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Original Article

High risk occupational exposure and family history were risk factors in young lung cancer in Chinese

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Abstract: Objective: This study aimed to analyze lung cancer characteristics and risk factors in young Chinese below 45 years of age. Method: This retrospective study assessed pathologically confirmed lung cancer patients aged <45 years between 2000 and 2013. Gender-matched control patients were identified at the internal medicine and thoracic surgery departments (non-pulmonary disease) as young individuals without cancer during the same period. Results: A total of 420 patients with lung cancer were enrolled, and the control group consisted of 1673 patients. In the lung cancer group, there were a higher percentage of males (male to female ratio of 1.31:1); cancer was mainly adenocarcinoma at stage IV. Multivariate analysis demonstrated that high-risk occupations (OR: 10.9; 95% CI 3.7 to 33.2, P=0.004), smoking or smoking history (OR: 9.9; 95% CI 4.9 to 39.7, P=0.005), family history of lung cancer (OR: 13.8; 95% CI 6.1 to 22.4, P=0.030) were significant risk factors for lung cancer in young Chinese. Compared to collateral relative, the odd ration of lung cancer in first-degree relative (OR: 19.9; 95% CI 7.2 to 35.8, P<0.001), and second-degree relative (OR: 3.5; 95% CI: 1.0 to 5.1, P=0.005). Conclusion: The present study demonstrated that high risk occupational exposure, smoking, family history of lung cancer relatives, and age are significant risk factors for the development of lung cancer in young Chinese.

Keywords: Lung cancer, stage, risk factors, young Chinese

Introduction

Lung cancer is one of the malignant tumors with highest prevalence and mortality worldwide, accounting for 13.5% of all tumors; its mortality ranks first among many tumors [1]. Accordingly, the National Central Cancer Registry (NCCR) reported that lung cancer had the highest incidence in 2010 among Chinese: an overall incidence of 46.08 per 100,000 population (61.86 per 100,000 men and 29.54 per 100,000 women) was found, with more than 600,000 patients newly-diagnosed yearly [2, 3]. In the following year the overall incidence rose to 48.32 per 100,000 population [4]. In agreement, Beijing Cancer Registry (BCR) data indicate that in terms of incidence, lung cancer is now the No. 1 in males and No. 2 in females of Beijing, China [5].

It is widely accepted that lung cancer incidence increases with age, with a high rate in people ≥35 years old as well as in males; Indeed, elderly people (50-80 years old) constitute the group with highest risk for lung cancer, although the disease is not uncommon in young people (less than 44 years old is the new cutoff age segmentation proposed by World Health Organization). A great deal of effort has been made to assess lung cancer incidence and characteristics in young individuals. For instance, a British study analyzed the National Lung Cancer Audit database and found that young patients with lung cancer accounted for about 0.5%, with adenocarcinoma cases amounting to 48%, a higher rate compared with other age groups [6]. Another study in the United States investigated lung cancer data in 1998-2003, and found that young patients (age ≤40 years) with lung cancer accounted for about 1.17% of the total population [7]. Studies in Shanghai (China) showed that lung cancer incidence in the young population (<45 years) was significantly elevated, with lung cancer patients aged 18-45 years reaching 5.275% of

total lung cancer cases [8], a higher rate compared with those obtained in other regions of the world. The reasons for the unexplained high lung cancer rates in young people remain unknown.

Smoking, air pollution, exposure to carcinogens (such as asbestos), and ionizing radiation are known risk factors for lung cancer in the general population [9-12]; however, specific risk factors for young patients remain under studied, especially the role of occupational and genetic factors. Therefore, we aimed in this study to assess the epidemiological and clinical characteristics of lung cancer in young people. Interestingly, occupational exposure, smoking, family history of lung cancer, relatives, and age turned out to be significant risk factors for lung cancer development in this age group. Our findings highlight the social significance of lung cancer prevention and treatment in young individuals.

Methods

Patients

This retrospective study consecutively assessed pathologically confirmed lung cancer patients aged 18 to 45 years (young subjects) admitted to either Department of Thoracic Surgery (People's Hospital of Peking University) or Departments of Pulmonary Tumor and Respiration (Affiliated Hospital of Military Medical Sciences) between 2000 and 2013. Patients were contacted by telephone to confirm the accuracy of related information. The case subjects were patients newly diagnosed with pathologic lung cancer, had no cancer history, aged 18 to 45 years, and had the informed consent. The exclusive criteria included: 1) age more than 45 years; 2) had no cancer history; 3) missing data more than 75 percentage. The control subjects were sex-matched patients who admitted to the Departments of Thoracic Surgery and Respiration during the same period with aged <45 years, at a ratio of 1:4. Written informed consent was obtained from all patients. All information related to patients' privacy and details was strictly confidential. This study was approved by the local ethics committee.

Data collection

The data collected included the following demographic variables, for case and control subjects: gender, ethnicity, age at diagnosis (cases) or interview (controls), education level, smoking status, and pack years smoked, and histological classification (cases only), permanent residence, occupations, smoking status, and family history of tumor. Questions regarding these data were addressed by the original study investigator.

High risk occupational exposure population referred to individuals with exposure to soot, dust particles, and toxic gases: cooks, construction workers, teachers, people exposed to carcinogens, and miners. Never smokers were individuals who reported smoking less than 100 cigarettes per lifetime. Former smokers were individuals who reported smoking cessation at least 2 years prior to interview. No family history was defined as individuals without a history of cancer within the family for three generations. First-degree relatives referred to parents, second-degree relatives to grandparents, and collateral relatives to uncles and aunts.

Statistics analysis

Descriptive data were generated for each variable corresponding to the specific questions in the survey. A multivariable logistic regression analysis model was employed to identify factors associated with lung cancer. A stepwise approach was used for variable selection in the multivariate regression model. Variables exhibiting a statistically significant association ($P<0.05$) with lung cancer in univariate analyses were further evaluated by multivariate analyses. Two-sided $P<0.05$ was considered statistically significant. All analyses were carried out using SPSS for Windows version 14.0 (SPSS, Chicago, IL, USA).

Results

Characteristics of the study population

A total of 420 young lung cancer patients and 1673 gender-matched individuals without lung cancer (control group) were enrolled in this study. The main characteristics of the study population are listed in **Table 1**. Study subjects were aged 15 to 45 years, with a median age of 38 years. About 17.5% of all subjects were engaged in high-risk occupational exposure, including 176/420 (41.9%) and 190/1673 (11.4%) in study and control populations, respectively.

Table 1. Basic characteristics of population

	Total (n=2093, %)	Younger lung cancer (n=420, %)	Control (n=1673, %)	*P*-value
Gender				
M	1222 (58.4)	238 (56.7)	984 (58.8)	0.424
F	871 (41.6)	182 (43.3)	689 (41.2)	
Age				
18-25	788 (37.6)	6 (1.4)	782 (41.3)	<0.001
26-30	271 (12.9)	34 (8.1)	237 (12.5)	0.001
31-35	315 (15.1)	85 (20.2)	230 (12.2)	0.001
36-40	456 (21.8)	158 (37.6)	298 (15.7)	<0.001
41-45	458 (21.9)	137 (32.6)	321 (17.0)	<0.001
Age, median (range)	38 (15-45)	39 (20-45)	32 (15-45)	<0.001
High-risk Occupational exposure	366 (17.5)	176 (41.9)	190 (11.4)	<0.001
Smoking history	1341 (64.1)	304 (72.4)	1037 (62.0)	<0.001
Smoking (cigarettes/year)				
Non-smoking	752 (35.9)	116 (27.6)	636 (38.0)	<0.001
≤100	147 (7.0)	39 (9.3)	108 (6.5)	0.042
101-400	862 (41.2)	106 (25.2)	756 (45.2)	<0.001
401-1000	260 (12.4)	140 (33.3)	120 (7.2)	<0.001
>1000	72 (3.4)	19 (4.5)	53 (3.2)	0.173
Family history[c]	153 (7.3)	112 (26.7)	41 (2.5)	<0.001
Relatives with tumor (n=112)				
Collateral relative	25 (15.3)	18 (16.1)	7 (17.1)	0.02
First-degree relative	103 (63.2)	82 (73.2)	21 (51.2)	0.502
Second-degree relative	35 (21.5)	22 (19.6)	13 (31.7)	0.098

[c]Refers to a history of cancer within 3 generations.

Table 2. Characteristics of lung cancer incidence in the young population

Variable	Number of cases (n=420)	Constituent ratio %
Type		
Adenocarcinoma	284	67.6
Small cell carcinoma	52	12.4
Squamous cell carcinoma	31	7.4
Others*	53	12.6
Mixed adenosquamous carcinoma	15	3.6
Neuroendocrine carcinoma	6	1.4
Non-small cell carcinoma	5	1.2
Uncommon lung cancer	27	6.4
Staging		
I	47	11.2
II	15	3.6
III	54	12.9
IV	304	72.4

*Mixed adenosquamous carcinoma, Neuroendocrine carcinoma, Non-small cell carcinoma and some uncommon lung cancer type were included in the others.

Current smokers or individuals with a history of smoking accounted for 64.1% of the total study population; they included 304/420 (72.4%) and 1037/1673 (62.0%) in study and control populations, respectively.

Lung cancer properties in young patients

The 420 young patients diagnosed with lung cancer included 56.7% males and 43.3% females, indicating that males were more affected by the disease with (**Table 2**). In addition, adenocarcinoma was the main tumor type, accounting for 67.6% of cases, consistent with lung cancer characteristics in the general population. It was followed by small cell lung cancer (SCLC), which represented 12.4%, and squamous carcinoma

Table 3. Univariate and multivariate analyses of risk factors for young lung cancer patients

Factors	Crude OR (95% CI)	*P-value*	Adjusted OR (95% CI)	*P-value*
Age				
15~25	Reference		Reference	
26~30	19.3 (3.6, 37.2)	0.003	18.9 (3.2, 35.3)	<0.001
31~35	39.7 (9.8, 73.4)	<0.001	36.7 (9.2, 69.4)	<0.001
36~40	58.3 (15.7, 89.4)	<0.001	57.1 (14.9, 88.3)	<0.001
41~45	55.6 (14.7, 88.5)	<0.001	51.9 (13.2, 83.1)	<0.001
Gender				
Male	Reference			
Female	1.1 (0.8, 1.9)	0.230		
Occupational exposure[a]				
General	Reference		Reference	
High-risk	13.1 (4.4, 39.5)	0.002	10.9 (3.7, 33.2)	0.004
Smoking[b]				
Non-smoking	Reference		Reference	
In smoking or had smoking history	12.9 (5.1, 43.2)	0.003	9.9 (4.9, 39.7)	0.005
Smoking history (cigarettes/year)				
Non-smoking	Reference		Reference	
≤100	0.6 (0.2, 5.1)	0.010	0.4 (0.2, 4.9)	0.010
101-400	16.7 (5.9, 21.5)	0.004	15.3 (5.3, 19.7)	0.007
401-1000	29.1 (7.9, 43.7)	<0.001	27.9 (7.1, 42.6)	<0.001
>1000	7.5 (4.6, 8.8)	<0.001	6.9 (4.3, 8.4)	<0.001
Family history[c]				
No	Reference		Reference	
Yes	15.7 (6.7, 24.9)	0.010	13.8 (6.1, 22.4)	0.030
Relatives[d]				
Collateral relative	Reference		Reference	
First-degree relative	21.3 (7.7, 39.6)	<0.001	19.9 (7.2, 35.8)	<0.001
Second-degree relative	3.7 (0.9, 5.3)	0.008	3.5 (1.0, 5.1)	0.005

[a]High risk population refers to individuals with exposure to soot, dust particles, and toxic gases: cooks, construction workers, traffic policemen, teachers, people exposedto carcinogens, and miners. General population refers to people without high risk exposure. [b]Non-smoking refers to smoking <100 cigarettes or never smoking over the lifetime. [c]Refers to a history of cancer within 3 generations. [d]First-degree relatives referred to parents, second-degree relatives to grandparents, and collateral relatives to uncles and aunts.

with 7.2%; together, the other types amounted to <7%. For disease staging, the most common grade was Stage IV (72.4%), followed by III (12.9%), consistent with characteristics of insidious incidence and late diagnosis of lung cancer.

Univariate and multivariate analyses of risk factors for lung cancer in the young population

Generally, lung cancer is more likely to occur in young males than females, and the clinical characteristics of lung cancer tend to differ among young individuals of different ages. In this study, lung cancer rates showed a significant elevation trend in young subjects >35 years old (**Table 3**). Smoking is one of the major causes of lung cancer, and an incidence as high as 22.7% was found in current smokers or people with a history of smoking, a rate significantly higher than that of non-smokers (15.4%) (P=0.003). Therefore, the smoking status has a significant impact on disease incidence. Compared with never smoking individuals or those smoking ≤100 cigarettes/year, lung cancer incidence tended to increase with the amounts of cigarettes used; Specifically, cancer incidence was significantly elevated in young individuals smoking 401-1000 cigarettes/year (49.6%). Next, we analyzed the effect of family

history on cancer incidence. We found significantly higher lung cancer incidence in people with relatives within three generations having the disease compared with the rates obtained for those without a family history of lung cancer (27.4% vs. 18.0%, P=0.03). As for collateral relatives, the population with a history of cancer in parents presented an even higher probability of lung cancer (41.2%), followed by those with second-degree relatives affected (28.6%). A relatively low incidence of lung cancer was found in younger individuals compared with older age groups, and the probability of lung cancer increased with age in the study population.

Multivariate analysis revealed five factors significantly associated with lung cancer in young individuals: high-risk occupations (OR=10.9, 95% CI: 3.7 to 33.2, P=0.004), smoking or with history of smoking (OR=9.9, 95% CI: 4.9 to 39.7, P=0.005), family history of lung cancer (OR=13.8, 95% CI: 6.1 to 22.4, P=0.030), relative, and age (**Table 3**). Compared with collateral relatives, the risk for lung cancer in first-degree relatives was OR=19.9 (95% CI: 7.2 to 35.8, P<0.001), and that in second-degree relatives was OR=3.5 (95% CI: 1.0 to 5.1, P=0.005). Similarly, the risk for lung cancer significantly increased with age and amount of cigarettes used (**Table 3**).

Discussion

This study found that among young patients with lung cancer (<45 years old), males were more represented than females; disease incidence was likely to be associated with occupational exposure, family history of lung cancer, smoking status, relative, and age. The risk for lung cancer increased with age and amounts of cigarettes used.

Lung cancer is less common in young individuals compared with the elderly population. Of note, the definition of young patients with lung cancer differs according to studies, with cut-offs of 30, 40, and 50 years old adopted in addition to the commonly used 45 years old. As shown above, lung cancer incidence showed a significantly trend of increase after 35 years old. A study conducted by Strand et al. on 1108 patients aged 20-44 years with malignant lung cancer between 1954-1998 revealed a continuously increasing rate in female aged 40-44 years; this was not the case in males of the same age group after 1970 [13]. In contrast, Tian et al. assessed 92 patients <40 years old who received surgical resection for primary lung cancer between 1978 and 1996, and found a significantly higher rate in males compared with females (3.38:1) [14]. Our results revealed a trend of increase in young females, with incidence peak shifted to an earlier age segmentation, which requires confirmation with a large-scale study.

Smoking is directly related to lung cancer [15-17], as confirmed in this study. Randomized controlled studies conducted in the United States and some European countries also confirmed smoking as a risk factor for lung cancer in young individuals (<45 years old); meanwhile, the risk for lung cancer in young subjects with a smoking duration of more than 20 years was 5 times that of non-smoking population. In this study, lung cancer incidence showed an increasing trend in non-smoking young females. While cigarette smoking is normally considered the primary cause for gender difference in lung cancer incidence. Besides cigarette smoking, higher exposure to other risk factors, such as work-related air pollution or carcinogens in men, may also contribute to the increased susceptibility in men [18, 19]. Between women and men, some differences may exist in risk factors for lung cancer. For example, passive smoking and household exposure were demonstrated to be important causes of female's lung cancer [20, 21]. Moreover, young individuals are more likely to experience exposures in high-risk occupations and to carcinogens. However, previous studies do not show an association between high-risk occupations/carcinogens and lung cancer in young patients. Interestingly, we found smoking and occupational exposure are important risk factors for lung cancer in the young population.

A possible correlation between family history and lung cancer is worth exploring. As shown above, lung cancer incidence was higher in individuals with a history of cancer in relatives within three generations than in the normal population, and more elevated in patients with a history of cancer in the first-degree relatives (parents) than in the second-degree relatives. These findings suggest a close monitoring of young individuals with a family history of cancer, in agreement with Coté et al. [22].

The disease classification used in this study is consistent with that of the literature. Kong et al. found that squamous cell carcinoma is more likely to occur in males, and adenocarcinoma more frequent in females. In the past 25 years, the proportion of adenocarcinoma in the female population has increased by 31.4%, and that of squamous cell carcinoma reduced by 25.6%. However, adenocarcinoma and small cell carcinoma proportions were shown to be significantly increased in both males and females [23].

Numerous studies have reported that adenocarcinoma and squamous cell carcinoma are more likely to occur in the young population, also in other cancer types [24-26]. Yang et al. adopted a cutoff of 50 years old, and reported that adenocarcinoma and squamous cell carcinoma accounted for 52% and 9%, respectively, in young patients with lung cancer, while adenocarcinoma accounted for 55% and squamous cell carcinoma for 24% in the elderly group [5]. Tian et al. revealed that among the lung cancer patients <40 years old, squamous cell carcinoma presented the highest proportion among the histological types, while adenocarcinoma and small cell carcinoma rates did not show a statistically significant difference [14]. Yazgan adopted a cutoff of 50 years old and found that squamous cell carcinoma was most significant in young patients with lung cancer (56%), followed by adenocarcinoma (22%) [27]. Elci et al. analyzed 912 males with lung cancer in Turkey with a cutoff of 45 years old, and showed the risk of smoking-related lung squamous cell carcinoma significantly increased with age, while small cell carcinoma decreased; the relative risk of adenocarcinoma was not increased. In other words, the risk of smoking-related small cell carcinoma is very high in lung cancer patients younger than 45 years old [28].

The possible reasons for a high adenocarcinoma rate in young lung cancer patients may include changes of smoking habits; in addition, filter-tipped cigarettes tend to promote finer cigarettes which transfer carcinogens into peripheral lung, the favorite location of adenocarcinoma, thereby inducing lung cancer. Furthermore, compared with other pathological types, adenocarcinoma induction is easier, i.e. it can be induced by fewer carcinogens or gene mutations. It has been proposed that the molecular phenotype of young patients with lung cancer may differ from that of middle-aged and elderly patients [29]. However, there is a lack of molecular phenotype data in this study, due to its retrospective nature.

Furthermore, numerous studies have revealed that most young patients are diagnosed at advanced lung cancer stages. Elci et al. adopted a cutoff of 45 years old and demonstrated that advanced lung cancer (III/IV stages) was significantly higher in the young population than in the elderly group (46% vs. 16.6%), with stage I lung cancer rarely found in the young population [28]. Yang et al. also reported that advanced lung cancer (III/IV stages) was significantly higher in the young population <50 years old than in the elderly group (72%/47%) [5]. Importantly, Wang et al. found that lung cancer in the young population was easy to be misdiagnosed [30], which might be one of the reasons for the late stage lung cancer in the young population at diagnosis, suggesting that lung cancer in the young population is worthy of more attention.

This study is not without limitations. For example, both lung cancer and control patients were from two centers, with a possibility of selection bias. Between groups, the age was difference, which was the cofound factor for the study. Unclear answers regarding some confounding factors were obtained in the control group, which tends to increase the analysis uncertainty of lung cancer related risk factors, thereby requiring a larger-scale, multicenter prospective study for confirmation in the future.

In conclusion, we demonstrated that occupational exposure, smoking, family history of lung cancer, relatives, and age are risk factors for lung cancer development. This study provides clinical information for preventing lung cancer in the young population and screening this high-risk population.

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Disclosure of conflict of interest

None.

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