Jpn. J. Cancer Res. 85, 1196–1199, December 1994

Risk of Lung Cancer among Cigarette Smokers in Relation to Tumor Location

Hiroyuki Shimizu,[1] Chisato Nagata,[1] Eiju Tsuchiya,[2] Ken Nakagawa[3] and Siu-Yuhe Weng[4]

[1]Department of Public Health, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500, [2]Department of Pathology, Cancer Institute and [3]Department of Chest Surgery, Cancer Institute Hospital, 1-37-1 Kami-Ikebukuro, Toshima-ku, Tokyo 170 and [4]Uchida Hospital, 2-39 Senju, Adachi-ku, Tokyo 120

To evaluate the effect of cigarette smoking on lung cancer by tumor location and histological type, we compared the smoking history obtained from medical records of 605 patients with squamous cell carcinoma (194 males and 10 females) or adenocarcinoma (219 males and 182 females) of the lung and 183 patients with metastatic lung cancer (82 males and 101 females) who had been aged 40 years or over at the time of surgical resection at the Cancer Institute in Tokyo from 1973–1991. The tumors which developed in a main or segmental bronchus were classified as central type, and those in a subsegmental or more distal bronchi were categorized as peripheral type. Cases with adenocarcinoma were classified by a pathologist into two histological subtypes, papillary and tubular types, according to the WHO lung carcinoma classification. Risk of squamous cell carcinoma was strongly associated with cigarette smoking for both central (OR (odds ratio) = 10.3 in males and 4.4 in females) and peripheral sites (OR = 10.7 in males and 6.5 in females). There was no significant association between cigarette smoking and adenocarcinoma for any tumor site or histological subtype in both sexes.

Key words: Lung neoplasm — Smoking — Squamous cell carcinoma — Adenocarcinoma — Tumor location

It has long been known that cigarette smoking plays a role in the etiology of squamous cell type of lung cancer.[1)] For adenocarcinoma of the lung, however, the association with cigarette smoking has been disputed. Some previous studies have found a positive association with cigarette smoking that is less strong than that for squamous cell carcinoma,[2–4)] but others have not.[5, 6)] It is probable that part of the difficulty in characterizing the effect of cigarette smoking on adenocarcinoma of the lung is the histological heterogeneity of the tumors. Only a few epidemiologic studies have paid attention to histological classification in evaluating the effect of smoking on adenocarcinoma of the lung.[7)]

The degree of carcinogenicity of cigarette smoke may be related to the location of the particle deposition. The geometrical sites of preferential particle deposition in the central airway have been demonstrated to be favored sites of cancer induction,[8, 9)] but the deposition pattern in the distal part of the bronchial trees remains to be elucidated. If squamous cell carcinoma and adenocarcinoma of the lung have cigarette smoking as a common major etiologic factor, the associations with cigarette smoking according to tumor site for these histological types might be similar to each other, i.e. they should correspond to the smoke deposition pattern. Although adenocarcinoma is known to be predominant in peripheral sites of the lung,[10, 11)] it is possible that the risk of adenocarcinoma in the central part of the lung is closely related to cigarette smoking, as is the case for the central type of squamous cell carcinoma (we assume here that squamous cell carcinoma in the central site of the lung is strongly associated with cigarette smoking because it is known that squamous cell carcinoma is relatively common in the central site of the lung[10, 11)]).

We conducted a case-control study to evaluate the effect of cigarette smoking on two major histological types of lung cancer, taking into account their geometric distribution as well as histological subtype.

MATERIALS AND METHODS

We included primary lung cancer patients diagnosed as squamous cell carcinoma and adenocarcinoma, who were aged 40 years or over at diagnosis and underwent surgical resection at the Cancer Institute Hospital in Tokyo from 1973 to 1991. Two hundred and seven males and 10 females with squamous cell carcinoma and 228 males and 194 females with adenocarcinoma were accumulated. We excluded from the following analyses 22 males (13 cases with squamous cell carcinoma and 9 cases with adenocarcinoma) and 12 females with adenocarcinoma whose smoking status was unknown. Eighty-two males and 101 females with metastatic lung cancer who were also aged 40 years or over at diagnosis and underwent surgical resection at the same hospital over the same period were selected as controls. Seven male and 6 female metastatic lung cancer patients were excluded from the controls because their smoking status was not known. Information on the primary site of cancer was taken from the medical records, and the patients with smoking-related

cancers such as laryngeal, pharyngeal, and cervical cancers were not included in controls. Table I shows the age and sex distribution of cases and controls. Major primary sites of the cancers in controls were the colon and rectum (30.3%), breast (11%), and others, including several kinds of sarcomas (34.8%).

All cases included in the study were histologically confirmed by one pathologist according to the WHO lung carcinoma classification.[12] We divided adenocarcinoma into two categories; 1) papillary type (papillary adenocarcinoma and bronchiolo-alveolar carcinoma) and 2) tubular type (acinar adenocarcinoma and solid carcinoma with mucus formation). The tumors which developed in a main or segmental bronchus were classified as "central type" and those in subsegmental or more distal bronchi were assigned as "peripheral type."

Lifelong smoking histories were collected from all study subjects through interview at their first visit to the hospital. Number of cigarettes smoked per day and years of smoking were obtained from current and ex-smokers.

To estimate the association between cigarette smoking and risk of different subsite and histological type/subtype of lung cancer, the age-adjusted odds ratios (ORs) and 95% confidence intervals were calculated using the Mantel-Haenszel method.[13] Current and ex-smokers were combined into cigarette smokers. When there was zero frequency in a cell of the stratum-specific tables, the value 0.5 was assigned. The subjects were divided into three age strata (40–59, 60–69 and 70+ years old). Tests for linear trend were performed on ordinal variables.

Table I. Age and Sex Distribution of Lung Cancer Patients with Diagnosis of Squamous Cell Carcinoma (SQ) and Adenocarcinoma (AD) and Controls

Age group (years old)	Males			Females		
	SQ	AD	Controls	SQ	AD	Controls
40–59	51	76	36	3	77	44
60–69	86	75	31	1	62	36
70+	57	68	15	6	43	21
Total	194	219	82	10	182	101

RESULTS

Sixty-five (79.3%) male and 21 (20.8%) female controls were cigarette smokers. Table II shows that there is a large difference in the ORs for cigarette smokers between squamous cell carcinoma and adenocarcinoma in both sexes, but the OR of squamous cell carcinoma for females was smaller than that for males. There was no significant association between cigarette smoking and any subtype of adenocarcinoma in both sexes. As the risks were similar for papillary and tubular types, subtype classification for adenocarcinoma was not used in further analyses considering tumor location.

When histological type and tumor subsite were considered in the stratified analysis, the increased ORs of squamous cell carcinoma were found for both central and peripheral sites in males and females (Table III). No association with cigarette smoking was observed for any subsite of adenocarcinoma in both sexes. The tumor sites could not be localized for 31 squamous cell carcinomas and 27 adenocarcinomas in males, and 19 adenocarcinomas in females. The proportions of cigarette smokers for such unlocalized tumors were 90.3%, 77.8%, and 26.3%, respectively.

The analysis was restricted to males when we estimated the ORs by subsite according to the number of cigarettes smoked per day and the duration of cigarette smoking because the number of cigarette smokers among females was too few to allow meaningful analysis. Subsite classification was only provided for squamous cell carcinoma since most adenocarcinoma is of peripheral type and the OR of central type of adenocarcinoma was not different from that of peripheral type. Tables IV and V present statistically significant trends ($P<0.001$) in risk of squamous cell carcinoma in both subsites with increasing number of cigarettes smoked per day and years of smoking. Risk of adenocarcinoma for men who smoked

Table II. Age-adjusted Odds Ratios (ORs) of Lung Cancer with Cigarette Smoking by Sex and Histological Type

	Males				Females			
	No.	%[a]	OR[b]	95% CI[c]	No.	%	OR	95% CI
SQ[d]	194	97.9	12.8	(5.1–32.3)	10	70.0	7.4	(2.2–25.5)
AD[e]	219	84.9	1.5	(0.8–2.9)	182	22.0	1.1	(0.6–1.9)
Papillary	139	84.9	1.6	(0.8–3.2)	154	20.1	1.0	(0.5–1.8)
Tubular	74	86.5	1.7	(0.7–4.0)	25	36.0	1.9	(0.7–5.0)

a) Percentage of cigarette smokers in cases.
b) Based on category for non-smokers.
c) 95% confidence interval.
d) Squamous cell carcinoma of the lung.
e) Adenocarcinoma of the lung.

Table III. Age-adjusted Odds Ratios (ORs) of Squamous Cell Carcinoma and Adenocarcinoma with Cigarette Smoking by Sex and Tumor Location

	Males				Females			
	No.	%[a]	OR[b]	95% CI[c]	No.	%	OR	95% CI
Squamous cell carcinoma								
Central	78	98.7	10.3	(2.8–37.6)	3	66.7	4.4	(0.8–25.7)
Peripheral	85	98.8	10.7	(3.2–35.8)	7	71.4	6.5	(1.6–26.0)
Adenocarcinoma								
Central	4	75.0	0.5	(0.1–3.2)	6	16.7	1.3	(0.2–7.3)
Peripheral	188	87.2	1.8	(0.9–3.6)	157	21.7	1.0	(0.6–1.9)

a) Percentage of cigarette smokers in cases.
b) Based on category for non-smokers.
c) 95% confidence interval.

Table IV. Age-adjusted Odds Ratios (ORs) of Squamous Cell Carcinoma and Adenocarcinoma for Males According to the Number of Cigarettes Smoked per Day

	1–20 cigarettes/day		21+ cigarettes/day	
	OR[a]	95% CI[b]	OR	95% CI
Squamous cell carcinoma				
Central	5.0	(1.1–21.7)	18.6	(4.9–70.3)
Peripheral	8.2	(2.1–30.4)	15.5	(4.4–55.2)
Adenocarcinoma				
Central+peripheral	1.1	(0.6–2.3)	2.1	(1.0–4.5)

a) Based on category for non-smokers.
b) 95% confiidence interval.

Table V. Age-adjusted Odds Ratios (ORs) of Squamous Cell Carcinoma and Adenocarcinoma for Males According to the Number of Years of Smoking

	1–40 years of smoking		41+ years of smoking	
	OR[a]	95% CI[b]	OR	95% CI
Squamous cell carcinoma				
Central	5.1	(1.2–21.2)	16.5	(3.8–70.5)
Peripheral	6.0	(1.4–25.3)	20.7	(5.2–82.0)
Adenocarcinoma				
Central+peripheral	1.1	(0.5–2.2)	2.2	(0.9–5.6)

a) Based on category for non-smokers.
b) 95% confidence interval.

more than 20 cigarettes per day achieved statistical significance and there was a trend ($P<0.05$) in risk of adenocarcinoma with increasing number of cigarettes smoked per day but not of years of smoking.

DISCUSSION

We found a marked difference in the association with cigarette smoking between squamous cell carcinoma and adenocarcinoma of the lung, regardless of the histological subtype and tumor site.

For squamous cell carcinoma, Sobue *et al.*[14] observed that the risk increase related to cigarette smoking for the central type was similar to that for the peripheral type. There is no report on the association between cigarette smoking and risk of adenocarcinoma according to the tumor site of the lung. However, there is an informative study by Yang *et al.*[9] They observed the incidence rates of different histological types of respiratory tract cancers according to anatomic subsite along the central airway, except for the region distal to the lobar bronchi. When the surface area of each subsite was taken into account to evaluate the distribution of incidence per unit area, squamous cell carcinoma and adenocarcinoma had commonly elevated incidence rates (per unit area) at the glottis and main bronchi. They suggested that the particle deposition pattern in the respiratory tract is important in cancer pathogenesis because the sites with high incidence per unit area corresponded closely with preferential sites of smoke deposition.

Several experimental or theoretical studies have been presented on the intrabronchial deposition pattern of cigarette smoke.[15–17] Martonen[16] showed that particles concentrate at bifurcations using his mathematical model, while total deposition appears to be favored in the peripheral lung.

In the present study, close linkage with cigarette smoking was observed in both subsites for squamous cell carcinoma. The OR for peripheral type was similar to that for central type in each sex. Although we cannot deduce that the estimated ORs would be indices of the surface concentration of smoke deposits by subsite, relative particle deposition per surface unit in peripheral sites might not be less than that in central sites. At least, the concentration of deposits in peripheral sites might be sufficient to contribute to the risk excess of squamous cell carcinoma. Bifurcations (branching sites) would be preferential sites for smoke deposition even in peripheral

regions. However, the increases in risk of adenocarcinoma associated with cigarette smoking for central and peripheral sites were much smaller than those of squamous cell carcinoma.

As this study was based on relatively small numbers of cases, analyses for subgroups, especially for central type of adenocarcinoma lack statistical power, so we must be cautious in interpreting the results.

The possibility of selection bias should also be considered because we included only surgically resected cases. However, it seems unlikely that their smoking status would have been different from that among non-resected cases.

One study by Suzuki *et al.*[7] examined the relationship of histological classification of adenocarcinoma to cigarette smoking. Although they found increased ORs for male current smokers for tubular type (OR=3.7) as well as papillary type of adenocarcinoma (OR=6.1), no clear difference in the risk pattern was seen between papillary and tubular types. We could not confirm an elevated risk of either type of adenocarcinoma. Selection of controls from metastatic lung cancer patients might have influenced the magnitudes of ORs. However, comparison of the ORs between different histological types or tumor sites is valid in our study because the effect of bias in control selection is independent of histological and subsite classification. Similar risks of papillary and tubular types observed in our study were in agreement with the result by Suzuki *et al.*[7] As histological or subsite classification by the pathologist also does not appear to have depended directly upon the smoking status, the possibility of misclassification bias could be neglected.

A total of 31 squamous cell carcinomas and 46 adenocarcinomas could not be localized because most of the tumors extended into both central and peripheral regions. As the ORs were calculated with correction for zero frequency cells, the association with smoking appeared to be weaker for central or peripheral type of squamous cell carcinoma than that for the entire group of squamous cell carcinoma. However, the proportion of cigarette smokers for unlocalized tumors was intermediate between those for central and peripheral types for both squamous cell carcinoma and adenocarcinoma cases. Therefore, the tumors with unassigned sites should not have affected the ORs observed in our study.

(Received June 2, 1994/Accepted August 29, 1994)

REFERENCES

1) Watkin, S. W. Temporal, demographic and epidemiologic variation in histologic subtypes of lung cancer: a literature review. *Lung Cancer,* **5,** 69–81 (1989).
2) Osann, K. E., Culver, H. A., Kurosaki, T. and Taylor, T. Sex differences in lung-cancer risk associated with cigarette smoking. *Int. J. Cancer,* **54,** 44–48 (1993).
3) Lubin, J. H. and Blot, W. J. Assessment of lung cancer risk factors by histologic category. *J. Natl. Cancer Inst.,* **73,** 383–389 (1984).
4) Morabia, A. and Wynder, E. L. Cigarette smoking and lung cancer cell type. *Cancer,* **68,** 2074–2078 (1991).
5) Yesner, R., Gelfman, A. and Feinstein, A. A reappraisal of histopathology in lung cancer and correlation of cell type with antecedent cigarette smoking. *Am. Rev. Respir. Dis.,* **107,** 790–797 (1973).
6) Auerbach, O., Garfinkel, L. and Parks, V. R. Histologic type of lung cancer in relation to smoking habits, year of diagnosis and sites of metastases. *Chest,* **67,** 382–387 (1975).
7) Suzuki, T., Sobue, T., Fujimoto, I., Doi, O. and Tateishi, R. Association of adenocarcinoma of the lung with cigarette smoking by grade of differentiation and subtype. *Cancer Res.,* **50,** 444–447 (1990).
8) Schlesinger, R. B. and Lippmann, M. Selective particle deposition and bronchogenic carcinoma. *Environ. Res.,* **15,** 424–431 (1978).
9) Yang. C. P., Gallagher, R. P., Band, P. R., Thomas, D. B. and Russell, D. A. Differences in incidence rates of cancers of respiratory tract by anatomic subsite and histologic type: an etiologic implication. *J. Natl. Cancer Inst.,* **81,** 1829–1831 (1989).
10) McDowell, E. M. and Beals, T. F. Epithelial neoplasms. *In* "Biopsy Pathology of the Bronchi," pp. 309–357 (1986). Chapman and Hall, London.
11) Gatter, K. C. and Dunnill, M. S. Tumors of the lung. *In* "Oxford Textbook of Pathology, Volume 2a, Pathology of System," pp. 1032–1042 (1992). Oxford University Press, Tokyo.
12) World Health Organization. The World Health Organization histological typing of lung tumours. Second Edition. *Am. J. Clin. Pathol.,* 77, 123–136 (1981).
13) Breslow, N. E. and Day, N. E. Classical methods of analysis of data. *In* "Statistical Methods in Cancer Research. Volume 1, The Case-control Studies," pp. 122–159 (1980). IARC. Lyon.
14) Sobue, T., Suzuki, T., Horai, T., Matsuda, M. and Fujimoto, I. Relationship between cigarette smoking and histologic type of lung cancer, with special reference to sex difference. *Jpn. J. Clin. Oncol.,* **18,** 3–13 (1988).
15) Muller, W. J., Hess, G. D. and Scherer, P. W. A model of cigarette smoke particle deposition. *Am. Ind. Hyg. Assoc. J.,* **51,** 245–256 (1990).
16) Martonen, T. B. Deposition patterns of cigarette smoke in human airways. *Am. Ind. Hyg. Assoc. J.,* **53,** 6–18 (1992).
17) Lippmann, M., Yeates, D. B. and Albert, R. E. Deposition, retention, and clearance of inhaled particles. *Br. J. Ind. Med.,* **37,** 337–362 (1980).