Jpn. J. Cancer Res. **91**, 960–965, October 2000

Birth Cohort Effects on Incidence of Lung Cancers: A Population-based Study in Nagasaki, Japan

Hiroshi Soda,[1, 2, 5] Mikio Oka,[1, 3] Midori Soda,[4] Katsumi Nakatomi,[1] Shigeru Kawabata,[1] Mitsuhiro Suenaga,[1] Takashi Kasai,[1] Yasuaki Yamada,[2] Shimeru Kamihira[2] and Shigeru Kohno[1, 3]

[1]Second Department of Internal Medicine and [2]Department of Laboratory Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, [3]Division of Molecular and Clinical Microbiology, Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Medical Sciences, 1-12-4 Sakamoto, Nagasaki 852-8523 and [4]Radiation Effects Research Foundation, 1-8-6 Nakagawa, Nagasaki 850-0013

Smoking prevalence remains high (around 60%) among Japanese males, but smoking initiation among males born in the 1930s decreased by approximately 10% due to economic difficulties following World War II. The present study was designed to examine whether this temporary decline in smoking initiation influenced the subsequent incidence of lung cancers, especially adenocarcinoma. Trends of lung cancer incidence by histological type in both sexes were investigated using data from the population-based cancer registry in Nagasaki, Japan, from 1986 through 1995. During this period, 5668 males and 2309 females were diagnosed as having lung cancer, and the overall incidence of lung cancers among both sexes remained stable. However, males aged 55–59 years showed a decrease in the age-specific incidence of adenocarcinoma and squamous-cell carcinoma ($P<0.05$ and $P<0.01$, respectively). In birth cohort analyses, the incidence of adenocarcinoma and squamous-cell carcinoma was lower in the 1935–1939 birth male cohort than in the successive cohorts. The incidence of lung cancers among females with low smoking prevalence did not change with birth cohort. The low smoking initiation among the 1935–1939 birth male cohort appeared to have resulted in a decreased incidence of adenocarcinoma and squamous cell carcinoma among middle-aged Japanese males. The present study suggests that smoking prevention has an effect in reducing the incidence of lung adenocarcinoma, as well as squamous-cell carcinoma, among smokers.

Key words: Lung cancer — Epidemiology — Adenocarcinoma — Smoking

Lung carcinoma is a common cause of cancer death, and the incidence of lung adenocarcinoma has increased in many countries.[1–3] A recent case-control study has demonstrated that cigarette smoking has a higher influence on the development of lung adenocarcinoma than previously thought.[4] Nitrosamines in cigarettes are known to induce lung adenocarcinoma in rodents, and filter cigarettes with low nicotine contain high concentrations of nitrosamines.[5] It has been postulated that smokers of filter-tipped cigarettes inhale carcinogens more forcefully and deeply to compensate for the low nicotine, leading to the development of adenocarcinoma in the peripheral lung.[5] In contrast, the incidence of adenocarcinoma has increased among Asian females in whom smoking prevalence is rare,[1] and adenocarcinoma is predominant among lifetime non-smokers in the United States.[6]

[5] To whom correspondence should be addressed at the Department of Laboratory Medicine, Nagasaki University School of Medicine.
E-mail: soda@net.nagasaki-u.ac.jp

Smoking prevalence is still higher among Japanese males, and the prevalence reached a peak of 83.7% in 1966.[7] The production of filter cigarettes in Japan started a decade later than in the United States, and filter cigarette availablility in the market increased from 3 to 90% in the 1960s.[8] The average number of cigarettes smoked per day increased from 19.3 cigarettes in 1964 to 25.0 in 1981, and thereafter remained stable.[10] The prevalence of smoking, however, gradually decreased from the mid-1970s but was still as high as 57.5% in 1996.[7] However, the economic difficulties following World War II resulted in a temporary reduction in the rate of smoking initiation by approximately 10% among males born in the 1930s.[9–11] In contrast, smoking prevalence among Japanese females remained constant at around 14%,[7] and the percentage of new female smokers did not change following World War II.[9, 10] Findings from the 1930s birth cohort of Japanese males may provide clues to the etiology of the increased incidence of lung adenocarcinoma. The present study was designed to examine whether the temporary decrease in smoking initiation influenced the incidence of lung adeno-

carcinoma, and to evaluate the risk of cigarettes for lung adenocarcinoma development among smokers.

SUBJECTS AND METHODS

Trends of lung cancer incidence by histological type were investigated using data from the population-based cancer registry in Nagasaki Prefecture of Japan.[12] The population of Nagasaki Prefecture is 736 729 males and 826 230 females according to the 1990 census. Nagasaki Prefectural Cancer Registry collected cancer reports from medical institutions, and obtained a limited summary of cancer deaths from the vital statistics of Nagasaki Prefecture, with the permission of the Ministry of Health and Welfare. For ethical reasons, the data of registered individuals is protected by anonymity. The reliability of the cancer registry was confirmed by the low proportion of cases registered by death information only: 13.1% for cases aged 0–79 years and 43.8% for those older than 79 years. In cases aged ≥79 years, the higher proportion is possibly due to difficulties in applying invasive diagnostic procedures to the elderly.

The histological type of lung cancer was classified according to the International Classification of Disease for Oncology[13]: adenocarcinoma (codes 8050, 8140–8143, 8211, 8250–8251, 8260, 8310, 8480, 8490, and 8550), squamous-cell carcinoma (8051, 8052, and 8070–8075), small-cell carcinoma (8041–8045), large-cell carcinoma (8012, 8030–8032, and 8230), adenosquamous carcinoma (8560), adenoid cystic carcinoma (8200), mucoepidermoid carcinoma (8430), carcinoid (8240–8246), undifferentiated carcinoma (8020–8022) and others.

Cases of newly diagnosed lung cancer from 1986 through 1995 were included in the present study. The overall incidence was age-adjusted by the direct method to the world standard population, and expressed as per 100 000 population with 95% confidence intervals (95% CI). The age-specific incidence was calculated according to age at diagnosis (45–74 years of age), and evaluated by the Mantel-extension test for trend. The difference in lung cancer incidence among birth cohorts (1915–1949 of calendar year) was evaluated by analysis of covariance for the adjustment of age at diagnosis. The age-specific incidence was restricted to adenocarcinoma and squamous-cell carcinoma due to the small numbers of other types.

RESULTS

During the study period, 5668 male and 2309 female cases were newly diagnosed as having lung cancer, and the age-adjusted incidence was 44.8 (95% CI: 43.3–46.3) for males and 12.7 (95% CI: 11.9–13.5) for females. Histology was confirmed in 78.0% of cases aged 0–79 years and 41.7% of those aged more than 79 years. Table I lists histologically confirmed cases of 4090 males and 1545 females. Adenocarcinoma and squamous-cell carcinoma were major types among males, and adenocarcinoma was predominant among females. The age-adjusted incidence of each histological type among males and females was as follows: 13.7 (95% CI: 12.8–14.5) and 6.9 (95% CI: 6.4–7.5) for adenocarcinoma, 11.8 (95% CI: 11.0–12.6) and 1.1 (95% CI: 0.9–1.3) for squamous-cell carcinoma, and 4.7 (95% CI: 4.2–5.2) and 0.7 (95% CI: 0.5–0.8) for small-cell carcinoma, respectively.

The overall incidence of lung cancers and the incidence of each histological type among both sexes remained stable between 1986 and 1995. However, the age-specific

Table I. Histologically Confirmed Lung Cancers in Nagasaki, Japan, 1986–1995

Histological type	Males (%)	Females (%)
Adenocarcinoma	1663 (40.7)	1115 (72.2)
Squamous-cell carcinoma	1499 (36.7)	211 (13.7)
Small-cell carcinoma	580 (14.2)	122 (7.9)
Large-cell carcinoma	183 (4.5)	38 (2.5)
Undifferentiated carcinoma	74 (1.8)	24 (1.6)
Adenosquamous carcinoma	52 (1.3)	17 (1.1)
Carcinoid	9 (0.2)	5 (0.3)
Adenoid cystic carcinoma	5 (0.1)	2 (0.1)
Mucoepidermoid carcinoma	5 (0.1)	2 (0.1)
Others	20 (0.5)	9 (0.6)
Total	4090 (100)	1545 (100)

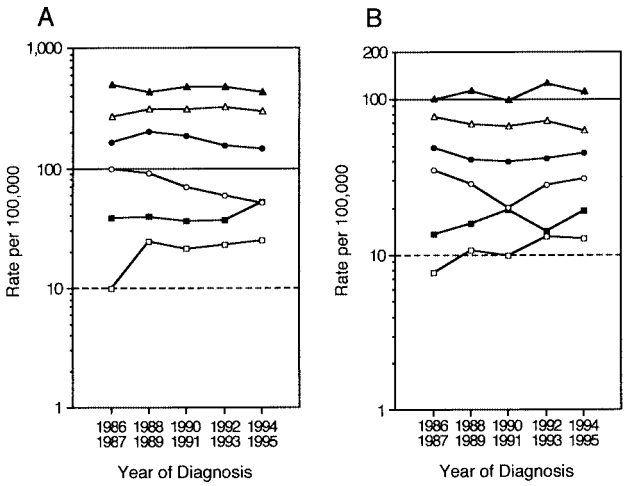

Fig. 1. Time trends of age-specific incidence of lung cancers for males (A) and females (B) in Nagasaki according to age at diagnosis: □ 45–49, ■ 50–54, ○ 55–59, ● 60–64, △ 65–69, ▲ 70–74 years.

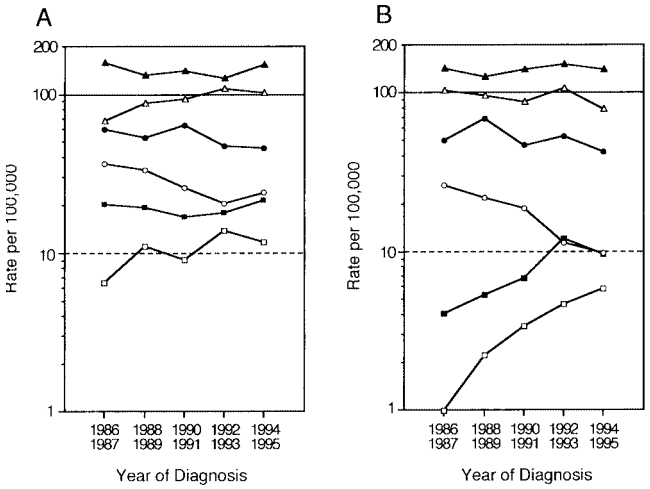

Fig. 2. Time trends of age-specific incidence of adenocarcinoma (A) and squamous-cell carcinoma (B) for males in Nagasaki according to age at diagnosis: □ 45–49, ■ 50–54, ○ 55–59, ● 60–64, △ 65–69, ▲ 70–74 years.

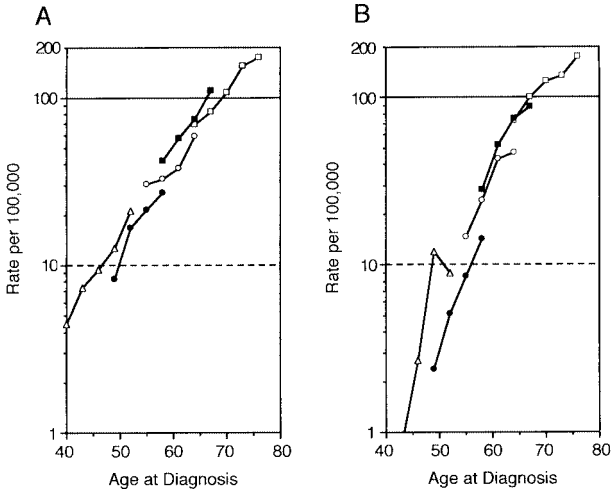

Fig. 4. Incidence of adenocarcinoma (A) and squamous-cell carcinoma (B) for males in Nagasaki according to birth cohort: □ 1915–1924, ■ 1925–1929, ○ 1930–1934, ● 1935–1939, △ 1940–1949.

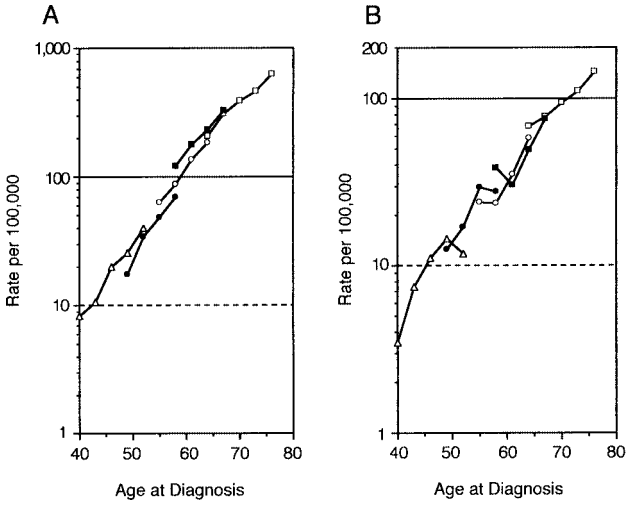

Fig. 3. Incidence of lung cancers for males (A) and females (B) in Nagasaki according to birth cohort: □ 1915–1924, ■ 1925–1929, ○ 1930–1934, ● 1935–1939, △ 1940–1949.

incidence of lung cancers among males changed during the period (Fig. 1A). The incidence of lung cancers decreased among males aged 55–59 and 60–64 years ($P<0.001$ and $P<0.05$, respectively), whereas it increased among those aged 45–49 years ($P<0.05$). The incidences of lung cancers among males aged 55–59 years were 99.4 (95% CI: 79.4–119.4) in 1986–1987 and 51.2 (95% CI: 36.6–65.8) in 1994–1995. The incidence of lung cancers among males aged 50–54 years slightly surpassed that among males aged 50–59 years in 1994–1995.

A similar trend was observed in adenocarcinoma and squamous-cell carcinoma among males (Fig. 2). Males aged 55–59 years showed a decrease in the age-specific incidences of adenocarcinoma and squamous-cell carcinoma ($P<0.05$ and $P<0.01$, respectively). The incidences of adenocarcinoma among males aged 55–59 years were 36.6 (95% CI: 24.5–48.7) in 1986–1987 and 23.9 (95% CI: 13.9–33.9) in 1994–1995. The incidences of squamous-cell carcinoma among those aged 55–59 years were 26.2 (95% CI: 15.9–36.4) in 1986–1987 and 9.8 (95% CI: 3.4–16.2) in 1994–1995. The incidence of adenocarcinoma increased among males aged 45–49 and 65–69 years ($P<0.05$ each), whereas that of squamous-cell carcinoma rose among those aged 45–49 and 50–54 years ($P<0.05$ each). The magnitude of change in the incidence was larger in squamous-cell carcinoma than in adenocarcinoma. In contrast to males, the incidences of lung cancers and each histological type among females remained constant in each age group (Fig. 1B).

The incidence of lung cancers according to birth cohort was consistent with the trends of age-specific incidence (Fig. 3). The incidence of lung cancers declined among the 1935–1939 birth male cohort, compared to the 1925–1929 and 1940–1949 birth cohorts ($P<0.05$ each; Fig. 3A). In contrast, the incidence of lung cancers among females remained stable in each birth cohort (Fig. 3B). In detail, the incidence of adenocarcinoma was lower among the 1935–1939 birth male cohort than the 1940–1949 birth cohort ($P<0.05$, Fig. 4A). Also, the incidence of

squamous-cell carcinoma dropped among the 1935–1939 birth male cohorts, compared to the 1930–1934 and 1940–1949 birth cohorts ($P<0.05$ each; Fig. 4B). In females, the incidence of both histological types did not change with birth cohort (data not shown).

DISCUSSION

The present study demonstrated a decreased incidence of lung adenocarcinoma and squamous-cell carcinoma among males aged 55–59 years. In birth cohort analyses, the incidence of both histological types declined among the 1935–1939 birth male cohort with low smoking initiation, but not among females without change in smoking initiation. The birth cohort effect cannot be explained by diagnostic advances or changes in histological classification. The change in incidence of adenocarcinoma and squamous-cell carcinoma among males was consistent with the change in smoking initiation.

The risk of smoking for lung cancer development is related to smoking initiation, behavior, the amount of cigarettes per day, and cessation. According to a recent survey by the Japanese Government, smoking initiation and cessation were 82.0% and 30.2% for the 1920s birth male cohort, 70.7% and 20.3% for the 1930s birth cohort, and 74.1% and 17.0% for the 1940s birth cohort, respectively.[9] The proportion of those who smoke more than 20 cigarettes per day is 9.9% for the 1920s birth male cohort, 17.3% for the 1930s birth cohort, and 26.0% for the 1940s birth cohort.[9] These trends were confirmed in another national survey: smoking initiation and cessation was 85.3% and 31.3% for the 1920s birth male cohort, 77.8% and 25.9% for the 1930s birth cohort, and 82.8% and 16.4% for the 1940s birth cohort, respectively.[10] The low smoking initiation among the 1930 birth male cohort is considered to be due to the economic difficulties following World War II.[11] Smoking cessation has increased with age, possibly due to increased health awareness. Although the effects of smoking cessation on lung cancer development begin to appear 5 years after cessation, the relative risk reaches the level of never-smokers only >20 years after cessation.[14–16] The influence of smoking initiation on lung cancer incidence is larger than that of smoking cessation.

The 1930s birth male cohorts show less smoking initiation and moderate cessation, resulting in more never- and ex-smokers among this cohort. The incidences of adenocarcinoma and squamous-cell carcinoma were decreased among the 1935–1939 birth male cohort, compared to the successive cohorts with more smoking initiation. Previous case-control studies showed that smoking was weakly associated with adenocarcinoma, and the relative risk of smoking was approximately two to five times.[4, 14] However, a recent case-control study has found a higher relative risk: 19.0 for males and 8.1 for females.[4] Furthermore, poorly differentiated adenocarcinoma is frequently found in smokers,[17] and mutations of K-*ras* oncogene and *p53* tumor suppressor gene are more often detected in adenocarcinoma of smokers.[18–20] These findings suggest that smoking is closely related to the development of adenocarcinoma.

A radical change from non-filter to filter cigarettes occurred in the Japanese market in the 1960s.[8] The 1940s birth male cohort, with more smoking initiation and less cessation, mainly includes lifetime filter cigarette smokers. Additionally, the proportion of those who smoke more than 20 cigarettes per day is higher in the 1940s birth male cohort.[9] It was claimed that the filter removes a large proportion of the carcinogens in cigarette smoke and reduces their deposition on the central airways, where squamous-cell carcinoma preferentially develops. A recent case-control study has shown that filter cigarettes slightly reduce the risk of squamous-cell carcinoma, albeit insignificantly for males but significantly for females.[21] In the present study, the incidence of squamous-cell carcinoma as well as adenocarcinoma increased again among the 1940s birth male cohorts. The effect of filter use does not seem to be large enough to reduce the incidence of squamous-cell carcinoma to the level of never-smokers. High smoking prevalence and more cigarettes smoked per day in the 1940s birth male cohort appear to have led to an increase in the incidence of lung cancers again.

Among males aged 65–69 years, the incidence of adenocarcinoma increased, but that of squamous-cell carcinoma remained constant. Although the birth cohort analyses did not statistically account for this discrepancy, the 1920s birth male cohort has been reported to show more smoking cessation.[9, 10] A similar inconsistent trend has been observed in several countries.[22–24] In the United States and the Netherlands, where smoking control activities commenced in the 1960s, the increased incidence of adenocarcinoma has recently leveled off and even changed to a decrease, and the incidence of adenocarcinoma reached a peak 10 years later than that of squamous-cell carcinoma.[23, 24] Several case-control studies have suggested that smoking cessation rapidly reduces the development of squamous-cell carcinoma, but only slowly reduces the development of adenocarcinoma.[14–16] This suggests that the period of observation was too short to note a fall in adenocarcinoma among males aged 65–69 years.

The present study involves some limitations. First, risk factors other than smoking may influence the incidence of lung cancers. Some potential risk factors for lung cancer have been reported, such as dietary nutrition, air pollution, and occupational exposure.[1] However, these factors are unlikely to explain the decreased incidence among the 1930s birth male cohort. Second, changes in histological classification may have some influence on the incidence of each histological type. Several investigators have reported

that the changes in classification and pathological techniques apparently increase the proportion of adenocarcinoma.[1)] Although pathological specimens were not reviewed in the present study, the proportion of undifferentiated or large-cell carcinoma was small and did not change during the study period. Third, the reason why lung adenocarcinoma is predominant among non-smoking females remains unclear. The temporary decline in smoking initiation among males had no effect on the incidence of lung cancers among females. Recent studies have revealed only a weak association of environmental tobacco smoke and lung adenocarcinoma.[25)] Further studies are necessary to search for new etiologic factors among non-smoking females.

In conclusion, the incidences of adenocarcinoma and squamous-cell carcinoma among males changed with the trends of smoking initiation. The present study suggests that cigarettes increase the risk of adenocarcinoma as well as squamous-cell carcinoma, and that smoking prevention has an effect in reducing the incidence of lung adenocarcinoma among smokers.

(Received May 19, 2000/Revised July 13, 2000/Accepted July 18, 2000)

REFERENCES

1) Charloux, A., Quoix, E., Wolkove, N., Small, D., Pauli, G. and Kreisman, H. The increasing incidence of lung adenocarcinoma: reality or artifact? A review of the epidemiology of lung adenocarcinoma. *Int. J. Epidemiol.*, **26**, 14–23 (1997).
2) Wingo, P. A., Ries, L. A. G., Giovino, G. A., Miller, D. S., Rosenberg, H. M., Shopland, D. R., Thun, M. J. and Edwards, B. K. Annual report to the nation on the status of cancer, 1973–1996, with a special section on lung cancer and tobacco smoking. *J. Natl. Cancer Inst.*, **91**, 675–690 (1999).
3) Sobue, T., Ajiki, W., Tsukuma, H., Oshima, A., Hanai, A. and Fujimoto, I. Trends of lung cancer incidence by histologic type: a population-based study in Osaka, Japan. *Jpn. J. Cancer Res.*, **90**, 6–15 (1999).
4) Thun, M. J., Lally, C. A., Flannery, J. T., Calle, E. E., Flanders, W. D. and Heath, C. W., Jr. Cigarette smoking and changes in the histopathology of lung cancer. *J. Natl. Cancer Inst.*, **89**, 1580–1586 (1997).
5) Wynder, E. L. and Hoffmann, D. Smoking and lung cancer: scientific challenges and opportunities. *Cancer Res.*, **54**, 5284–5295 (1994).
6) Muscat, J. E. and Wynder, E. L. Lung cancer pathology in smokers, ex-smokers and never smokers. *Cancer Lett.*, **88**, 1–5 (1995).
7) Health and Welfare Statistics Association. Tobacco. *J. Health Welfare Statist.*, **44**, 101–104 (1997) (in Japanese).
8) Hanai, A., Benn, T., Fujimoto, I. and Muir, C. S. Comparison of lung cancer incidence rates by histological type in high and low incidence countries, with reference to the limited role of smoking. *Jpn. J. Cancer Res.*, **79**, 445–452 (1988).
9) Ministry of Health and Welfare of Japan. "Report of the Fourth National Survey for Cardiovascular Diseases, 1990" (1993). Koken Press, Tokyo (in Japanese).
10) Ministry of Health and Welfare of Japan. "Smoking and Health," Second Ed. (1993). Hoken Dojin Co., Tokyo (in Japanese).
11) Yamaguchi, N., Mizuno, S., Akiba, S., Sobue, T. and Watanabe, S. A 50-year projection of lung cancer deaths among Japanese males and potential impact evaluation of anti-smoking measures and screening using a computerized simulation model. *Jpn. J. Cancer Res.*, **83**, 251–257 (1992).
12) Soda, H., Tomita, H., Kohno, S. and Oka, M. Limitation of annual screening chest radiography for the diagnosis of lung cancer: a retrospective study. *Cancer*, **72**, 2341–2346 (1993).
13) World Health Organization. "International Classification of Disease for Oncology," Second Ed. (1990). WHO, Geneva.
14) Lubin, J. H. and Blot, W. J. Assessment of lung cancer risk factors by histologic category. *J. Natl. Cancer Inst.*, **73**, 383–389 (1984).
15) Higgins, I. T. and Wynder, E. L. Reduction in risk of lung cancer among ex-smokers with particular reference to histologic type. *Cancer*, **62**, 2397–2401 (1988).
16) Pohlabeln, H., Jöckel, K.-H. and Müller, K.-M. The relation between various histological types of lung cancer and the number of years since cessation of smoking. *Lung Cancer*, **18**, 223–229 (1997).
17) 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).
18) Westra, W. H., Slebos, R. J., Offerhaus, G. J., Goodman, S. N., Evers, S. G., Kensler, T. W., Askin, F. B., Rodenhuis, S. and Hruban, R. H. K-ras oncogene activation in lung adenocarcinomas from former smokers. Evidence that K-ras mutations are an early and irreversible event in the development of adenocarcinoma of the lung. *Cancer*, **72**, 432–438 (1993).
19) Westra, W. H., Offerhaus, G. J., Goodman, S. N., Slebos, R. J., Polak, M., Baas, I. O., Rodenhuis, S. and Hruban, R. H. Overexpression of the p53 tumor suppressor gene product in primary lung adenocarcinomas is associated with cigarette smoking. *Am. J. Surg. Pathol.*, **17**, 213–220 (1993).
20) Hecht, S. S. Tobacco smoke carcinogens and lung cancer. *J. Natl. Cancer Inst.*, **91**, 1194–1210 (1999).
21) Stellman, S. D., Muscat, J. E., Thompson, S., Hoffman, D. and Wynder, E. L. Risk of squamous cell carcinoma and

adenocarcinoma of the lung in relation to lifetime filter cigarette smoking. *Cancer*, **80**, 382–388 (1997).
22) Levi, F., Franceschi, S., La Vecchia, C., Randimbison, L. and Te, V.-C. Lung carcinoma trends by histologic type in Vaud and Neuchâtel, Switzerland, 1974–1994. *Cancer*, **79**, 906–914 (1997).
23) Zeng, T., Holford, T. R., Boyle, P., Chen, Y., Ward, B. A., Flannerg, J. and Mayne, S. T. Time trend and the age-period-cohort effect on the incidence of histologic types of lung cancer in Connecticut, 1960–1989. *Cancer*, **74**, 1556–1567 (1994).
24) Janssen-Heijnen, M. L. G., Nab, H. W., van Reek, J., van der Heijden, L. H., Schipper, R. and Coebergh, J. W. W. Striking changes in smoking behavior and lung cancer incidence by histological type in south-east Netherlands, 1960–1991. *Eur. J. Cancer*, **31**, 949–952 (1995).
25) Zhong, L., Goldberg, M. S., Parent, M.-É. and Hanley, J. A. Exposure to enivironmental tobacco smoke and the risk of lung cancer: a meta-analysis. *Lung Cancer*, **27**, 3–18 (2000).