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# Association of Adenocarcinoma of the Lung with Cigarette Smoking by Grade of Differentiation and Subtype[1]

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## ABSTRACT

**A hospital-based case-control study was carried out in order to evaluate the risk of adenocarcinoma of the lung associated with cigarette smoking according to grade of differentiation and subtype. The cases studied were 238 patients with adenocarcinomas of the lung (158 males and 80 females) that were surgically resected at the Center for Adult Diseases, Osaka. For each case, 2 controls were chosen at the same hospital from outpatients who had not been diagnosed as having smoking-related diseases, matched by sex, age, and year of first visit. When the male cases with adenocarcinoma were classified according to the grade of differentiation, the odds ratios (ORs) associated with exsmokers and current smokers were: 1.0, 2.1 for well-differentiated; 4.1, 7.7 for moderately differentiated; and 8.5, 7.9 for poorly differentiated adenocarcinoma. The OR associated with current smokers for poorly and moderately differentiated adenocarcinoma combined was significantly higher than that for well differentiated adenocarcinoma. Approximately the same pattern of ORs was observed in females. For poorly and moderately differentiated adenocarcinoma, a significant dose-response relationship was observed in males. Comparison between the ORs for papillary type and tubular type showed no difference.**

## INTRODUCTION

The association of cigarette smoking with lung cancer differs according to histological type (1–9). The association of squamous cell carcinoma and small cell carcinoma with cigarette smoking is well established, and the relative risks for these two histological types have been reported as 3.1–20.9 for males and 2.2–7.4 for females in Europe and North America (1–4) and 3.9–10.4 for males and 3.6–14.4 for females in Asian countries (5–9). For adenocarcinoma, however, the association with cigarette smoking is less clear. Most of the studies found a positive association, in which the relative risk reported was 1.9–3.5 for males and 1.7–2.9 for females (2–4, 7–9), although some studies found no significant association (1, 5–6).

Adenocarcinoma is known to show great diversity in terms of histological appearance (10, 11) and clinical features (12–15). According to WHO classification (16), adenocarcinoma is classified into 3 categories according to grade of differentiation and 2 major subtypes, tubular and papillary. Furthermore, there have been many studies which tried to classify adenocarcinoma into subgroups, using findings from electron microscopy (17–19) or immunohistochemical staining (20, 21). Thus far, very little attention has been paid in epidemiological studies to this diversity of adenocarcinoma. The present study aims to evaluate the role of cigarette smoking in the etiology of adenocarcinoma of the lung according to grade of differentiation and subtype.

## MATERIALS AND METHODS

The case series comprised 238 pulmonary adenocarcinoma patients (158 males and 80 females) who were surgically resected at the Center for Adult Diseases, Osaka, from 1978 to 1986. These were adenocarcinomas diagnosed microscopically with the use of hematoxylin-eosin staining of the surgically resected specimen. Histological diagnosis of the grade of differentiation and subtype was also determined by the same slide. According to the WHO lung carcinoma classification (16), grades of differentiation were classified into 3 categories, well-differentiated, moderately differentiated, and poorly differentiated, and subtypes were classified into 2 categories, tubular and papillary. The grade of differentiation was determined mostly by the presence of a poorly differentiated portion. No systematic review of pathological slides was conducted, because most of the histological diagnoses were determined by one pathologist.

For each case, two controls were selected at the same hospital from outpatients who had not been diagnosed with pulmonary neoplasms, matched by sex, age (±3 years), and year of the first visit (±3 years). Patients with smoking-related diseases [carcinomas of the oral cavity, esophagus, larynx, bladder, kidney, pancreas, and uterus; coronary heart disease; arteriosclerosis; chronic obstructive lung disease; and peptic ulcers (22)] were excluded from the control series (23). As a result, 476 controls were eligible with one of the following diseases: gastrointestinal (23.4%); neoplasms (16.0%); circulatory (15.8%); genitourinary (8.7%); and respiratory (6.9%). All other disease categories did not exceed 5% in the control series.

Smoking habits for cases and controls were reviewed from medical records, in which routine questions are asked of all outpatients at the time of the first visit to the hospital. The questions included whether they smoke or not at present, and if so, the age at which the smoker started, kind of tobacco smoked, and the average amount smoked per day. If the smoker had quit smoking, the age at which the smoker quit smoking was also asked. A uniform questionnaire was used during the study period. For lung cancer cases, medical records on admission were also reviewed, when the data on first visit were not satisfactorily collected, resulting in comprehensive smoking information for all cases. For controls, 6.5% patients were missing smoking information on the first visit, and these were not used as controls. Smoking habits were classified into 3 categories, never, exsmoker, and current smoker. Exsmoker was defined as a person who had smoked regularly in the past and quit smoking 1 year or more before the date of first visit. For current smokers, smoking intensity was classified according to pack-year, which is calculated by the average number of packs smoked per day times the number of years smoked.

The significance in differences of proportion was evaluated by the $\chi^2$ test (24). The significance of differences in age distribution between grade of differentiation and subtype was evaluated by the Median test (25). Sex- and age-adjusted OR[3] was estimated using the Mantel-Haenszel method (26) in comparison among case series. For subgroup analysis, age-adjusted ORs with 95% CI values were estimated using the maximum likelihood method for conditional logistic regression analysis (26). Weighted regression analyses for trend with category scores given by consecutive integers were used to test the linear trend (27). Unmatched analyses were also conducted with all controls pooled. However, since the results obtained were approximately the same, only the ORs estimated by matched analysis were shown.

## RESULTS

**Case Distribution.** Table 1 shows the distribution of adenocarcinoma cases according to grade of differentiation and subtype by sex. Regarding the grade of differentiation, moderately

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[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.



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Table 1 *Distribution of adenocarcinoma according to grade of differentiation and subtype by sex*

| Sex | Grade of differentiation | | | Subtypes | | Total |
|---|---|---|---|---|---|---|
| | Well | Moderate | Poor | Tubular | Papillary | |
| Males | 37 (60)[a] | 73 (63) | 48 (59.5) | 55 (60) | 103 (64) | 158 (62) |
| Females | 32 (61) | 36 (68) | 12 (54.5) | 18 (63.5) | 62 (61) | 80 (62) |

[a] Numbers in parentheses, median age at diagnosis.

differentiated adenocarcinomas are prominent in both sexes. The proportion of poorly differentiated adenocarcinoma cases was higher in males than in females, and the difference was statistically significant ($P < 0.01$). Median age at diagnosis was higher in moderately differentiated adenocarcinoma and lower in poorly differentiated adenocarcinoma in both sexes, but the differences were not statistically significant ($P > 0.63$ for males and $P > 0.44$ for females). Papillary adenocarcinoma was frequent as a subtype category in both sexes. The proportion of tubular type was higher in males than in females, but the difference was not statistically significant ($P > 0.05$). Median age at diagnosis for each subtype was not significantly different in both sexes ($P > 0.27$ for males and $P > 0.33$ for females).

**Cigarette Smoking and ORs.** When the matched sets were ignored, the exsmoker and current smoker rates were 15.8 and 75.3% for male cases, 17.4 and 51.3% for male controls, 6.3 and 25.0% for female cases, and 4.4 and 12.5% for female controls, respectively. The ORs for exsmokers and current smokers of adenocarcinomas as a whole were 3.2 (95% CI, 1.52–6.63) and 5.0 (95% CI, 2.71–9.27) for males and 1.6 (95% CI, 0.48–5.51) and 2.4 (95% CI, 1.19–4.86) for females.

The ORs for each grade of differentiation associated with smoking are shown in Table 2. Significant increases of ORs were observed in male exsmokers and current smokers for moderately differentiated adenocarcinoma, male exsmokers and current smokers for poorly differentiated adenocarcinoma, and female current smokers for poorly differentiated adenocarcinoma. Although the estimated values of ORs rose as the grade of differentiation became poor for both sexes, the 95% CIs for three grades of differentiation were overlapped. However, when moderately and poorly differentiated adenocarcinoma were combined and this group was taken as cases and well differentiated adenocarcinoma as controls, age- and sex-adjusted OR of current smoker *versus* nonsmoker was estimated as 2.43 with a 95% CI of 1.09–5.40. This indicates that ORs of current smoker were significantly different between well differentiated *versus* moderately and poorly differentiated adenocarcinoma.

For males, the ORs were calculated, dividing current smoker into different smoking intensity categories by pack-year (Table 3). Within each category of smoking intensity, the ORs for moderately and poorly differentiated adenocarcinomas were greater than that for well differentiated adenocarcinoma, although CIs of these estimates were overlapped. For combined moderately and poorly differentiated adenocarcinoma cases, there were significant linear trends between the ORs and smoking intensities.

The ORs for each subtype are shown in Table 4. Significant increases of ORs were observed in male exsmokers and current smokers for tubular type and in male current smokers for papillary type. No definite differences in OR patterns were seen between tubular and papillary types.

## DISCUSSION

This study showed that smoking raises the risk of adenocarcinoma, as well as squamous cell and small cell carcinoma of the lung. When adenocarcinomas were classified into 3 categories in terms of the grade of differentiation, poorly and moderately differentiated adenocarcinomas were more strongly correlated with smoking than well differentiated adenocarcinoma. These findings were consistent for both males and females. In males, the ORs for moderately and poorly differentiated adenocarcinomas were greater than that for well differentiated adenocarcinoma in the same smoking intensity. This means that the greater ORs for moderately and poorly differentiated adenocarcinoma cannot be explained by the different distribution of smoking intensity between these groups. Furthermore, for combined poorly and moderately differentiated adenocarcinoma cases, significant dose-response relationships were observed in males, which suggests that the associations between incidence of adenocarcinoma and cigarette smoking are real. Morita and Urano (28) reported that the proportion of smokers was higher in poorly differentiated than in well differentiated adenocarcinoma, based on the autopsy data. Although this study did not report ORs, it is thought to be consistent with our findings.

The sex difference of ORs for adenocarcinoma as a whole associated with cigarette smoking observed in this study was

Table 2 *ORs for smoking according to grade of differentiation*

| Smoking Status | Grade of differentiation | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Well | | | Moderate | | | Poor | | |
| | CA/CO[a] | OR | 95% CI | CA/CO | OR | 95% CI | CA/CO | OR | 95% CI |
| Males | | | | | | | | | |
| Nonsmoker | 6/21 | 1.0 | | 5/43 | 1.0 | | 3/35 | 1.0 | |
| Exsmoker | 4/12 | 1.0 | 0.23–4.44 | 13/32 | 4.1 | 1.26–13.1 | 8/11 | 8.5 | 1.87–38.7 |
| Current smoker | 27/41 | 2.1 | 0.80–5.67 | 55/71 | 7.7 | 2.58–23.1 | 37/50 | 7.9 | 2.30–26.9 |
| Females | | | | | | | | | |
| Nonsmoker | 24/52 | 1.0 | | 27/59 | 1.0 | | 4/22 | 1.0 | |
| Exsmoker | 3/4 | 1.7 | 0.32–9.06 | 0/3 | —[b] | | 2/0 | — | |
| Current smoker | 5/8 | 1.3 | 0.41–4.37 | 9/10 | 2.3 | 0.77–6.66 | 6/2 | 10.6 | 1.25–89.0 |

[a] CA/CO, number of cases/number of controls when matched sets were ignored.
[b] —, exsmoker excluded from the model due to lack of exsmoker in cases or controls.



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Table 3 *ORs for different smoking intensity according to grade of differentiation among male current smokers*

| | Grade of differentiation | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Well | | | Moderate | | | Poor | | |
| Smoking Status | CA/CO[a] | OR | 95% CI | CA/CO | OR | 95% CI | CA/CO | OR | 95% CI |
| Nonsmoker | 6/21 | 1.0 | | 5/43 | 1.0 | | 3/35 | 1.0 | |
| Exsmoker | 4/12 | 1.0 | 0.21–4.35 | 13/32 | 4.1 | 1.25–13.1 | 8/11 | 9.9 | 2.10–47.8 |
| Current smoker | | | | | | | | | |
| <30[b] | 6/14 | 1.2 | 0.32–4.26 | 8/18 | 3.9 | 0.95–15.7 | 8/15 | 6.6 | 1.50–29.0 |
| 30–59 | 13/23 | 1.9 | 0.61–5.89 | 29/44 | 6.5 | 2.09–20.4 | 20/27 | 7.8 | 2.14–28.0 |
| 60+ | 8/4 | 15.6 | 1.70–143 | 18/9 | 22.1 | 2.58–87.3 | 9/8 | 17.5 | 3.48–88.2 |
| Test for linear trend | | NS | | $P < 0.02$ | | | $P < 0.05$ | | |

[a] CA/CO, number of cases/number of controls when matched sets were ignored; NS, not significant.
[b] Pack-year.

Table 4 *ORs for smoking according to subtype*

| | Subtype | | | | | |
|---|---|---|---|---|---|---|
| | Tubular | | | Papillary | | |
| Smoking status | CA/CO[a] | OR | 95% CI | CA/CO | OR | 95% CI |
| Males | | | | | | |
| Nonsmoker | 5/32 | 1.0 | | 9/67 | 1.0 | |
| Exsmoker | 12/16 | 4.7 | 1.40–15.6 | 13/39 | 2.5 | 0.97–6.42 |
| Current smoker | 38/62 | 3.7 | 1.37–10.3 | 81/100 | 6.1 | 2.78–13.6 |
| Females | | | | | | |
| Nonsmoker | 9/34 | 1.0 | | 46/99 | 1.0 | |
| Exsmoker | 1/1 | 2.0 | 0.13–32.0 | 4/6 | 1.4 | 0.37–5.52 |
| Current smoker | 8/1 | —[b] | | 12/19 | 1.4 | 0.60–3.06 |

[a] CA/CO, number of cases/number of controls when matched sets were ignored.
[b] —, estimate too unstable with positive relation.

partly explained by the different distribution of the grade of differentiation between both sexes. This implies that the variable values of ORs in previous studies may be partly due to the different distribution of grade of differentiation.

Although the diagnostic criteria to differentiate adenocarcinoma from other histological types are well established at the light microscopic level, recent electron microscopic studies revealed that most adenocarcinoma have epidermoid components, *i.e.*, well developed desmosomes and tonofilament bundles, which show a differentiation toward squamous cell carcinoma (17). These are more frequently observed for poorly differentiated adenocarcinoma than for well differentiated adenocarcinoma. Also, in a immunohistochemical study, poorly differentiated adenocarcinoma tends to be more keratin positive than well differentiated adenocarcinoma, which is a marker for epithelial differentiation (21). From these findings, it can be understood that poorly differentiated adenocarcinoma shares common etiological characteristics with squamous cell carcinoma. This will support the theory that adenocarcinoma and squamous cell carcinoma have common progenitor cells. Moreover, it can be thought that cigarette smoking causes these cells to tend toward squamous cell differentiation as well as having a carcinogenic effect.

This study contains some methodological problems to be discussed. First, pathological diagnoses tend to be unstable especially for poorly differentiated carcinoma (29, 30). This indicates that some poorly differentiated adenocarcinoma diagnosed in this series might include poorly differentiated carcinoma which should be diagnosed as other histological types, in particular squamous cell carcinoma and large cell carcinoma. In this study, however, almost all cases of adenocarcinomas were diagnosed by one pathologist familiar with pathology of the lung. The study on concordance of histological diagnosis of lung cancer among Japan, the United Kingdom, and WHO Collaborating Center for Histological Classification of Tumours, in which the above pathologist was involved, showed very high agreement between Japan, the United Kingdom, and WHO, especially for the diagnosis of adenocarcinoma (31). In this study, most of the discrepancy occurred between squamous cell carcinoma and large cell carcinoma. This indicates that histological differentiation of adenocarcinoma from the other histological types can be done with greater reliability than that between other histological types. Within adenocarcinoma, however, some cases might be misdiagnosed in terms of the grade of differentiation, because of less clear diagnostic criteria. This can weaken the differences among the grade of differentiation, if misdiagnosis occurs randomly. Usually, pathologists do not pay attention to smoking status at the diagnosis of the grade of differentiation; it is likely that the differences between ORs by grade might be underestimated because of random error.

Second, hospital outpatients were used as controls. Although hospital controls may not be representative of the people from whom cases arise, they have good comparability with cases in terms of the methods of collecting exposure information (32). In this control series, established smoking-related diseases were excluded. As a result, rates of current smokers were almost the same as those observed in the general population, which are 70.1% for males and 15.4% for females in 1982 (9).

Third, since only the surgically resected cases, which was about 30% of all adenocarcinomas cases diagnosed at our Center in the same period, were included in this study, caution must be exercised in the interpretation. Intuitively, the proportion of poorly differentiated adenocarcinoma may become lower in resected cases, because it is more likely to metastasize and become nonresectable. In terms of estimating OR associated with smoking by the grade of differentiation, however, this may not cause the result bias as long as the smoking status was not biased in resected cases from nonresected cases. Actually, there was no difference on smoking status between resected and nonresected cases in this study period. On the basis of autopsy data, Morita and Urano (28) reported that the proportion of poorly differentiated adenocarcinoma was higher in males than in females, which was the same as that found in our cases. This indicates that there was no differential selection from all cases to resected cases between males and females, in terms of grade of differentiation.

Fourth, methods to collect smoking information were somewhat different between cases and controls. To delete controls with missing data may cause biased results. Usually, in patients with missing data on smoking, the proportion of nonsmokers tends to be higher than that for others. If this was true, observed smoking rates in controls were overestimated, which caused an underestimation of ORs. However, the proportion of missing smoking information was fairly small, and there were no differences on missing rates by grade of differentiation; it was unlikely that this problem will change the findings in this study crucially.

Fifth, no other risk factors were considered in this study.



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Thus far, however, potent risk factors for adenocarcinoma, *i.e.*, passive smoking (33), asbestos exposure (34), way of cooking (35), decreased intake of β-carotene (36), and past history of lung disease (37), seem to have small influences as confounding factors.

Recently, several studies reported that the proportion of adenocarcinoma is increasing, particularly in Japan (38–40) and the United States (41–46). Further studies are necessary to reveal risk factors for adenocarcinoma in the future, taking the grade of differentiation into account.

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## REFERENCES

1. Doll, R., Hill, A. B., and Kreyberg, L. The significance of cell type in relation to the aetiology of lung cancer. Br. J. Cancer, *11:* 43–48, 1975.
2. Stayner, L. T., and Wegman, D. H. Smoking, occupation and histopathology of lung cancer: a case-control study with the use of the third national cancer survey. J. Natl. Cancer Inst., *70:* 421–426, 1983.
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. Damber, L. A., and Larrson, L.-G. Smoking and lung cancer with special regard to type of smoking and type of cancer. A case-control study in north Sweden. Br. J. Cancer, *53:* 673–681, 1986.
5. Koo, L. C., Ho, J. H-C., and Lee, N. An analysis of some risk factors for lung cancer in Hong Kong. Int. J. Cancer, *35:* 149–155, 1985.
6. Segi, M., Kurihara, M., Ishikawa, S., and Haenszel, W. Epidemiological survey on lung cancer and smoking (in Japanese). Lung Cancer (Official J. Jpn. Lung Cancer Soc.), *19:* 157–169, 1979.
7. Shimizu, H., Hisamichi, S., Motomiya, M., Oizumi, K., Konno, K., Hashimoto, K., and Nakada, T. Risk of lung cancer by histologic type among smokers in Miyagi Prefecture. Jpn. J. Clin. Oncol., *16:* 117–121, 1986.
8. Nakamura, M., Hanai, A., Fujimoto, I., Matsuda, M., and Tateishi, R. Relationship between smoking and four major histologic types of lung cancer (in Japanese). Lung Cancer (Official J. Jpn. Lung Cancer Soc.), *26:* 137–148, 1986.
9. 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.
10. Shimosato, Y., Kodama, T., and Kameya, T. Morphogenesis of peripheral type adenocarcinoma of the lung. *In:* Y. Shimosato, M. R. Melamed, and P. Nettesheim (eds.), Morphogenesis of Lung Cancer, Vol. 1, pp. 65–89. Boca Raton, FL: CRC Press, Inc., 1982.
11. Herrera, G. A., Alexander, B., and DeMoraes, H. P. Ultrastructural subtypes of pulmonary adenocarcinoma. A correlation with patient survival. Chest, *84:* 581–586, 1983.
12. Tateishi, R., Doi, O., Kodama, K., and Kurokawa, E. Postoperative survival in patients with pulmonary adenocarcinoma with respect to histological subtypes (in Japanese). Lung Cancer (Official J. Jpn. Lung Cancer Soc.), *25:* 381–385, 1985.
13. Saijo, N., Niitani, H., Tominaga, K., Eguchi, K., Koketsu, H., and Fujino, T. Comparison of survival in nonresected well differentiated and poorly differentiated adenocarcinoma of the lung. J. Cancer Res. Clin. Oncol., *97:* 71–79, 1980.
14. Bennett, D. E., Sasser, W. F., and Ferguson, T. B. Adenocarcinoma of the lung in men. Cancer (Phila.), *23:* 431–439, 1969.
15. Cox, J. D., and Yesner, R. A. Adenocarcinoma of the lung: recent results from the Veterans Administration Lung Group. Am. Rev. Respir. Dis., *120:* 1025–1029, 1979.
16. The World Health Organization. Histological typing of lung tumors, second edition. Am. J. Clin. Pathol., *77:* 123–136, 1981.
17. McDowell, E. M., Harris, C. C., and Trump, B. F. Histogenesis and morphogenesis of bronchial neoplasms. *In:* Y. Shimosato, M. R. Melamed, and P. Nettesheim (eds.), Morphogenesis of Lung Cancer, Vol. 1, pp. 1–36. Boca Raton, FL: CRC Press, Inc., 1982.
18. Mollo, F., Canese, M. G., and Campobasso, O. Human peripheral lung tumours: light and electron microscopic correlation. Br. J. Cancer, *27:* 173–182, 1973.
19. Rainio, P., Sutinen, S., and Sutinen, S. H. Histological subtypes or grading of pulmonary adenocarcinoma. A histochemical and electron microscopic study. Acta Pathol. Microbiol. Immunol. Scand., *91:* 227–234, 1983.
20. Kimula, Y. A histochemical and ultrastructural study of adenocarcinoma of the lung. Am. J. Surg. Pathol., *2:* 253–264, 1978.
21. Kawai, T., Torikata, C., and Suzuki, M. Immunohistochemical study of pulmonary adenocarcinoma. Am. J. Clin. Pathol., *89:* 455–462, 1988.
22. United States Department of Health, Education, and Welfare. Smoking and health: a report of the advisory committee to the Surgeon General of the Public Health Service. Washington, DC: Government Printing Office, 1979.
23. Pearce, N., and Checkoway, H. Case-control studies using other diseases as controls: problems of excluding exposure-related diseases. Am. J. Epidemiol., *127:* 851–856, 1988.
24. Armitage, P., and Berry, G. Statistical Methods in Medical Research, Ed. 2, pp. 205–208. Oxford, United Kingdom: Blackwell Scientific Publications, 1987.
25. Siegel, S. Nonparametric Statistics for the Behavioral Sciences, pp. 111–116. New York: McGrow-Hill Book Company, 1956.
26. Breslow, N. E., and Day, N. E.; Davis, W. (technical editor). Statistical Methods in Cancer Research, Vol. 1. IARC Scientific Publications No. 32. Lyon, France: International Agency for Research on Cancer, 1980.
27. Rothman, K. J. Modern Epidemiology, p. 348. Boston: Little Brown and Company, 1986.
28. Morita, T., and Urano, Y. An autopsy study of lung cancer with special reference to the relationship between cigarette smoking and histological differentiation of adenocarcinoma and squamous cell carcinoma. Jpn. J. Clin. Oncol., *19:* 94–101, 1989.
29. Feinstein, A. R., Gelfman, N. A., Yesner, R., Auerbach, O., Hackel, D. B., and Pratt, C. P. Observer variability in the histopathologic diagnosis of lung cancer. Am. Rev. Respir. Dis., *101:* 671–684, 1970.
30. Yesner, R., Gelfman, N. A., and Feinstein, A. R. A reappraisal of histopathology in lung cancer and correlation of cell types with antecedent cigarette smoking. Am. Rev. Respir. Dis., *107:* 790–797, 1973.
31. Hanai, A., Whittaker, J. S., Tateishi, R., Sobin, L. H., Benn, R. T., and Muir, C. S. Concordance of histological classification of lung cancer with special reference to adenocarcinoma in Osaka, Japan, and the North-west region of England. Int. J. Cancer, *39:* 6–9, 1987.
32. Smith, A. H., Pearce, N. E., and Callas, P. W. Cancer case-control studies with other cancers as controls. Int. J. Epidemiol., *17:* 298–306, 1988.
33. Brownson, R. C., Reif, J. S., Keefe, T. J., Ferguson, S. W., and Pritzl, J. A. Risk factors for adenocarcinoma of the lung. Am. J. Epidemiol., *125:* 25–34, 1987.
34. Vena, J. E., Byers, T. E., Cookfair, D., and Swanson, M. Occupation and lung cancer risk. An analysis by histologic subtypes. Cancer (Phila.), *56:* 910–917, 1985.
35. MacLennan, R., Da Costa, J., Day, N. E., Law, C. H., Ng, Y. K., and Shanmugaratnam, K. Risk factors for lung cancer in Singapore Chinese, a population with high female incidence rates. Int. J. Cancer, *20:* 854–860, 1977.
36. Wu, A. H., Henderson, B. E., Pike, M. C., and Yu, M. C. Smoking and other risk factors for lung cancer in women. J. Natl. Cancer Inst., *74:* 747–751, 1985.
37. Wu, A. H., Yu, M. C., Thomas, D. C., Pike, M. C., and Henderson, B. E. Personal and family history of lung disease as risk factors for adenocarcinoma of the lung. Cancer Res. *48:* 7279–7284, 1988.
38. Hanai, A., Hiyama, T., Nakai, K., Matsuo, S., Suzuki, T., Fujimoto, I., and Tateishi, R. Trends of histological types of lung cancer in Osaka (in Japanese). Jpn. J. Cancer Clin., *28:* 1589–1596, 1982.
39. Watanabe, S., Tsugane, S., Arimoto, H., Shimosato, Y., Suemasu, K., Arai, H., and Urano, Y. Trend of lung cancers in the National Cancer Center of Japan and comparison with that of Japanese pathological autopsy records. Jpn. J. Cancer Res., *78:* 460–466, 1987.
40. Tsugane, S., Watanabe, S., Sugimura, H., Urano, Y., and Matsubara, S. Recent trends in different histological types of lung cancer in Tokyo based on pathological autopsy records. Jpn. J. Cancer Res., *78:* 162–169, 1987.
41. Vincent, R. G., Pickren, J. W., Lane, W. W., Bross, I., Takita, H., Houten, L., Gutierrez, A. C., and Rzepka, T. The changing histopathology of lung cancer. A review of 1682 cases. Cancer (Phila.), *39:* 1647–1655, 1977.
42. Valaitis, J., Warren, S., and Gamble, D. Increasing incidence of adenocarcinoma of the lung. Cancer (Phila.), *47:* 1042–1046, 1981.
43. Dodds, L., Davis, S., and Polissar, L. A population-based study of lung cancer incidence trends by histologic type, 1974–81. J. Natl. Cancer Inst., *76:* 21–29, 1986.
44. Butler, C., Samet, J. M., Humble, C. C., and Sweeney, E. S. Histopathology of lung cancer in New Mexico, 1970–72 and 1980–81. J. Natl. Cancer Inst. *78:* 85–90, 1987.
45. Greenberg, E. R., Korson, R., Baker, J., Barrett, J., Baron, J. A., and Yates, J . Incidence of lung cancer by cell type: a population-based study in New Hampshire and Vermont. J. Natl. Cancer Inst., *72:* 599–603, 1984.
46. Wu, A. H., Henderson, B. E., Thomas, D. C., and Mack, T. M. Secular trends in histologic types of lung cancer. J. Natl. Cancer Inst., *77:* 53–56, 1986.

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