

# **Epidemiology & Bulletin**

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Smoking and passive smoking in  
relation to lung cancer by  
histological category

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## **Smoking and passive smoking in relation to lung cancer by histological category**

### **INTRODUCTION**

Since 1982, malignant neoplasms have been the most common cause of death in Taiwan, and lung cancer has been the most common cancer. Because of its high case-fatality rate, lung cancer accounts for 18 percent of all cancer deaths (20 percent in males and 15 percent in females). In 1989, the mortality rate of lung cancer among males in Taiwan was 22.77 per 100,000 population, and among females the rate was 10.13.<sup>(1)</sup> Since the 1950s, the age-adjusted mortality rate of lung cancer has been increasing in Taiwan. Over this period, there was an eight-fold increase in lung cancer mortality, this rate of increase was the fastest one among all malignant neoplasms.<sup>(1,2)</sup>

Studies conducted in Mainland China and Taiwan have shown that smoking is the principal risk factor for lung cancer,<sup>(3,4)</sup> and the smokers experienced a 2.17-fold increased risk of lung cancer.<sup>(4)</sup> However, the relationship between passive smoking and lung cancer remains controversial in different Chinese epidemiological studies.<sup>(3,5-8)</sup> A case-control study was conducted in this study to evaluate the relationship between lung cancer histologic types (adenocarcinoma, squamous cell carcinoma, small/oat cell carcinoma) and smoking, passive smoking.

### **MATERIALS AND METHODS**

A total of 143 eligible cases of primary adenocarcinoma, squamous and small cell carcinoma were newly cytologic or pathologic diagnosed lung cancer between May 1990 and July 1991 in Tri-Service General Hospital (TSGH), Taipei, Taiwan. Of the 143 eligible cases, 10 were too ill or discharged as interviewer visited the cases in the ward, and the patients or relatives refused to be interviewed in the ward or at home, the other two cases lived in the Kim-men island and the matching neighborhood controls were not available to be interviewed. A total of 131 case interviews were completed, 72 (55%) were adenocarcinoma, 39 (30%)

were squamous cell carcinoma and 20 (15%) were small cell carcinoma. Although those who were not interviewed were more likely to have distant metastases (AJCC, stage IV 80%) compared to those who were interviewed (57%), the percentage distribution of three different histological categories between the interviewed and not interviewed cases were almost identical.

Two control groups were studied: 262 hospital controls, two-to-one matched with each case on sex, date of birth ( $\pm 5$  yrs of birth date), date of interview ( $\pm 4$  weeks) and insurance status were selected from the TSGH Ophthalmologic Department; and 262 neighborhood controls, two-to-one matched on age, sex, and residence where the case lived at date of diagnosis were randomly selected from eligible neighbors.

Cases and hospital controls were interviewed in the ward and neighborhood controls were interviewed at home with the use of a structured questionnaire to elicit information on personal smoking habits, exposure to passive smoking, incense burning, mosquito coil burning, types of cooking, coal as cooking fuels, past lung diseases, dietary intake of vitamin A. We also obtained a lifetime history of all jobs (job title, activities, and exposure) of at least 3 months' duration. The questionnaires were checked by the supervisor on the day following the interview. If the questionnaire answers were incomplete, additional information was obtained by another interview, or by telephone interview. A random sample of five percent of the interviews were checked by supervisor.

Smokers were defined as people having smoked one cigarette or more per day (or 30 gm of tobacco a month) during at least 1 year. For each smoker a detailed smoking history was obtained including the type of tobacco product (cigarettes, cigars, pipes), the daily consumption, intensity of inhalation, age when smoking started regularly, and age at any major change of smoking habits. Childhood exposure to passive smoke was measured by asking subjects whether, as a child, they had lived together with father or mother who smoked for a year or more in their presence. Those who answered yes were asked the number of years their parents smoked in their presence. The adult exposure to passive smoke at home were defined as their spouse or children who smoked for a year or more in their presence, and the hours stayed together at home being more than five hours per day. Exposure to passive smoke at work was defined as their coworkers smoked for a year or more in their presence and the hours worked together being more than five hours per day. The adult exposure to passive smoke on the basis of their friends' smoking behavior was defined as their friends smoked for a year or more in their presence and the mean hours got together indoors being one hour or more per day.

The squamous cell and small/oat cell carcinoma were combined to be analyzed because too few small/oat cell carcinoma to conduct separate analysis and because these two cell types of lung cancer are more strongly associated with smoking than adenocarcinoma of the lung.<sup>(3,9-11)</sup>

Several methods were used in the statistical analysis. Matched odds ratio of

lung cancer were estimated using the Mantel-Haenszel method. The Mantel-Haenszel summary Chi-square value was used to test the statistic significance of odds ratio.<sup>(12)</sup> The different parameters characterizing the exposures were analyzed by a conditional logistic regression<sup>(13)</sup> taking into account the full matching of each case with two original controls. Finally, the multiple conditional logistic regression method<sup>(13)</sup> were used to estimate the adjusted odds ratio of lung cancer with smoking and passive smoking as the confounding factors were controlled.

## RESULTS

Table 1 shows that the frequency distributions of age, sex, medical insurance status, education, religion of cases and controls by different histological types were comparable. The mean age of adenocarcinoma cases, hospital and neighborhood controls was  $60.00 \pm 12.64$ ,  $60.60 \pm 12.63$ , and  $59.92 \pm 12.15$ , respectively. The mean age of squamous/small cell carcinoma cases, hospital and neighborhood controls was  $63.59 \pm 10.58$ ,  $63.91 \pm 10.67$ , and  $63.41 \pm 10.94$ , respectively. Cases and controls were closely matched on age and sex but cases of adenocarcinoma were slightly more educated than neighborhood controls ( $df = 5$ ,  $X^2 = 7.48$ ,  $p = 0.12$ ). For religion, the percent of Catholicism, Buddhism, and Taosim those that burn incense for worship was comparable between cases and both control groups by different histological types.

## SMOKING HABITS

There was a significant association between tobacco smoking and squamous/small cell carcinoma, but not for adenocarcinoma. For squamous/small cell carcinoma, the matched odds ratio (OR) for smoking was 4.30 (comparing cases and hospital controls), 3.86 (comparing cases and neighborhood controls). For adenocarcinoma, the matched odds ratio was 0.85 (comparing with cases and hospital controls), 1.19 (comparing with cases and neighborhood controls) for adenocarcinoma. Furthermore, the odds ratios (ORs) showed significantly increased risks for squamous/small cell carcinoma in all smoking categories, such as the daily consumption, duration, intensity of inhalation of tobacco smoking.

## PASSIVE SMOKING

Table 3 shows that little association between childhood, adult home, and workplace passive smoke exposure with the lung cancer, except the spouse and friend with squamous/small cell carcinoma.

## MULTIVARIATE ANALYSIS

Table 4 shows the results of multiple conditional logistic regression analysis in 72 cases, 144 hospital controls and 144 neighborhood controls for adenocarcinoma of lung.

The multiple conditional logistic regression method was conducted to examine the effects of smoking, passive smoking from different sources as the confounding factors were controlled. The smoking and passive smoking were not correlated with adenocarcinoma of lung, except in the category who smoked 11 to 20 cigarettes per day (only in comparing with cases and neighborhood controls). However, no dose-response in number of cigarettes smoked per day and adenocarcinoma of lung cancer was noted.

Table 5 demonstrates the results of multiple conditional logistic regression analysis in 59 cases, 118 hospital controls and 118 neighborhood controls for adenocarcinoma of lung. The multiple logistic regression method was conducted to examine the effects of smoking, passive smoking from different sources as the confounding factors were controlled. The smoking and passive smoking from friends were significantly associated with squamous/small cell lung cancer, and the adjusted odds ratios increased significantly with increasing number of cigarettes smoked per day.

## DISCUSSION

Smoking is associated with a significantly increased risk of lung cancer, but risks were higher for squamous and small cell carcinoma than for adenocarcinoma.<sup>(3,9-11)</sup> The relative risk (RR) for all lung cancers tended to rise with increasing numbers of cigarettes smoked per day and with increasing duration of smoking in Mainland China and in Taiwan.<sup>(3,4,8,11)</sup> However, our study revealed that smoking was associated only with squamous/small cell carcinoma and not with adenocarcinoma. Our results were similar to those in a study carried out in Beijing, Mainland China.<sup>(14)</sup> In our study, the smoking rates for 43 male adenocarcinoma cases were 76.7%, and 79.7%, 68.6% for hospital, neighborhood controls, respectively. The smoking rates for 29 female adenocarcinoma cases were 6.9%, and 8.6%, 12.1% for two controls, respectively. The smoking rates for 49 male squamous/small cell carcinoma cases were 93.9%, and 78.6%, 76.5% for two controls, respectively. The smoking rates for 10 female squamous/small cell carcinoma cases were 20.0% and 5.0%, 15.0% for two controls, respectively. Therefore, the relationship between smoking and lung cancer by different histologies were consistent across sex.

Sidestream cigarette smoke (from passive smoking) contains higher concentrations of toxic components than mainstream smoke (from active smoking),<sup>(15,16)</sup> it is diluted in the ambient air to varying degrees (depending on the size and shape of the room, proximity to the smoker and ventilation) by the time it reaches the passively exposed person.<sup>(17)</sup> It is difficult to promote the validity of the measurements of passive smoking in interviews. Therefore, the relationship between passive smoking and lung cancer remains controversial in different Chinese epidemiological studies. Two case-control studies from Hong Kong are unable to find any significant increase in RR from women with smoking husbands.<sup>(5,6)</sup> Two case-control studies carried out in Shanghai and north-east China revealed no significant increase in risk for overall exposure to passive smoking.<sup>(7,8)</sup> However, a significant association of passive cigarette smoking with squamous cell carcinoma, small cell carcinoma and adenocarcinoma of the lung are

observed in a hospital-based case-control study carried out in Taipei metropolitan area.<sup>(3)</sup>

Adenocarcinoma is the most common histologic type of lung cancer in nonsmokers, especially in women.<sup>(18)</sup> Wynder and Goodman hypothesize that inhaled sidestream smoke increase the risk for this peripheral lung cancer. This is because sidestream smoke, with its appreciable amounts of gaseous components, might be more likely to penetrate into the peripheral parts of the lung. In contrast, active smoking, with its larger amounts of particulate matter, would be less likely to penetrate so deeply.<sup>(19)</sup>

To test this hypothesis, passive smoking from different sources were tested by different histological groups in our study. The relationship of passive smoking from source of friend appeared correlated with the squamous/small cell lung cancer. In contrast, adenocarcinoma did not appear to be associated with passive smoking. This result might be similar to the active smoking, and matched the Kreyberg hypothesis for lung cancer in active smoking men with suggests that passive smoking may act as no more than a diluted form of active smoking in its carcinogenic pathways.<sup>(20)</sup>

Most of the subjects who reported passive smoke exposure from friends reported this exposure occurred while playing Mar-Jan. Ten years ago, playing Mar-Jan was illegal entertainment in Taiwan. Therefore the men who played Mar-Jan would close the doors and windows to conceal the noisy sound of playing Mar-Jan from neighbors. The intensity of passive smoke exposure from friends in playing Mar-Jan was very strong under poor ventilation and long duration (about three hours or more).

In summary, the present study confirms that smoking and passive smoking from friends were the major determinants of squamous/small cell lung cancer. The most common lung cancer in Taiwan is adenocarcinoma.<sup>(21)</sup> Further investigation of adenocarcinoma of lung and smoking and other potential risk factors are needed in Taiwan area.

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**Table 1. Characteristics of cases, hospital controls and neighborhood controls by different histological types**

Variables	Adenocarcinoma			Squamous and small cell carcinoma			
	Cases	Controls		Cases	Controls		
		Hospital	Neighborhood		Hospital	Neighborhood	
	(n=72) %	(n=144) %	(n=144) %	(n=59) %	(n=118) %	(n=118) %	
Age	< 41	10	10	9	2	3	4
	41-50	11	8	12	13	12	11
	51-60	25	28	27	15	13	16
	61-70	38	34	30	36	42	37
	70 +	16	20	22	34	30	32
Sex	Male	60	60	60	83	83	83
	Female	40	40	40	17	17	17
Medical Insurance status							
	Civilians	21	14	22	14	8	16
	Officers	30	31	22	20	28	24
	Labors	21	23	32	20	20	28
	Farmer	6	6	7	15	22	13
	Army or veteran	22	26	17	31	22	19
Education (Years)							
	0	20	20	17	17	20	25
	1-6	19	29	38	42	32	31
	7-9	17	16	11	13	11	13
	10-12	25	15	20	14	16	15
	12 +	19	19	14	14	21	16
Religion							
	None	20	23	27	32	26	24
	Christianity	11	2	8	5	5	8
	Catholicism	10	3	4	5	3	1
	Buddhism	43	51	38	29	40	40
	Taoism	16	21	23	29	26	27

**Table 2. Matched OR of the different histological lung cancer according to variables characterizing cigarette consumption**

Smoking habits	Adenocarcinoma					Squamous and small cell carcinoma				
	Cases	Controls		Matched odds ratio		Cases	Controls		Matched odds ratio	
	(No)	Hos (No)	Neigh (No)	Cases/ Hospital controls	Cases/ Neighborhood controls	(No)	Hos (No)	Neigh (No)	Cases/ Hospital controls	Cases/ Neighborhood controls
Ever smoking										
No	37	71	78	1 00	1 00	11	40	40	1 00	1 00
Yes	35	73	66	0 85	1 19	48	78	78	4 30**	3 86**
No of cigarettes smoked per day										
Non-smokers	37	71	78	1 00	1 00	11	40	40	1 00	1 00
1-10	9	22	25	0 76	0 81	9	33	23	1 85	2 32
11-20	21	37	29	1 04	1 68	20	39	48	3 59**	2 93*
> 20	5	14	12	0 66	1 05	19	6	7	20 92***	19 79***
Duration of smoking (years)										
Non-smokers	37	71	78	1 00	1 00	11	40	40	1 00	1 00
1-30	14	18	33	1 44	1 38	6	17	20	1 93*	1 28
> 30	21	55	43	0 57	1 06	42	61	58	6 05***	6 77***
Frequency of inhalation										
Non-smokers	37	71	78	1 00	1 00	11	40	40	1 00	1 00
Never	5	33	17	0 28	0 56	10	26	26	2 13	2 45
Part of time	12	12	30	2 15	0 82	13	29	30	2 81	2 86
Most times	18	28	19	1 28	2 38*	25	23	22	6 08***	6 87***
Depth of inhalation										
Non-smokers	37	71	78	1 00	1 00	11	40	40	1 00	1 00
Slightly	12	39	29	0 49	0 85	17	42	37	2 69	3 00*
Moderately	7	14	19	0 79	0 82	9	13	14	5 59**	2 16
Deeply	16	20	18	1 52	2 18	22	23	17	6 44***	9 57***

\* 0 05 &lt; P &lt; 0 10

\*\* 0 01 &lt; P &lt; 0 05

\*\*\* 0 001 &lt; P &lt; 0 01



**Table 3. Matched OR of the different histological lung cancer according to variables characterizing passive smoking**

Source of passive smoking	Adenocarcinoma					Squamous and small cell carcinoma				
	Cases (No)	Controls		Matched odds ratio		Cases (No)	Controls		Matched odds ratio	
		Hos (No)	Neigh (No)	Cases/Hospital controls	Cases/Neighborhood controls		Hos (No)	Neigh (No)	Cases/Hospital controls	Cases/Neighborhood controls
<b>Childhood</b>										
<b>Mother</b>										
No	58	129	128	1 00	1 00	50	107	109	1 00	1 00
Yes	14	15	16	1 97*	1 83	9	11	9	1 89	2 22
<b>Father</b>										
No	23	47	57	1 00	1 00	26	45	54	1 00	1 00
Yes	49	97	87	1 03	1 45	33	73	64	0 76	1 07
<b>Adult at home</b>										
<b>Spouse</b>										
No	54	103	112	1 00	1 00	45	103	99	1 00	1 00
Yes	18	41	32	0 77	1 28	14	15	19	2 84**	2 10
<b>Children</b>										
No	56	100	112	1 00	1 00	43	85	93	1 00	1 00
Yes	16	44	32	0 67	1 00	16	33	25	0 96	1 38
<b>Workplace</b>										
<b>Coworkers</b>										
No	27	63	67	1 00	1 00	19	50	49	1 00	1 00
Yes	45	81	77	1 34	1 55	40	68	69	1 74	1 63
<b>Entertainment</b>										
<b>Friends</b>										
No	58	125	121	1 00	1 00	42	99	99	1 00	1 00
Yes	14	19	23	1 65	1 29	17	19	19	2 15**	2 28**

\*: 0 05 &lt; P &lt; 0 10

\*\*: 0 01 &lt; P &lt; 0 05

**Table 4. Results of the conditional logistic regression analysis  
in 72 cases, 144 hospital controls, and 144 neighborhood  
controls for adenocarcinoma of lung**

Risk factors	Adjusted Odds Ratio <sup>a</sup>	
	Cases/Hospital controls	Cases/Neighborhood
<b>Smoking</b>		
No. of cigarettes smoked per day		
0	1.00	1.00
1-10	0.72	0.42
11-20	1.48	2.86**
21 +	0.69	1.11
<b>Source of passive smoking</b>		
<b>Childhood</b>		
<b>Mother</b>		
No	1.00	1.00
Yes	1.02	1.04
<b>Father</b>		
No	1.00	1.00
Yes	1.04	1.11
<b>Adult at home</b>		
<b>Spouse</b>		
No	1.00	1.00
Yes	0.78	1.34
<b>Children</b>		
No	1.00	1.00
Yes	0.67	0.73
<b>Workplace</b>		
<b>Coworkers</b>		
No	1.00	1.00
Yes	1.01	1.61
<b>Entertainment</b>		
<b>Friends</b>		
No	1.00	1.00
Yes	1.89	1.42

a : Odds Ratio was adjusted for incense burning, asbestos-related job, working as a cook or the daily consumption of cigarettes

\*\* :  $0.01 < P < 0.05$

**Table 5. Results of the conditional logistic regression analysis in 59 cases, 118 hospital controls, and 118 neighborhood controls for quamous and small cell carcinoma of lung**

Risk factors	Adjusted Odds Ratio <sup>b</sup>	
	Cases/Hospital controls	Cases/Neighborhood
<b>Smoking</b>		
No of cigarettes smoked per day		
0	1.00	1.00
1-10	1.58	1.27
11-20	2.44	2.06
21 +	16.58***	15.30***
<b>Source of passive smoking</b>		
Childhood		
Mother		
No	1.00	1.00
Yes	1.00	0.97
Father		
No	1.00	1.00
Yes	0.58	0.64
Adult at home		
Spouse		
No	1.00	1.00
Yes	1.57	1.75
Children		
No	1.00	1.00
Yes	0.94	1.64
<b>Workplace</b>		
Coworkers		
No	1.00	1.00
Yes	2.07	1.69
<b>Entertainment</b>		
Friends		
No	1.00	1.00
Yes	2.81**	2.96**

b : Odds Ratio was adjusted for use coal as cooking fuel, asbestos-related jobs or passive smoking from friends or daily consumption of cigarettes

\*\* : 0.01 < P < 0.05

\*\*\* : 0.001 < P < 0.01