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Association between Smoking and Tumor Progression in Japanese Women with Adenocarcinoma of the Lung

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We studied the effect of smoking on tumor progression in 3312 patients with lung cancer registered at the National Matsudo Hospital and National Cancer Center Hospital East between 1977 and 1996. The odds ratios of the following variables for tumor extent (localized versus advanced disease) and hazard ratios for survival were calculated in both sexes separately using the logistic regression and Cox proportional hazard models, respectively: smoking history, number of cigarettes smoked per day, pack-years smoked, age, histological type, and the year of admission. Of the 943 women, 367 (38.9%) were smokers and 694 (73.6%) had adenocarcinoma, whereas of the 2369 men, 2255 (95.2%) were smokers and 1010 (42.6%) had adenocarcinoma. In female adenocarcinoma patients, the odds ratio (95% confidence interval) for advanced disease and the hazard ratio (95% confidence interval) for survival with an increase of 30 cigarettes smoked per day were 2.86 (1.49–5.49) and 1.52 (1.13–2.04), respectively, but in those with non-adenocarcinoma, the odds ratio and hazard ratio were 0.96 (0.41–2.23) and 1.13 (0.75–1.70), respectively. In male patients, smoking history influenced tumor progression regardless of histological type, but the odds ratios and hazard ratios were lower than those for women with adenocarcinoma. In conclusion, smoking habit was closely correlated with progression of adenocarcinoma in women. This association was not observed in women with non-adenocarcinoma and was weaker in men, suggesting various effects of smoking on lung cancer development depending on gender and the histological type of the tumor.

Key words: Smoking — Lung adenocarcinoma — Women — Progression — Survival

The association between cigarette smoking and the occurrence of lung cancer has been repeatedly demonstrated. The strength of the association is influenced by several factors, especially by the histological type of the tumor.[1,2] The relative risk for lung cancer among smokers over non-smokers is reported to be 2–10 for adenocarcinoma, usually found in the periphery of the lung, and more than 10 for squamous cell carcinoma and small cell carcinoma, mainly located centrally in the respiratory tract.[1,2] The effects of smoking on lung cancer occurrence also vary between men and women. Although there are epidemiological data indicating no gender difference in risk of lung cancer associated with smoking,[1] recent studies suggest that female smokers are at higher risk of lung cancer than male smokers if the degree of smoking is controlled.[3,4]

According to the recent hypothesis of multistep carcinogenesis, several genes are probably involved at different steps in neoplastic evolution.[5] The degree of exposure to external carcinogens may influence the genes in the late step that is essential for lung cancer progression.[6] Thus, smoking may affect the extent and prognosis of lung cancer as well as the occurrence of the disease. Several reports on the association between smoking and prognosis of lung cancer are available, but they present inconsistent results.[7–13] In addition, they contained critical problems, such as only limited subgroups of patients investigated, lack of detailed information on smoking habits, and both men and women included simultaneously in a model in spite of great differences in smoking habit and tumor histology between the two sexes. In this study, we investigated the association between smoking and both disease extent at initial presentation and outcome of lung cancer, and the influences of tumor histology and gender on this association.

MATERIALS AND METHODS

Between 1977 and 1991, 2474 lung cancer patients were registered at the National Matsudo Hospital and between 1992 and 1996, 899 were registered at the

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National Cancer Center Hospital East (the National Matsudo Hospital became the National Cancer Center Hospital East in 1992). Sixty-one patients were excluded from the study because smoking history data were not available. Thus, the subjects of the study were a cohort of 3312 patients that included 1198 surgically treated and 2114 medically treated patients. The median observation period of the study population was 11 months (range, 0–207), and that for censored cases was 46 months (range, 0–206). Patients who were alive at the end of the observation period were defined as censored cases. Smoking history was obtained from the Lung Cancer Data Base, which contains clinical data obtained at the time of admission, including number of cigarettes smoked per day and pack-years smoked (the number of cigarettes smoked per day×years smoked/20). Histological types were determined according to the World Health Organization classification of lung tumors[14] and were combined into two groups, adenocarcinoma and non-adenocarcinoma, the latter including squamous cell carcinoma, small cell carcinoma, large cell carcinoma, adenosquamous carcinoma, and unclassified carcinoma. Histological confirmation of the specific carcinoma diagnosis in medically treated patients was based on examination of biopsy, autopsy, and/or cytology specimens. Transbronchoscopic lung biopsy, percutaneous needle biopsy, exploratory thoracotomy, biopsy of metastatic sites, and cytological examinations were positive in 1192, 171, 29, 135 and 1879 patients, respectively, and autopsies were performed in 115 cases. Histological type was confirmed by histological examination in 1508 (71%) of the 2114 medically treated patients and by cytological examination alone in 606 (29%). The histological diagnoses were reviewed by one of the authors. Clinical staging was used to estimate tumor extent in both surgically and medically treated patients according to the TNM staging system of the Union Internationale Contre Cancer, issued in 1986.[15] We categorized the stages into two groups: localized disease consisting of stage I and II, and advanced disease consisting of stage III and IV, the latter group being potentially uncurable.

We studied the association between smoking history and tumor extent separately for each sex using the logistic regression model. The outcome variable was defined as tumor extent, which was coded as "zero" to indicate localized disease, or "one" to indicate advanced disease. Explanatory variables were age, smoking history (no or yes), number of cigarettes smoked per day, pack-years smoked, histological type, and year of admission. The years were categorized into the following four groups to enable the study cohort to be also categorized by hospital: 1977–1981, 1982–1986, 1987–1991, and 1992–1995. The variables of age, number of cigarettes smoked per day, and pack-years smoked were included in the model as continuous variables. The association between survival and smoking history was investigated in the advanced disease cohort by using the Cox proportional hazard model. We excluded the localized disease population from this analysis, because more than 60% of the cohort were censored cases. Survival curves were plotted using the Kaplan-Meier method. Survivals of patients with and without smoking history were compared by means of the log-rank test. All calculations were carried out using the STATISTICA (Stat-Soft) software system.

Table I. Characteristics of Patients

	Female (%) (n=943)	Male (%) (n=2369)	Total (%) (n=3312)
Age median (range)	65 (25–92)	67 (22–91)	66 (22–92)
Smoking history			
No	576 (61.1)	114 (4.8)	690 (20.8)
Yes	367 (38.9)	2255 (95.2)	2622 (79.2)
Histological diagnosis			
Adenocarcinoma	694 (73.6)	1010 (42.6)	1704 (51.4)
Squamous cell carcinoma	112 (11.9)	845 (35.7)	957 (28.9)
Adenosquamous carcinoma	15 (1.6)	40 (1.7)	55 (1.7)
Large cell carcinoma	29 (3.1)	145 (6.1)	174 (5.3)
Small cell carcinoma	90 (9.5)	325 (13.7)	415 (12.5)
Unclassified carcinoma	3 (0.3)	4 (0.2)	7 (0.2)
Stage			
I	278 (29.5)	468 (19.8)	746 (22.5)
II	24 (2.5)	104 (4.4)	128 (3.9)
IIIa	140 (14.8)	496 (20.9)	636 (19.2)
IIIb	147 (15.6)	503 (21.2)	650 (19.6)
IV	354 (37.5)	798 (33.7)	1152 (34.8)

Table II. Univariate Analysis of the Association between Tumor Extent and Smoking History in Female Lung Cancer Patients

Variables		Odds ratios (95% confidence interval)		
		All histologies included (*n*=943)	Adenocarcinoma (*n*=694)	Non-adenocarcinoma (*n*=249)
Age	a 10-year increment	1.05 (0.94–1.18)	1.06 (0.94–1.20)	0.65 (0.45–0.93)
Smoking history	No	1	1	1
	Yes	1.87 (1.40–2.51)	1.81 (1.25–2.63)	0.61 (0.29–1.35)
No.[a)]	an increase of 30	2.86 (1.78–4.62)	2.84 (1.49–5.41)	1.03 (0.47–2.26)
PY[b)]	a 40-PY increase	1.90 (1.37–2.62)	1.99 (1.23–3.22)	0.90 (0.54–1.51)
Histology	Adenocarcinoma	1	—	—
	Non-adenocarcinoma	2.41 (1.70–3.43)	—	—
Years	1977–81	1	1	1
	1982–86	1.81 (1.14–2.87)	1.43 (0.84–2.44)	3.65 (1.39–9.56)
	1987–91	0.92 (0.60–1.41)	0.73 (0.44–1.20)	1.82 (0.76–4.37)
	1992–96	0.74 (0.48–1.14)	0.55 (0.33–0.90)	2.93 (1.05–8.19)

a) Number of cigarettes smoked per day.
b) Pack-years smoked.

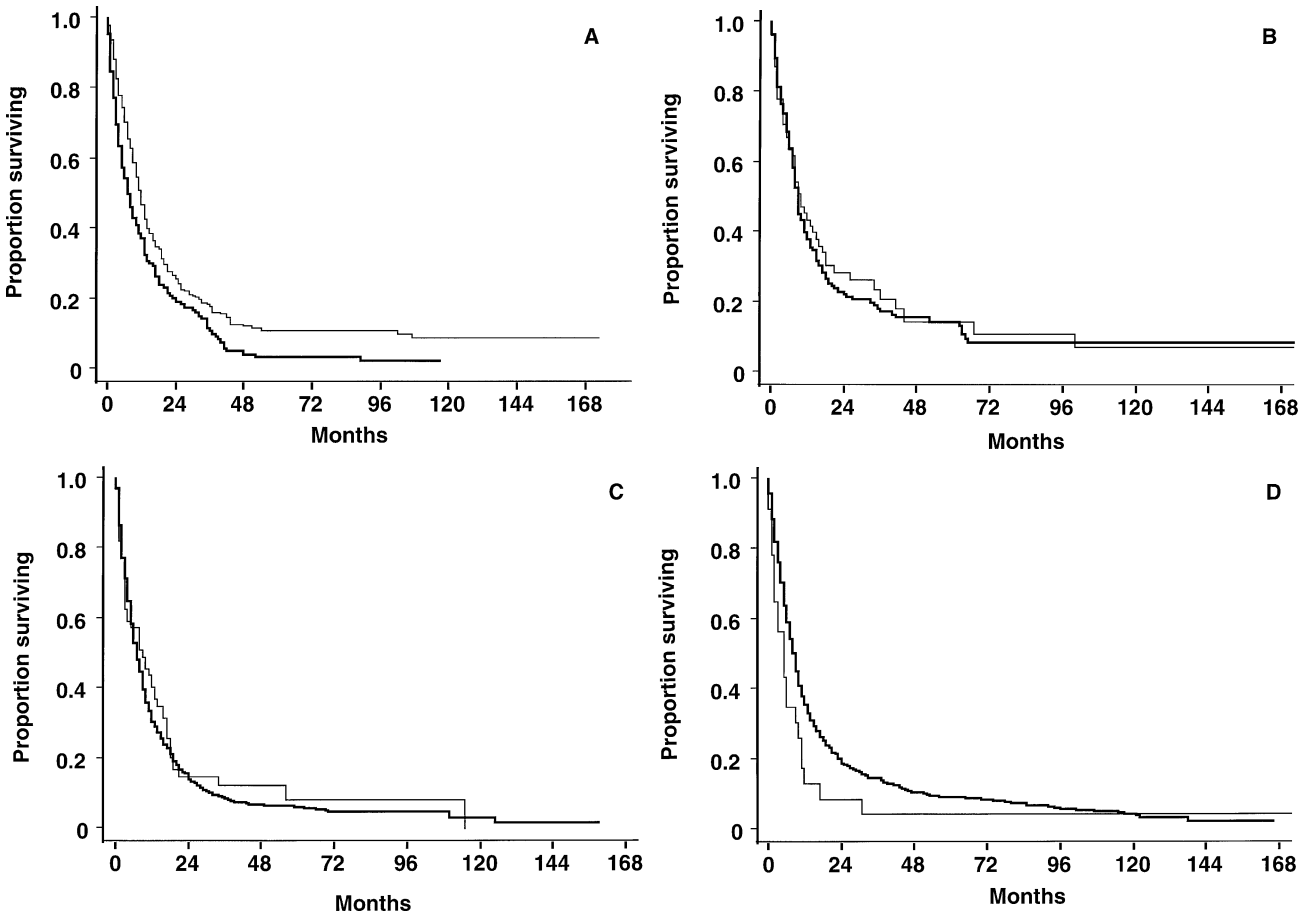

Fig. 1. Survival time in patients with advanced lung cancer according to gender and smoking history. A) Women with adenocarcinoma (*n*=440). Smokers had significantly poorer survival than never-smokers (*P*=0.002 by the log-rank test). B) Women with non-adenocarcinoma (*n*=201). C) Men with adenocarcinoma (*n*=759). D) Men with non-adenocarcinoma (*n*=1038). Thin line, never-smokers, and thick line, smokers.

RESULTS

The study population of 3312 patients included 943 (28.5%) women and 2369 men aged 25–92 years (median: 65 years) and 22–91 years (median: 67 years), respectively. The predominant smoking history and histological types differed between the sexes. Of the 943 women, 576 (61.1%) were never-smokers and 694 (73.6%) had adenocarcinoma histologically, whereas of the 2369 men, 2255 (95.2%) had a history of smoking and 1010 (42.6%) and 845 (35.7%) had adenocarcinoma and squamous cell carcinoma, respectively, histologically (Table I). The gender difference in distribution of smoking status was greater when compared within each histological category. Never-smokers accounted for 512 (73.8%) of the 694 women patients with adenocarcinoma and 64 (25.7%) of the 249 with non-adenocarcinoma, whereas never-smokers accounted for only 81 (8.0%) of the 1010 male patients with adenocarcinoma and 33 (2.4%) of the 1359 with non-adenocarcinoma. The distribution of tumor extent was also slightly different: advanced disease was noted in 641 (68.0%) of the women, but in 1797 (75.9%) of the men (Table I).

In female patients, advanced tumors accounted for 60% (307/512) and 73% (133/182) of never-smokers and smokers with adenocarcinoma, respectively, and they

Table III. Univariate Analysis on the Association between Tumor Extent and Smoking History in Male Lung Cancer Patients

Variables		Odds ratios (95% confidence interval)		
		All histologies included (n=2369)	Adenocarcinoma (n=1010)	Non-adenocarcinoma (n=1359)
Age	a 10-year increment	0.94 (0.86–1.03)	0.98 (0.86–1.11)	0.90 (0.79–1.03)
Smoking history	No	1	1	1
	Yes	1.08 (0.70–1.66)	0.92 (0.54–1.57)	1.42 (0.67–3.01)
No.[a)]	an increase of 30	1.37 (1.11–1.69)	1.31 (0.94–1.83)	1.40 (1.06–1.85)
PY[b)]	a 40-PY increase	1.23 (1.09–1.40)	1.26 (1.02–1.55)	1.21 (1.03–1.43)
Histology	Adenocarcinoma	1	—	—
	Non-adenocarcinoma	1.07 (0.88–1.29)	—	—
Years	1977–81	1	1	1
	1982–86	1.79 (1.31–2.45)	2.50 (1.50–4.15)	1.45 (0.98–2.16)
	1987–91	1.30 (0.97–1.73)	1.63 (1.02–2.60)	1.14 (0.79–1.64)
	1992–96	1.21 (0.90–1.64)	1.22 (0.77–1.93)	1.33 (0.89–1.98)

a) Number of cigarettes smoked per day.
b) Pack-years smoked.

Table IV. Multivariate Analysis on the Association between Tumor Extent and Smoking History

Variables		Odds ratios (95% confidence interval)		
		All histologies included[c)]	Adenocarcinoma[d)]	Non-adenocarcinoma[d)]
Female				
Smoking history	No	1	1	1
	Yes	1.46 (1.05–2.02)	1.81 (1.24–2.64)	0.61 (0.27–1.39)
No.[a)]	an increase of 30	2.01 (1.21–3.34)	2.86 (1.49–5.49)	0.96 (0.41–2.23)
PY[b)]	a 40-PY increase	1.45 (1.03–2.06)	1.99 (1.22–3.24)	0.95 (0.55–1.64)
Male				
Smoking history	No	1	1	1
	Yes	1.06 (0.69–1.65)	0.92 (0.54–1.58)	1.42 (0.66–3.04)
No.[a)]	an increase of 30	1.33 (1.07–1.65)	1.28 (0.91–1.80)	1.34 (1.01–1.78)
PY[b)]	a 40-PY increase	1.26 (1.10–1.43)	1.28 (1.03–1.59)	1.24 (1.04–1.47)

a) Number of cigarettes smoked per day.
b) Pack-years smoked.
c) Adjusted for age, histological type and year.
d) Adjusted for age and year.

Table V. Multivariate Analysis on the Association between Patient Survival and Smoking History in Patients with Advanced Lung Cancer

Variables		Hazard ratios (95% confidence interval)		
		All histologies included[c]	Adenocarcinoma[d]	Non-adenocarcinoma[d]
Female				
Smoking history	No	1	1	1
	Yes	1.41 (1.17–1.69)	1.52 (1.23–1.89)	1.19 (0.84–1.67)
No.[a]	an increase of 30	1.35 (1.07–1.71)	1.52 (1.13–2.04)	1.13 (0.75–1.70)
PY[b]	a 40-PY increase	1.17 (1.00–1.37)	1.22 (0.97–1.55)	1.13 (0.89–1.43)
Male				
Smoking history	No	1	1	1
	Yes	1.02 (0.81–1.29)	1.10 (0.83–1.46)	0.77 (0.50–1.19)
No.[a]	an increase of 30	1.09 (0.97–1.23)	1.23 (1.03–1.47)	1.01 (0.90–1.14)
PY[b]	a 40-PY increase	1.04 (0.96–1.13)	1.13 (1.04–1.22)	0.99 (0.92–1.07)

a) Number of cigarettes smoked per day.
b) Pack-years smoked.
c) Adjusted for age, histological type, stage and year.
d) Adjusted for age, stage and year.

accounted for 86% (55/64) and 79% (146/185) of never-smokers and smokers with non-adenocarcinoma, respectively. The effects of smoking on tumor progression differed in the two histological categories. Univariate analysis showed that smoking history increased the risk of advanced disease in adenocarcinoma patients, but not in non-adenocarcinoma patients, and these results were consistent after other variables were adjusted (Tables II and IV). Patient survival was poorer in female smokers than in female non-smokers with adenocarcinoma, but smoking had no impact on survival in women with non-adenocarcinoma (Table V and Fig. 1).

In males, an advanced tumor was found in 70–77% of patients regardless of smoking history or tumor histology. In contrast to women, number of cigarettes and pack-years smoked influenced tumor extent in patients with both adenocarcinoma and non-adenocarcinoma, but the odds ratios were lower than for women with adenocarcinoma (Tables III and IV). These two variables were also associated with survival of male patients with adenocarcinoma, but not those with non-adenocarcinoma (Table V).

DISCUSSION

It has been argued that adenocarcinoma of the lung is only weakly associated with smoking, because smokers are less common among adenocarcinoma patients and the relative risk of smoking for this histological diagnosis is lower than for others.[16, 17] This study, however, showed that degree of smoking is correlated with the stage and prognosis of adenocarcinoma in women. This result is consistent with other studies on the association between smoking and survival in resected patients.[11, 13] A histopathological study showed a correlation between smoking habit and degree of differentiation of adenocarcinoma.[18] Thus, smoking probably promotes genetic changes critical for tumor differentiation in the histogenesis of adenocarcinoma of the lung, rather than changes involved in initiation, and as a consequence, tumors with highly malignant phenotypes progress rapidly. Although no responsible genes have been identified, *p53* tumor suppressor gene is probably one of them, because mutations of this gene have been linked to smoking, a high degree of nuclear atypia of adenocarcinoma cells, and the survival of patients with adenocarcinoma.[19, 20] Another possible explanation of the correlation between smoking and stage at the initial presentation may be that smoking women are not so health-conscious and respiratory symptoms are overlooked until the disease has reached the late stage. In addition, concomitant diseases common among smokers such as ischemic heart disease and pulmonary emphysema may influence their survival. In female non-adenocarcinoma patients, no association between smoking and either tumor extent or survival was observed. This may be explained by the fact that a high frequency (86%) of advanced disease was noted even in never-smokers, and being in this histological category itself was a risk factor for advanced disease.

In contrast to women, smoking in men was associated with tumor extent regardless of histological category, and with the outcome of lung adenocarcinoma, but odds ratios were weaker than those in women with adenocarcinoma. This gender difference is consistent with the difference in smoking effects on the occurrence of lung cancer, and can be explained, at least in part, by women being more susceptible to smoking-related carcinogens.[3, 4]

Although our results and other studies suggest an association between smoking and lung cancer development in women, little is still known about the causes of lung cancer in non-smoking women, who accounted for 61% of female lung cancer patients in this study. In contrast to male lung cancer patients, 80–90% of whom are smokers worldwide, the percentage of non-smokers among female patients varies with country and ethnic group, and ranges from 10–30% in Western countries to 50–90% in Asian countries.[10, 16, 17, 21] There are several possible causal factors in this population. First, women are more susceptible to tobacco carcinogens than men,[3, 4] and thus small amounts of environmental tobacco smoke may be sufficient to induce lung cancer in women. The relative risk of passive smoking for lung cancer was estimated to be 1.2 to 2.1 among non-smoking women whose husbands were smokers.[22, 23] Secondly, environmental carcinogens other than tobacco smoke may also affect carcinogenesis in women. Recent studies from China and Taiwan have suggested that exposure to fumes from several types of cooking oil may be linked to an increased risk for lung cancer in non-smoking women.[24–26] Although dietary habits and kitchen equipment differ between countries, certain cooking practices may be associated with lung cancer development in non-smoking women living in Asia. Lastly, genetically determined host factors may increase the risk of lung cancer in Asian women, although an effect of shared environment and lifestyle, but no inheritable effect, was found on lung cancer development in twin registry reports in both the United States and Sweden.[27, 28] Candidate factors include genomic instability that facilitates mutations of critical genes in the common carcinogenetic pathway, and genetic changes involving entirely different pathways that may play a central role in lung cancer development in this population.

Further discussion is required with respect to the inherent biases in this hospital-based case series. While this was an observational study conducted over 20 years and involving two hospitals, the smoking and tumor staging data were collected prospectively in the data base and managed by one of the authors in a consistent manner, and in addition, a "year" variable was included simultaneously in the multivariate model to adjust for these biases. All cases in our hospitals were first diagnosed by physicians, and the indications for operation were determined by both physicians and surgeons. Clinical staging is not as accurate as pathological staging, and that was especially true during the 1970s, but the categories "localized (stages I and II)" and "advanced (stages III and IV)" are so simple that they should minimize any inaccuracy. Histological accuracy may be a problem because the pathological diagnosis from both surgical and biopsy specimens was included simultaneously in this analysis. However, this should cause little bias in our adenocarcinoma and non-adenocarcinoma categories, because the biopsy diagnosis and postoperative tissue diagnosis agreed in more than 80% of the cases, except in small cell carcinoma and large cell carcinoma.[29] All these inaccuracies can be expected to be distributed randomly, with little influence on our results, because smoking data were collected in a blind manner with respect to histology, tumor stage, and patient survival.

In conclusion, smoking habit was closely correlated with progression of adenocarcinoma in women. This association was not observed in women with non-adenocarcinoma and was weaker in men, which suggests the involvement of a range of effects of smoking on lung cancer development, depending on gender and the histological type of the tumor.

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