], any emission from a plant, or an accidental event, may directly affect residents. In the present study, we found that a high proportion of female subjects with squamous/small cell carcinoma had resided within 1 km radius of an industrial district for more than 20 years; even smoking, occupational history, and other risk

Table 7. Adjusted odds ratios and population-attributable risk proportions (PAR%) of squamous/small cell carcinoma and adenocarcinoma of the lung associated with independent factors among women, Taiwan

Factor/category	SQ + SC[a]		AD[a]	
	OR[b] (95% CI)	PAR%	OR[b] (95% CI)	PAR%
Kitchen with fume extractor				
Yes	1.0	28.2	1.0	36.1
No	3.3 (1.2–9.2)		3.8 (2.1–6.8)	
Tuberculosis				
No	1.0	12.1	1.0	6.3
Yes	8.3 (1.2–55.8)		7.0 (1.3–37.4)	
Cooking fuels				
No cooking or gas	1.0	–[c]	1.0	30.2
Coal or coal ball	1.1 (0.4–3.1)		1.7 (0.9–3.3)	
Wood or charcoal	3.5 (0.9–12.9)		3.3 (1.4–8.0)	
Living adjacent to industrial district (years)				
No	1.0	19.2	–[c]	–[c]
1–20	2.1 (0.4–10.8)			
≥21	5.7 (2.0–16.2)			
Smoking				
No	1.0	15.9	–[c]	–[c]
Yes	6.0 (1.5–23.8)			
Frying after fumes emitted				
No	–[c]	–[c]	1.0	47.7
Yes			2.1 (1.1–3.0)	
Spouse smoking				
No	–[c]	–[c]	1.0	22.8
Yes			1.7 (1.0–2.8)	
Summary population-attributable risk proportion (%)		56.3		79.4

[a] SQ: squamous cell carcinoma, SC: small cell carcinoma, AD: adenocarcinoma.
[b] SQ + SC and AD cell types had independent reference groups; odds ratios were derived from a multivariate logistic regression model adjusted for the table's covariates, as well as residential area, education, socioeconomic status, and occupations.
[c] Non-valuation.

factors were taken into account. We also noticed that the dose–response OR of this factor among squamous/small cell carcinoma patients was significantly heterogeneous from that among adenocarcinoma patients. Despite no data for individual air pollution measurements being available, the findings are consistent with those shown by Barbone *et al*. [36] and Gottlieb [37] in industrial areas of Italy and the USA. Such evidence suggested that air pollution arising from an industrial complex should not be dismissed as a negligible risk factor of lung cancer, especially for squamous/small cell carcinoma of the lung in females.

Indoor exposure to smoke emitted from cooking fuels was explored in this female population both for squamous/small cell carcinoma and adenocarcinoma of the lung. However, significantly elevated risks were identified only for adenocarcinoma patients who cooked during their most active period of life (20–40 years of age) using wood or charcoal. Evidence available in the literature on the association of wood smoke with human lung cancer is limited; however, some potential human carcinogens such as benzo[*a*]pyrene and formaldehyde have been found in wood smoke [38], and their tumor-inducing activity has been demonstrated in an animal model [39]. One study did demonstrate that women using wood or straw as the main cooking fuels in Osaka had an elevated lung cancer risk. These studies also detected a significant adjusted risk for women who started to cook at the age of around 30 years, a cooking period that was similar to that of Taiwanese women [40]. Most other studies of this issue were conducted in China [11, 41] and Singapore [42] by methods of case–control; however, they could not detect a substantially increased risk in the population studied. Lack of power may explain the absence of any associations.

Taiwanese food preparation processes usually involve frying ingredients in oil, which can produce ample amounts of air pollutants, to which the cook is exposed. These pollutants consist of two types of fumes arising from, respectively, heating the cooking oil itself and frying the food with oil. Both types of fumes have been proven to be mutagenic and carcinogenic in several *in-vitro* short-term test systems [43–45], and some probable human carcinogens such as benzo[*a*]pyrene, dibenzo[*a*,*h*]anthracene and benzo[*a*]anthracene have even been identified in fumes of heated cooking oil [46]. In the present study, women who prepared meals in kitchens not equipped with a fume extractor were found to be at high risk of developing both squamous/small cell carcinoma and adenocarcinoma of the lung. As mentioned in our earlier studies, substances absorbed by the fume extractors may contain some specific toxic compounds that are potential carcinogens [3, 46–48]. However, this study further found that women who waited to cook (stir fry, fry, and deep fry) the food until the cooking oil has reached a high temperature had an independently higher risk of adenocarcinoma, but not of squamous/small cell carcinoma. The authors even detected the heterogeneity in exposure effects of frying food after the fumes were emitted across these two types of tumor. The results suggest that the development of adenocarcinoma may be associated with cooking-oil fumes emitted at high temperatures. The toxic compounds related to adenocarcinoma probably had more penetrating power in the lung than those related to squamous/small cell carcinoma.

Our study showed that cigarette smoking accounted for the biggest proportion of attributable risk of lung cancer in men, even for a tumor type such as adenocarcinoma that is only weakly linked to smoking. In contrast, the cooking-related factors explained the majority of attributable fractions of female lung cancer. These results were similar to findings obtained from Chinese populations in some cities on Mainland China. Gao *et al*. [31] in urban Shanghai, and Liu *et al*. [41] in Guangzhou, found that, while cigarette smoking was the main cause of all cell types of lung cancer in men, the rising risk of female lung cancer was correlated with the exposure to cooking vapors and living in a house with poor air circulation. Otherwise, Zhong *et al*. [49] in their large-scale case–control study found that specific cooking habits, such as heating cooking oils to high temperatures, were associated with elevated risks of nonsmoking female lung cancer. In this study, the authors demonstrated that risk factors for squamous/small cell carcinoma and adenocarcinoma of the lung were significantly heterogeneous across genders, and found that the cell type distribution of lung cancer between the sexes was notably different. The heterogeneity of risk factors in both sexes could explain part of the gender difference in the distribution of histologic type.

In summary, this present study indicated that the causal factors for primary lung cancer between men and women in Taiwan were heterogeneous. Significant differences in exposure effects of particular etiologic agents were also detected between squamous/small cell carcinoma and adenocarcinoma patients. The authors found that cigarette smoking was the main cause of squamous/small cell carcinoma and adenocarcinoma of the lung in men. For female lung cancer patients in Taiwan, risk factors of lung cancer depended on the type of cancer developed. Our results suggest that the causal factors of lung cancer might be specific for the type of tumor concerned. The gender-specific risk factors of lung cancer could partly explain the difference in cell type distribution between men and women.

Acknowledgement

This study was supported in part by a grant from the National Science Council (Grant No. NSC 84-0412-B-037-049, NSC 85-2331-B-037-065).

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