Surg Today (2014) 44:1004–1012
DOI 10.1007/s00595-013-0636-z

REVIEW ARTICLE

A worldwide trend of increasing primary adenocarcinoma of the lung

Haruhiko Nakamura · Hisashi Saji

Received: 6 January 2013 / Accepted: 13 May 2013 / Published online: 11 June 2013

Abstract The four major histological types of lung cancer are adenocarcinoma, squamous cell carcinoma (SQ), large cell carcinoma and small cell carcinoma. Over the past few decades, the incidence of lung adenocarcinoma has increased gradually in most countries as the most frequently occurring histological type, displacing SQ. Adenocarcinoma is the predominant type of lung cancer among lifelong non-smokers and among females. Especially in East Asian countries, the cause(s) of the increase in adenocarcinomas are not clear. Several genetic mutations specific to lung adenocarcinomas have been found, representing attractive targets for molecular therapy. Recently, the pathological classification of lung adenocarcinoma was revised by integrating the newer clinical and biological knowledge concerning this prevailing type. Additional epidemiological, pathological and genetic studies are required to better understand this type of lung cancer.

Keywords Adenocarcinoma · Chest surgery · Epidemiology · Lung cancer · Smoking

Introduction

Lung cancer is the leading cause of cancer-related death in most developed countries [1–3]. However, remarkable changes in the incidence and mortality of lung cancer have been observed in recent decades, during which the percentages of the four major histological types of lung cancer; adenocarcinoma (AD), squamous cell carcinoma (SQ), small cell carcinoma (SM) and large cell carcinoma (LA), have gradually changed. Until 30–40 years ago, SQ was the predominant type of lung cancer worldwide. Since then, the incidence of AD has increased steadily, and it is presently the most common type in the United States (US), Europe and East Asia, including Japan [4, 5]. Although the age-adjusted mortality from lung cancer for males has recently declined in most developed countries, the incidence of lung cancer in females has increased in the same regions. Because the major identifiable cause of lung cancer is tobacco smoke, the increase in lung cancer among females may be explained partly by the increases in female smokers. However, AD is increasing even among lifelong non-smoking females in East Asian countries and in other regions. Furthermore, the increases in lung cancer among lifetime non-smokers, irrespective of gender, cannot be explained completely by environmental tobacco smoke (ETS), or "secondhand smoke," alone. About 25 % of all lung cancers worldwide are not attributable to tobacco smoke [1]. In particular, lung cancer shows a much higher prevalence in lifetime non-smoking Asian females than in females in the Western countries. The predominant histological type of lung cancer developing in lifetime non-smokers is also AD [6, 7]. The increase in AD in both females and non-smokers (males and females) is likely to affect the prevention, screening, diagnosis and therapeutic strategies for lung cancer. The purpose of this review is to discuss the recent findings of clinicopathological, epidemiological and genetic studies on lung cancer, paying special attention to AD.

H. Nakamura (✉) · H. Saji
Department of Chest Surgery, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan
e-mail: h-nakamura@marianna-u.ac.jp

Global trends in the incidence and mortality of lung cancer

According to the global cancer statistics in 2008 [2], the age-adjusted incidence and mortality rates of lung cancer per 100,000 person-years in both genders were higher in more-developed regions (males 47.4 and 39.4, respectively; females 18.6 and 13.6) than in less-developed regions (males 27.8 and 24.6, females 11.1 and 9.7). The highest lung cancer incidence rates were reported from Central and Eastern Europe (males 57.0, females 9.6), Southern Europe (males 49.0, females 10.4), North America (males 48.5, females 35.8), Micronesia/Polynesia (males 46.5, females 15.9), East Asia (males 45.0, females 19.9) and Western Europe (males 44.7, females 16.7) [2]. However, the age-adjusted lung cancer death rates in males have been decreasing in most European countries, North America, Australia and Japan. The lung cancer incidence among females has been plateauing in the US, Canada, the United Kingdom (UK) and Australia.

Considering that tobacco smoking is the main identifiable cause of lung cancer, tobacco education, taxation and purchase age restriction in these Western countries over the past few decades appears to have contributed to reducing the lung cancer mortality in males, and may also be helping reduce the rate in females. In contrast, the lung cancer mortality in females was still reported to be increasing in Spain (6.2), France (10.8), Belgium (11.8), the Netherlands (22.1) and East Asia (16.3) [8]. Despite a relatively low population of smokers among Chinese females, they have higher lung cancer incidence rates (21.3) than those in certain European countries, such as Germany (16.4) and Italy (11.4) [2]. This is also the case in Japan, with the incidence of lung cancer increasing in lifetime non-smoking females. The reason(s) why lung cancer develops so frequently in Asian females who have never smoked remain unclear, although ETS may be partly responsible [9].

The characteristics of lung cancer vary from area to area and country to country, and are likely to reflect the biological, environmental, cultural and socio-economic factors of the specific regions. This variability dictates that caution should be exercised when generalizing from lung cancer data, as the information may not be applicable to disparate regions and countries. Careful etiological studies on lung cancer aiming to clarify what is shared and what is not between different regions, genders or ethnic groups are important.

The increase in primary lung adenocarcinoma

In the data from the Japanese Joint Committee of Lung Cancer Registry [10, 11], both the percentage of AD cases and the percentage of females increased gradually among patients undergoing lung resection for primary lung cancer from 1989 to 2004 (Fig. 1). Similarly, among all lung cancer patients registered in Norway from 1988 to 2007 [12], the percentages of cases presenting AD and those representing females have increased (Fig. 2). In Canada, the age-adjusted incidence rates of AD increased by 263 % in females and 4 % in males from 1972 to 2007 [13]. In the US, the incidence of AD also increased dramatically, by 83 % in males and by more than 200 % in females, from 1973 to 1998 [14]. Accordingly, an increase in AD was common in most developed countries, especially in the US and developed East Asian countries. However, in the US,

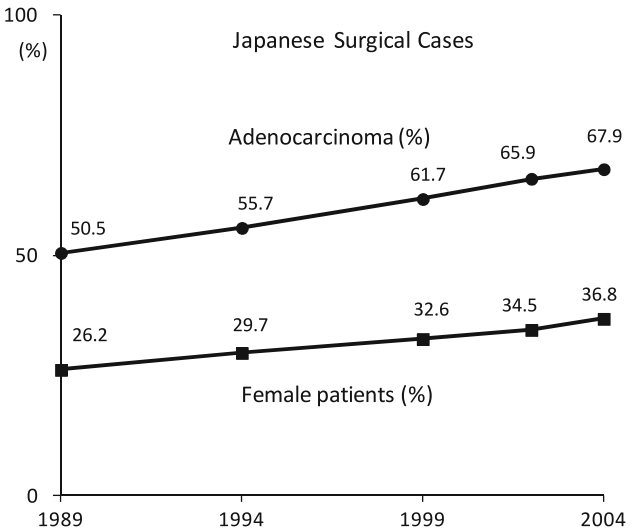

Fig. 1 Time trends in percentages of lung adenocarcinoma and female patients with lung cancer among Japanese surgical cases. Data from the Japanese Joint Committee for the Lung Cancer Registry [10, 11] were used

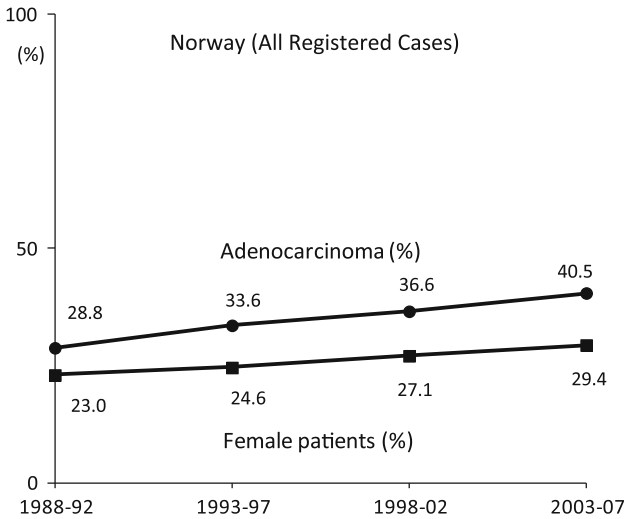

Fig. 2 Time trends in percentages of lung adenocarcinoma and female patients with lung cancer in Norway [12]

the incidence of AD started to decline in both genders beginning in 1999 [14]. The authors of the US study showing this decrease [14] suggested that several factors might help to explain the recent decline of AD in the US; one is the national regulation of air pollution beginning in the 1980s, while another is more strict regulation of ETS [14]. However, the sudden decrease of AD in both genders seems difficult to explain completely in terms of these factors. In Hong Kong, the incidence of AD increased until 1990 and then stabilized [15]. Therefore, it is necessary to carefully observe other regions or countries for possible future declines in the incidence of AD.

Differences in lung cancer by gender

AD is the most common histological type of lung cancer in females; and a significantly elevated risk of AD has been reported in female lifelong non-smokers in Asia [16, 17]. Exposure to cooking fumes has been suggested as possible risk factor for Chinese females working in unventilated kitchens. A case–control study identified rapeseed oil fumes as a possible cause of the increased risk for lung cancer [16]. Additional Chinese studies have also considered cooking oil fumes as a risk factor [18, 19]. However, since the increase in AD in lifetime non-smoking females was not limited to China, the increases in AD in other countries, including Japan, is difficult to explain in terms of cooking oil fumes, because of the more effective kitchen ventilation in these countries. In Western countries, the recent lung cancer increase in females was explained mainly by increased tobacco smoking [20, 21]. Smoking is generally much more common in Western females than in Asians, and the estimated risk of tobacco-associated lung cancer is higher in Caucasians than in Asians [21]. Accordingly, the increasing incidence of AD among Asian females is difficult to explain in terms of smoking or ETS.

The possibility of higher susceptibility to lung cancer in females has been widely discussed [22–24]. Several studies have suggested that females are more likely to develop lung cancer than similarly exposed males. For example, a hospital-based case–control study demonstrated that the dose–response odds ratios (ORs) during cumulative exposure to tobacco smoking were 1.2–1.7 times higher in females than in males [22]. However, other reports found that the risk for lung cancer from similar exposure to tobacco smoke was the same between genders [23, 25, 26]. A few molecular epidemiological studies have reported more numerous polycyclic aromatic hydrocarbon DNA adducts [27, 28], lower DNA repair capacity [29, 30] and a higher frequency of G-to-T transversion mutations in the gene for the p53 tumor suppressor protein [31, 32] in female than male smokers. In addition, non-small cell lung cancers (NSCLCs) were found to be more likely to harbor K-ras [33], HER-2 [32] or EGFR mutations [34] in specimens from females than from males. If females are biologically more vulnerable to the development of lung cancer, the causes of lung cancer in lifelong female non-smokers may include various industrial or automotive air pollutants that are present at relatively low concentrations.

In general, the prognosis of lung cancer in females is considered to be better than that in males. The case-fatality ratio, defined as the mortality (deaths) to incidence (cases), roughly suggests the prognosis of patients with the disease [24]. The calculated lung cancer fatality in 2008 [8] was lower in females than in males in more-developed regions, but was similar to or higher than that for males in less-developed regions, probably reflecting insufficient social support for females, including barriers to suitable medical care, in less-developed regions (Fig. 3). This illustrates that socio-economic factors, as well as biological factors, can be important determinants of the prognosis of lung cancer.

Reported studies show conflicting results concerning the overall survival difference between genders in NSCLC patients. In several large-scale clinical studies, the prognosis for female patients tended to be better than that for male patients, regardless of the disease stage or therapeutic modality [10, 12, 35]. In a meta-analysis including 39 articles published from 2000 to 2009 involving 86,880 patients, the post-treatment hazard ratio (HR) for females relative to males was 0.78, showing a significant survival benefit for females [36]. The reason(s) why women with lung cancer would survive longer than men are still unclear. However, in Japan, females were more likely to have AD and stage IA disease, which might account for their better prognosis [10]. Although the gender and smoking habit are closely associated in Japan, a postsurgical survival analysis in a Japanese population concluded that the smoking status was not a statistically significant or important determinant of survival, with the risk for current smokers relative to non-smokers being 1.00 ($p = 0.94$; 95 % confidence interval 0.93–1.09) [10].

Differences in lung cancer among ethnicities

In the most recent report of post-resection Japanese lung cancer patients who underwent surgery in 2004 ($n = 11\,663$), the overall 5-year survival rates were 69.6 % for all patients, 63.0 % for males and 80.9 % for females [11]. Among patients with the four major histological types of lung cancer, the highest 5-year survival rate, 74.9 %, was obtained for AD, showing statistically significant differences compared to other histological types [11]. These recent high postsurgical survival rates in Japanese patients imply that there are differences in the biological features of

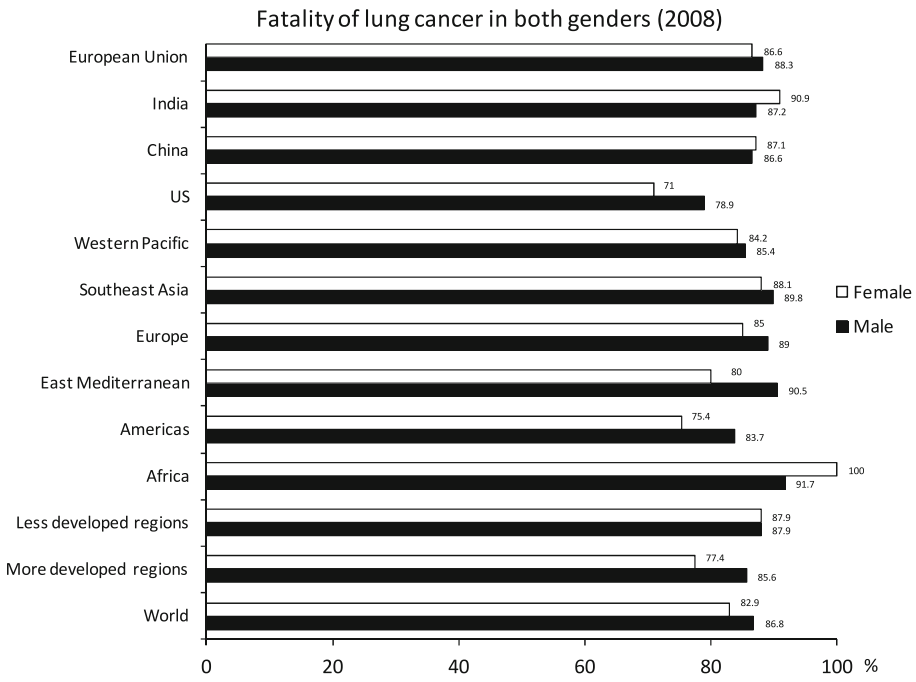

Fig. 3 Fatality (mortality/incidence) of lung cancer in various regions of the world. Data from GLOBOCAN 2008 [8] were used to calculate fatality

lung cancer between various ethnic groups. A direct comparison was performed between Japanese and Caucasian patients with NSCLC diagnosed between 1991 and 2001, a period preceding the introduction of epidermal growth factor receptor tyrosine kinase-inhibitor (EGFR-TKI) therapy, which is considered to be potentially effective for AD in Asian non-smokers [37]. That study [37] demonstrated that there was a significant survival difference between ethnicities. The overall survival for Japanese patients was significantly better than that for Caucasian patients, regardless of the therapeutic modality (surgery, radiation or chemotherapy). Although the survival in female patients was better than that of male patients in both ethnic groups, a significant survival difference related to the smoking status was found only in the Japanese population, suggesting that Japanese lifelong non-smokers with lung cancer had a better prognosis [37]. However, the percentage of lifelong non-smokers among female Japanese lung cancer patients (76.3 %) was much higher than among female Caucasian lifelong non-smoking patients (9.9 %), which may have affected the results.

However, confirming the decreased risk in Asians compared to Caucasians, a Southern California lung cancer database was generated covering the years from 1991 to 2005 that included four ethnic groups; White, Asian, Hispanic and African-American [38]. In that study of a specific region, the environmental influence could be minimized to facilitate ethnic comparisons. A multivariate survival analysis identified Asian ethnicity as a favorable prognostic factor for overall survival among both lifelong non-smokers and smokers. However, the socio-economic status was not considered in that study.

In a French population-based case–control study including patients newly diagnosed between 2001 and 2006, smoking was associated with an eightfold increase in lung cancer risk, identifying cigarette smoking as the most important cause of lung cancer in French females [21]. In that study, lifelong non-smokers accounted for 29 % of all lung cancer patients and 38 % of AD patients. Another French study [39] reported that the proportion of female lung cancer patients who had never smoked increased with age, from 13.5 % at ages under 50 to 74.1 % at ages over 70. A high lung cancer risk despite a low prevalence of smoking has also been observed in ethnic Chinese females who had migrated to Australia, San Francisco, Hawaii, Singapore and Western countries [17, 40, 41]. This may reflect ethnicity-specific biological or cultural factors shared by these Chinese females.

The associations between tobacco smoke and the risk of lung cancer development and mortality differ by ethnicity. For example, an international case–control study comparing American and Japanese males demonstrated an OR for lung cancer in male current smokers in the US relative to non-smokers of 40.4, but an OR of only 3.5 for male current smokers in Japan [42]. A possible explanation for this striking difference included higher concentrations of tobacco-specific nitrosamines in the US, wider use of cigarettes with activated charcoal filters in Japan, different inherited genetic susceptibilities and differences in lifestyle factors apart from smoking [42]. Other studies estimated

the relative risk (RR) of lung cancer death among smokers compared to non-smokers to be 4.5 for males and 3.6 for females in Japan, while the RR for males ranged from 11.6 to 23.2 and that for females ranged from 2.7 to 12.8 in the US and the UK [43–48]. In summary, both the estimated incidence and mortality risks for lung cancer in Japanese smokers were lower than those in US smokers, while the lung cancer death rates for lifelong non-smokers among Japanese were higher than those for lifelong non-smokers in the US.

Data from Europe and Canada [49] cast light upon the relationship between tobacco smoking and the histological type of lung cancer. The age-adjusted ORs relative to non-smokers for current male smokers with an average daily consumption over 30 cigarettes were 103.5 for SQ, 111.3 for SM and 21.9 for AD. In females, the corresponding ORs were 62.7, 108.6 and 16.8, respectively, [49].

Different distributions of somatic gene mutations in AD between Caucasians and Asians were found in the activating *EGFR* gene mutations. The prevalence of the EGFR-TKI-sensitive mutation was high in AD in an Asian population, but was low in Caucasians [50–54]. The full range of genetic factors involved in the susceptibility to lung cancer are still unclear, but some studies have suggested an association between family history and the risk of lung cancer, especially in the case of AD [55]. Recent genome-wide association studies identified four susceptibility loci for lung AD, 5p15.33 (OR = 1.41), 3q28 (OR = 1.25), 17q24.3 (OR = 1.20) and 6p21.3 (OR = 1.18) in the Japanese population [56]. The candidate lung cancer susceptibility genes in these loci are *TERT*, *TP63*, *BPTF* and *BTNL2*. The *TP63* gene was confirmed to be associated with lung cancer risk for Japanese, Korean and Chinese populations. Since the association was weaker in Europeans, differences in the extent of the contribution from these genes to lung cancer susceptibility may exist between ethnic groups [56].

Multiple studies have suggested that lung cancers in Asians are less invasive than those in Caucasians, because the survival in Asians typically is longer regardless of the therapeutic modality and disease stage [57]. If this is the case, different surgical approaches to lung cancer might be suggested based upon ethnicity. The sole randomized clinical trial to evaluate limited resection for c-T1N0 NSCLC in North America [58] demonstrated that lobectomy was more effective than sublobular limited resection, including wedge resection. A recent retrospective study using the database of the US national registry also showed that lobectomy was significantly better than segmentectomy for patients with stage-I NSCLC, regardless of the tumor size, in terms of both the overall and cancer-specific 5-year survival [59]. In contrast, multiple Japanese studies demonstrated segmentectomy to be comparable to lobectomy [60, 61]. Limited resection for lung cancer may therefore be appropriate for Asians, but not Caucasians, and this may be due to ethnic differences in the biological malignancy of lung cancer. The prognoses can differ considerably among the subtypes of AD [62]. Since the percentages of more precise subtypes of AD were not described in these reports, analyses considering further pathological classification among different ethnic groups should be carried out.

Lung cancer in lifelong non-smokers

Some 15 % of males and 53 % of females with lung cancer are believed to be lifelong non-smokers [1]. Important differences in the features of lung cancer between smokers and lifelong non-smokers include the frequencies of different histological types, the prognosis and the frequency of *EGFR*, *RAS* and other genetic mutations [63, 64]. Because of the large number of differences between them, the lung cancers in smokers and lifelong non-smokers might best be diagnosed and treated as different types of cancer.

The causes of lung cancer in lifelong non-smokers have been studied from different points of view, but decisive results have not yet been obtained. ETS [9] has attracted considerable interest as a possible etiology for lung cancer in lifetime non-smokers. Mainstream cigarette smoke is inhaled directly into the smokers' lungs, where it can induce carcinogenesis in airway cells. In lifelong non-smokers, both side-stream cigarette smoke emitted from a burning cigarette and mainstream cigarette smoke exhaled by smokers are inhaled. Mainstream cigarette smoke contains more than 4,000 chemicals, including 70 known carcinogens and 400 other toxic compounds. Representative carcinogens include 4(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), *N*′-nitrosonornicotine and tobacco-specific *N*-nitrosamines (TSNAs). TSNAs are formed by N-nitrosation of nicotine and other alkaloids. Increased nitrate, a major precursor for nitrogen oxides, leads to higher yields of NNK in the smoke. Other carcinogens present in tobacco smoke include polycyclic aromatic hydrocarbons (PAHs), aromatic amines (AAs), benzo[a]pyrene (BP) and trace metals. The side-stream smoke contains much more BP, 4-aminobiphenyl (4-ABP) and NNK than mainstream smoke. The International Agency for Research on Cancer estimated the increased risk for developing lung cancer due to ETS exposure to be 35 % in males and 25 % in females [65]. In a meta-analysis of 19 studies focused on females who never smoked, the increased risk from ETS was estimated to be 20 % [66]. Since not all studies detected a significantly increased risk of lung cancer due to ETS, further studies with accurate

information about personal ETS in a larger sample size are required to clarify the true effects of ETS in lifelong non-smokers.

In general, the frequency of *EGFR* gene mutations in smokers is low compared with that in lifelong non-smokers. In Korean lifelong non-smokers with lung cancer, the incidence of *EGFR* gene mutations was significantly lower in patients with ETS exposure than in those without (38.5 vs. 61.4 %) [67], suggesting that ETS tended to induce "smoker type" lung cancer. The reason why the EGFR mutation occurs frequently in lung AD in lifelong non-smokers remains unknown.

In China, up to 90 % of lung AD in lifelong non-smokers harbor known oncogenic driver mutations in only four genes: *EGFR*, *KRAS*, *ALK* and *HER2* [7]. The same group studied Chinese females with AD who had never smoked, and found that 76.2 % of tumors harbored *EGFR* mutations, 14.6 % had *HER2* mutations, 4.3 % had *EML4-ALK* fusions, 2.0 % had *KRAS* mutations and 0.6 % had *BRAF* mutations. Patients harboring *EGFR* mutations were found significantly more often in the older population, while patients harboring *HER2* mutations were found significantly more often in the younger population [68].

Plausible causes of the increase in lung adenocarcinoma

Since the smoking rates in developed counties are decreasing, the increases in AD are difficult to explain by tobacco smoke alone. Several hypotheses have attempted to explain why ADs are increasing worldwide. The effects of increased consumption of low-tar and low-nicotine cigarettes since 1970 represent one possible cause of the increase in lung AD. Smokers inhale smoke from these cigarettes more deeply to enhance the delivery of the smoke, with its numerous carcinogens, enabling it to reach the lung periphery, where ADs are most likely to develop. Cigarette filters might increase peripheral ADs by the same mechanism.

The air pollution induced by industrialization in more developed countries is another possible cause. The relationship between air pollution (S_2, CO, O_3, NOx) and the histological type of lung cancer was studied in Taiwan [69]. Traffic-related NOx and CO showed significant correlations with the lung cancer incidence in females but not in males. Moreover, a significant correlation was found between the AD/SQ ratio and the mean concentrations of NOx and CO in females. The AD incidence increased in both genders according to the intensity of air pollution.

Previously identified non-ETS risk factors in lifetime non-smokers include occupational exposure to silica or asbestos, chronic obstructive pulmonary disease (COPD), pneumonia, a family history of lung cancer, residential radon, tuberculosis and the household use of coal [70]. Calculated population-attributable fractions (PAFs) associated with the burden of lung cancer in lifetime non-smokers attributable to these risk factors in North America ranged from 0.40 to 19.93 %; because of differences in the prevalence of exposure, PAFs associated with several of these risk factors varied greatly by geographic region [70]. Further epidemiological studies will be necessary to elucidate the reason(s) for the increase of AD in lifetime non-smokers in specific areas and countries.

Revised classification of adenocarcinoma

The new classification of lung AD supported by the International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society (IASLC/ATS/ERS) appeared in 2011 as the future version of the World Health Organization classification [62]. This new classification was developed by an international multidisciplinary panel including pathologists, molecular biologists, oncologists, radiologists and thoracic surgeons (Table 1). AD in situ (AIS) was newly added as a preinvasive type of AD. Most tumors in this group were formerly classified as non-mucinous bronchioloalveolar carcinoma (BAC) which appear as focal pure ground glass opacity (GGO) on chest computed tomography (CT). These patients should have a 100 % 5-year disease-free survival after complete resection of the tumor. Minimally invasive AD (MIA) typically shows a solid component measuring 5 mm or less and has a near 100 % five-year disease-free survival after complete removal. Invasive ADs are classified according to the predominant subtype present in resected or biopsy specimens. Other, rare types of invasive ADs are classified as variants.

Interestingly, the frequency of driver mutations in lung AD seemed to be associated with the pathological subtypes of AD under the new classification [68]. For example, a higher prevalence of *KRAS* and *HER2* mutations was found in invasive mucinous AD, and the frequency of *EGFR* mutations was positively correlated with acinar-predominant invasive AD [68]. The associations between the new pathological classification of AD and specific genetic mutations should be explored further.

Future directions

The prevention of lung cancer is the most important issue related to the disease. Since the major known preventable

Table 1 The new classification of lung adenocarcinoma in resected specimens 2011 (IASLC/ATS/ERS)

Preinvasive lesions
Atypical adenomatous hyperplasia (AAH)
Adenocarcinoma in situ (≤3 cm pure lepidic growth without invasion)
Non-mucinous
Mucinous
Mixed non-mucinous/mucinous
Adenocarcinoma
Minimally invasive adenocarcinoma (≤3 cm lepidic predominant tumor with ≤5 mm invasion)
Non-mucinous
Mucinous
Mixed non-mucinous/mucinous
Invasive adenocarcinoma
Lepidic predominant (formerly non-mucinous BAC pattern, with >5 mm invasion)
Acinar predominant
Papillary predominant
Micropapillary predominant
Solid predominant
Variants of invasive adenocarcinoma
Invasive mucinous adenocarcinoma (formerly mucinous BAC)
Colloid
Fetal (low and high grade)
Enteric

BAC bronchioloalveolar carcinoma

cause is tobacco smoke, antismoking campaigns should be pursued aggressively, especially for females and younger people, in addition to strict governmental regulation of ETS. Screening to detect lung cancer early is the second priority. Low-dose chest CT seems to be the most powerful screening tool to detect peripherally located early ADs [71]. Since chest CT can find various small lesions including benign nodules mimicking early lung cancers, such as AIS and MIA, a definitive diagnosis should follow as safely and efficiently as possible [72]. Endobronchial ultrasound-guided lung biopsy is useful for the diagnosis of invasive ADs. For the definitive diagnosis of preinvasive AD or benign lesions, a lung biopsy by video-assisted thoracic surgery (VATS) is the most effective method. If the lesion is considered to be a preinvasive lung cancer based on the chest CT findings, organ-sparing limited lung resection may be the most reasonable treatment. Finally, the increase of ADs in lifetime non-smokers is a growing problem that needs to be solved. Well-designed epidemiological studies to find causes of ADs other than tobacco smoke, and genetic analyses of ADs in this population of patients, should be initiated to address this issue.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62:10–29.
4. Devesa SS, Bray F, Vizcaino AP, Parkin DM. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. Int J Cancer. 2005;117:294–9.
5. Morita T. A statistical study of lung cancer in the annual of pathological autopsy cases in Japan, from 1958 to 1997, with reference to time trends of lung cancer in the world. Jpn J Cancer Res. 2002;93:15–23.
6. Subramanian J, Govindan R. Lung cancer in never smokers: a review. J Clin Oncol. 2007;25:561–70.
7. Sun Y, Ren Y, Fang Z, Li C, Fang R, Gao B, et al. Lung adenocarcinoma from East Asian never-smokers is a disease largely defined by targetable oncogenic mutant kinases. J Clin Oncol. 2010;28:4616–20.
8. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Lung cancer incidence and mortality in 2008 summary. Cancer incidence and mortality worldwide: IARC CancerBase No. 10 (Internet). International Agency for Research on Cancer. GLOBOCAN 2008 v20 2010, Lyon. http://globocan.iarc.fr/factsheets/cancers/lung.asp.
9. Fontham ET, Correa P, Reynolds P, Wu-Williams A, Buffler PA, Greenberg RS, et al. Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. JAMA. 1994;271:1752–9.
10. Sakurai H, Asamura H, Goya T, Eguchi K, Nakanishi Y, Sawabata N, et al. Survival differences by gender for resected non-small cell lung cancer: a retrospective analysis of 12,509 cases in a Japanese Lung Cancer Registry study. J Thorac Oncol. 2010;5:1594–601.
11. Sawabata N, Miyaoka E, Asamura H, Nakanishi Y, Eguchi K, Mori M, et al. Japanese Joint Committee for Lung Cancer R: Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. J Thorac Oncol. 2011;6:1229–35.
12. Sagerup CM, Smastuen M, Johannesen TB, Helland A, Brustugun OT. Sex-specific trends in lung cancer incidence and survival: a population study of 40,118 cases. Thorax. 2011;66:301–7.
13. Jiang X, de Groh M, Liu S, Liang H, Morrison H. Rising incidence of adenocarcinoma of the lung in Canada. Lung Cancer. 2012;78:16–22.
14. Chen F, Bina WF, Cole P. Declining incidence rate of lung adenocarcinoma in the United States. Chest. 2007;131:1000–5.
15. Au JS, Mang OW, Foo W, Law SC. Time trends of lung cancer incidence by histologic types and smoking prevalence in Hong Kong 1983–2000. Lung Cancer. 2004;45:143–52.
16. Gao YT, Blot WJ, Zheng W, Ershow AG, Hsu CW, Levin LI, et al. Lung cancer among Chinese women. Int J Cancer. 1987;40:604–9.
17. Koo LC, Ho JH. Worldwide epidemiological patterns of lung cancer in nonsmokers. Int J Epidemiol. 1990;19(Suppl 1):S14–23.
18. Ko YC, Lee CH, Chen MJ, Huang CC, Chang WY, Lin HJ, et al. Risk factors for primary lung cancer among non-smoking women in Taiwan. Int J Epidemiol. 1997;26:24–31.
19. Yu IT, Chiu YL, Au JS, Wong TW, Tang JL. Dose–response relationship between cooking fumes exposures and lung cancer

among Chinese nonsmoking women. Cancer Res. 2006;66: 4961–7.
20. Wingo PA, Ries LA, Giovino GA, Miller DS, Rosenberg HM, Shopland DR, et al. 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. 1999;91:675–90.
21. Papadopoulos A, Guida F, Cenee S, Cyr D, Schmaus A, Radoi L, et al. Cigarette smoking and lung cancer in women: results of the French ICARE case–control study. Lung Cancer. 2011;74: 369–77.
22. Zang EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. J Natl Cancer Inst. 1996;88:183–92.
23. Bain C, Feskanich D, Speizer FE, Thun M, Hertzmark E, Rosner BA, et al. Lung cancer rates in men and women with comparable histories of smoking. J Natl Cancer Inst. 2004;96:826–34.
24. Kiyohara C, Ohno Y. Sex differences in lung cancer susceptibility: a review. Gend Med. 2010;7:381–401.
25. Engeland A, Haldorsen T, Andersen A, Tretli S. The impact of smoking habits on lung cancer risk: 28 years' observation of 26,000 Norwegian men and women. Cancer Causes Control. 1996;7:366–76.
26. Kreuzer M, Boffetta P, Whitley E, Ahrens W, Gaborieau V, Heinrich J, et al. Gender differences in lung cancer risk by smoking: a multicentre case–control study in Germany and Italy. Br J Cancer. 2000;82:227–33.
27. Ryberg D, Hewer A, Phillips DH, Haugen A. Different susceptibility to smoking-induced DNA damage among male and female lung cancer patients. Cancer Res. 1994;54:5801–3.
28. Kure EH, Ryberg D, Hewer A, Phillips DH, Skaug V, Baera R, et al. p53 mutations in lung tumours: relationship to gender and lung DNA adduct levels. Carcinogenesis. 1996;17:2201–5.
29. Wei Q, Cheng L, Amos CI, Wang LE, Guo Z, Hong WK, et al. Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. J Natl Cancer Inst. 2000;92:1764–72.
30. Mooney LA, Perera FP, Van Bennekum AM, Blaner WS, Karkoszka J, Covey L, et al. Gender differences in autoantibodies to oxidative DNA base damage in cigarette smokers. Cancer Epidemiol Biomarkers Prev. 2001;10:641–8.
31. Tang DL, Rundle A, Warburton D, Santella RM, Tsai WY, Chiamprasert S, et al. Associations between both genetic and environmental biomarkers and lung cancer: evidence of a greater risk of lung cancer in women smokers. Carcinogenesis. 1998;19:1949–53.
32. Guinee DG Jr, Travis WD, Trivers GE, De Benedetti VM, Cawley H, Welsh JA, et al. Gender comparisons in human lung cancer: analysis of p53 mutations, anti-p53 serum antibodies and C-erbB-2 expression. Carcinogenesis. 1995;16:993–1002.
33. Nelson HH, Christiani DC, Mark EJ, Wiencke JK, Wain JC, Kelsey KT. Implications and prognostic value of K-ras mutation for early-stage lung cancer in women. J Natl Cancer Inst. 1999;91:2032–8.
34. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst. 2005;97:339–46.
35. Cerfolio RJ, Bryant AS, Scott E, Sharma M, Robert F, Spencer SA, et al. Women with pathologic stage I, II, and III non-small cell lung cancer have better survival than men. Chest. 2006;130:1796–802.
36. Nakamura H, Ando K, Shinmyo T, Morita K, Mochizuki A, Kurimoto N, et al. Female gender is an independent prognostic factor in non-small-cell lung cancer: a meta-analysis. Ann Thorac Cardiovasc Surg. 2011;17:469–80.
37. Kawaguchi T, Matsumura A, Fukai S, Tamura A, Saito R, Zell JA, et al. Japanese ethnicity compared with Caucasian ethnicity and never-smoking status are independent favorable prognostic factors for overall survival in non-small cell lung cancer: a collaborative epidemiologic study of the National Hospital Organization Study Group for Lung Cancer (NHSGLC) in Japan and a Southern California Regional Cancer Registry databases. J Thorac Oncol. 2010;5:1001–10.
38. Ou SH, Ziogas A, Zell JA. Asian ethnicity is a favorable prognostic factor for overall survival in non-small cell lung cancer (NSCLC) and is independent of smoking status. J Thorac Oncol. 2009;4:1083–93.
39. Nagy-Mignotte H, Guillem P, Vesin A, Toffart AC, Colonna M, Bonneterre V, et al. Primary lung adenocarcinoma: characteristics by smoking habit and sex. Eur Respir J. 2011;38:1412–9.
40. Grulich AE, McCredie M, Coates M. Cancer incidence in Asian migrants to New South Wales, Australia. Br J Cancer. 1995;71:400–8.
41. Epplein M, Schwartz SM, Potter JD, Weiss NS. Smoking-adjusted lung cancer incidence among Asian-Americans (United States). Cancer Causes Control. 2005;16:1085–90.
42. Stellman SD, Takezaki T, Wang L, Chen Y, Citron ML, Djordjevic MV, et al. Smoking and lung cancer risk in American and Japanese men: an international case–control study. Cancer Epidemiol Biomarkers Prev. 2001;10:1193–9.
43. Ando M, Wakai K, Seki N, Tamakoshi A, Suzuki K, Ito Y, et al. Attributable and absolute risk of lung cancer death by smoking status: findings from the Japan Collaborative Cohort Study. Int J Cancer. 2003;105:249–54.
44. Akiba S, Hirayama T. Cigarette smoking and cancer mortality risk in Japanese men and women—results from reanalysis of the six-prefecture cohort study data. Environ Health Perspect. 1990;87:19–26.
45. Thun MJ, Lally CA, Flannery JT, Calle EE, Flanders WD, Heath CW Jr. Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst. 1997;89:1580–6.
46. McLaughlin JK, Hrubec Z, Blot WJ, Fraumeni JF Jr. Smoking and cancer mortality among US veterans: a 26-year follow-up. Int J Cancer. 1995;60:190–3.
47. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ. 1994;309:901–11.
48. Marugame T, Sobue T, Satoh H, Komatsu S, Nishino Y, Nakatsuka H, et al. Lung cancer death rates by smoking status: comparison of the Three-Prefecture Cohort study in Japan to the Cancer Prevention Study II in the USA. Cancer Sci. 2005;96: 120–6.
49. Pesch B, Kendzia B, Gustavsson P, Jockel KH, Johnen G, Pohlabeln H, et al. Cigarette smoking and lung cancer-relative risk estimates for the major histological types from a pooled analysis of case–control studies. Int J Cancer. 2012;131:1210–9.
50. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004;350:2129–39.
51. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;304:1497–500.
52. Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci USA. 2004;101:13306–11.
53. Yang SH, Mechanic LE, Yang P, Landi MT, Bowman ED, Wampfler J, et al. Mutations in the tyrosine kinase domain of the

epidermal growth factor receptor in non-small cell lung cancer. Clin Cancer Res. 2005;11:2106–10.
54. Helland A, Skaug HM, Kleinberg L, Iversen ML, Rud AK, Fleischer T, et al. EGFR gene alterations in a Norwegian cohort of lung cancer patients selected for surgery. J Thorac Oncol. 2011;6:947–50.
55. Wu AH, Fontham ET, Reynolds P, Greenberg RS, Buffler P, Liff J, et al. Family history of cancer and risk of lung cancer among lifetime nonsmoking women in the United States. Am J Epidemiol. 1996;143:535–42.
56. Shiraishi K, Kunitoh H, Daigo Y, Takahashi A, Goto K, Sakamoto H, et al. A genome-wide association study identifies two new susceptibility loci for lung adenocarcinoma in the Japanese population. Nat Genet. 2012;44:900–3.
57. Soo RA, Loh M, Mok TS, Ou SH, Cho BC, Yeo WL, et al. Ethnic differences in survival outcome in patients with advanced stage non-small cell lung cancer: results of a meta-analysis of randomized controlled trials. J Thorac Oncol. 2011;6:1030–8.
58. Ginsberg R, Rubinstein L. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg. 1995;60:615–22.
59. Whitson BA, Groth SS, Andrade RS, Maddaus MA, Habermann EB, D'Cunha J. Survival after lobectomy versus segmentectomy for stage I non-small cell lung cancer: a population-based analysis. Ann Thorac Surg. 2011;92:1943–50.
60. Okada M, Yoshikawa K, Hatta T, Tsubota N. Is segmentectomy with lymph node assessment an alternative to lobectomy for non-small cell lung cancer of 2 cm or smaller? Ann Thorac Surg. 2001;71:956–60.
61. Koike T, Yamato Y, Yoshiya K, Shimoyama T, Suzuki R. Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer. J Thorac Cardiovasc Surg. 2003;125:924–8.
62. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society. International multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 2011;6:244–85.
63. Gealy R, Zhang L, Siegfried JM, Luketich JD, Keohavong P. Comparison of mutations in the p53 and K-ras genes in lung carcinomas from smoking and nonsmoking women. Cancer Epidemiol Biomarkers Prev. 1999;8:297–302.
64. Thu KL, Vucic EA, Chari R, Zhang W, Lockwood WW, English JC, et al. Lung adenocarcinoma of never smokers and smokers harbor differential regions of genetic alteration and exhibit different levels of genomic instability. PLoS ONE. 2012;7:e33003.
65. International Agency for Research on Cancer. Tobacco smoke and involantary smoking. IARC Monogr Eval Carcinog Risks Hum. 2004;83:1431–8.
66. Vineis P, Alavanja M, Buffler P, Fontham E, Franceschi S, Gao YT, et al. Tobacco and cancer: recent epidemiological evidence. J Natl Cancer Inst. 2004;96:99–106.
67. Lee YJ, Cho BC, Jee SH, Moon JW, Kim SK, Chang J, et al. Impact of environmental tobacco smoke on the incidence of mutations in epidermal growth factor receptor gene in never-smoker patients with non-small-cell lung cancer. J Clin Oncol. 2010;28:487–92.
68. Zhang Y, Sun Y, Pan Y, Li C, Shen L, Li Y, et al. Frequency of driver mutations in lung adenocarcinoma from female never-smokers varies with histologic subtypes and age at diagnosis. Clin Cancer Res. 2012;18:1947–53.
69. Liaw YP, Ting TF, Ho KK, Yang CF. Cell type specificity of lung cancer associated with air pollution. Sci Total Environ. 2008;395:23–7.
70. Sisti J, Boffetta P. What proportion of lung cancer in never-smokers can be attributed to known risk factors? Int J Cancer. 2012;131:265–75.
71. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395–409.
72. Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA. 2012;307:2418–29.