Trends in Lung Cancer Incidence Rates by Histological Type in 1975–2008: A Population-Based Study in Osaka, Japan

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ABSTRACT

Background: Monitoring trends in lung cancer incidence and mortality is important for the evaluation of cancer control activities. We investigated recent trends in age-standardized incidence rates by histological type of lung cancer in Osaka, Japan.

Methods: Cancer incidence data for 1975–2008 were obtained from the Osaka Cancer Registry. Lung cancer mortality data with population data in Osaka during 1975–2012 were obtained from vital statistics. We examined trends in age-standardized incidence and mortality rates for all histological types and age-standardized incidence rates by histological type and age group using a joinpoint regression model.

Results: The age-standardized incidence rate of lung cancer levelled off or slightly increased from 1975–2008, with an annual percentage change of 0.3% (95% confidence interval [CI], 0.1%–0.4%) for males and 1.1% (95% CI, 0.9%–1.3%) for females, and the mortality rate decreased by 0.9% (95% CI, 1.2%–0.7%) for males and 0.5% (95% CI, 0.8%–0.3%) for females. The incidence rates of squamous cell carcinoma (SQC) and small cell carcinoma (SMC) significantly decreased for both genders, whereas that of adenocarcinoma (ADC) significantly increased among almost all age groups in both genders.

Conclusions: The incidence rates of SQC and SMC decreased with the decline in smoking prevalence, which probably explains the change in trends in the incidence rates of lung cancer from the mid-1980s. However, the reason for the increase in ADC remains unclear. Therefore, trends in incidence rates of lung cancer should be carefully monitored, especially for ADC, and the associations between ADC and its possible risk factors should be studied.

Key words: cancer; lung cancer; incidence; histological type; cancer registries

INTRODUCTION

In Japan, incidence rates of lung cancer have levelled off for males and are increasing for females. Mortality rates of lung cancer show a decreasing trend for males and have levelled off for females.1 It was previously reported that incidence rates of lung cancer in Osaka had levelled off for males but increased for females, and that mortality rates showed a slightly decreasing trend for males and females in an analysis using the joinpoint regression model.2

Smoking is a major risk factor for lung cancer. The population attributable fraction of active smoking to lung cancer mortality is about 70% for males and 20–40% for females.3,4 However, trends for lung cancer incidence vary by histological type. Previously, it was reported that incidence rates of adenocarcinoma (ADC) increased and incidence rates of squamous cell carcinoma (SQC) and small cell carcinoma (SMC) decreased for both genders in Osaka, Japan.5,6 Incidence rates of SQC and SMC increased among younger groups in their 40s and 50s and older groups aged more than 70 years in the 1990s, but decreased or levelled off among intermediate groups in their 60s. Incidence rates of ADC were reported to increase among most age groups.7

In the present study, we updated the trends in lung cancer incidence and mortality rates for all histological types and estimated incidence rates by histological type and age group in Osaka, Japan.

METHODS

Lung cancer incidence data for 1975–2008 were obtained from the Osaka Cancer Registry (OCR). Lung cancer
mortality data in Osaka from 1975–2012 were obtained from vital statistics. Population data by sex and 5-year age group in Osaka were obtained from the National Census. This study was approved by the data usage committee of the OCR at the Osaka Medical Center for Cancer and Cardiovascular Diseases (Osaka, Japan) in August 2014 (approval ID: No. 14-0008).

When analyzing incidence rates by histological type, we followed the histological classification for lung tumors published by the World Health Organization. Histological types were categorized as follows: SQC (International Classification of Diseases for Oncology Third Edition, Morphology [ICD-O-3M]: 8050–8078, and 8083–8084), ADC (ICD-O-3M: 8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8551, 8570–8574, and 8576), SMC (ICD-O-3M: 8041–8045, and 8246), unspecified malignant neoplasm (ICD-O-3M: 8000–8005), and other specified malignant neoplasm. The data from the OCR included cases without specific histological diagnosis and stage. To include the missing data for histological type and stage in our analysis, we applied multiple imputation (MI). For the imputation, we used a multinomial logistic regression model that included another incomplete variable and the complete variables: sex, age at diagnosis, period of diagnosis, and vital status. For the MI method, we used the ice command in Stata version 12 (STATA Corporation, College Station, TX, USA) and obtained 10 complete data sets. When analyzing incidence rates by age group, age at diagnosis was classified into three categories: 35–64 years old, 65–74 years old, and over 75 years old, which were age-standardized within those age ranges.

First, we calculated annual age-standardized incidence and mortality rates (ASR) of lung cancer for all histological types and truncated age-standardized incidence rates by age group. We used the Japanese model population for 1985 to standardize age distribution. When analyzing by histological type, we used the 10 complete data sets obtained from the MI method. Second, we applied the joinpoint regression model to identify the years when the statistically significant changes in incidence or mortality trends occurred using the Joinpoint Regression Program 4.1.0 (National Cancer Institute Surveillance Research Program Statistical Methodology and Applications Branch, Bethesda, MD, USA). In the joinpoint analysis, we used the logarithmic ASR as the dependent variable and the year of diagnosis or death as the independent variable. We found the best joinpoints (years when trends changed) using the permutation test method. Annual percentage change (APC) of each line segment between joinpoints was estimated in the model, and the APC was tested to see whether it was significantly different from 0 ($P < 0.05$). We set three joinpoints as a maximum number in each analysis. We used Stata version 12 for all analyses except the joinpoint regression analysis.

RESULTS

The characteristics of patients before and after multiple imputation are shown in Table 1. The proportion of patients with ADC increased while that with SQC and SMC decreased from the 1990s, and ADC has become a major histological type for both genders. The proportion of patients in the older age group (≥75 years old) increased, while that of the younger age group (<65 years old) decreased.

Trends in lung cancer incidence and mortality rates for all histological types are shown in Figure 1 and Table 2. Incidence rates steeply increased by 3.5% (95% CI, 2.9%–4.1%) per year for males and 3.7% (95% CI, 2.6%–4.8%) per year for females until 1985–86. Trends in incidence rates then slightly increased, as APC was 0.3% (95% CI, 0.1%–0.4%) for males and 1.1% (95% CI, 0.9%–1.3%) for females. Mortality rates levelled off from 1988 and slightly decreased from 1997 for males (APC = −0.9%; 95% CI, −1.2% to −0.7%). For females, mortality rates decreased from 1989 (APC = −0.5%; 95% CI, −0.8% to −0.3%).

Figure 2 and Table 3 show trends in lung cancer incidence rates by histological type. The peak incidence of SQC was observed in 1996 for males and in 1986 for females. Incidence rates of SQC decreased for males (APC = −1.9%; 95% CI, −2.4% to −1.5%) and females (APC = −1.3%; 95% CI, −1.7% to −0.9%). ADC increased by 1.1% (95% CI, 0.8%–1.5%) for males and by 2.3% (95% CI, 2.1%–2.5%) for females. The rates of SMC decreased from 1992 for males (APC = −0.9%; 95% CI, −1.3% to −0.4%) and from 1988 for females (APC = −1.3%; 95% CI, −1.9% to −0.7%). The incidence rate of ADC overtook that of SQC for males in the 1990s.

We also analyzed truncated age-standardized incidence rates by histological type and age group (eFigure 1, eFigure 2, eFigure 3, eTable 1, eTable 2, and eTable 3). eFigure 1 and eTable 1 show trends in truncated (35–64 years, 65–74 years, and ≥75 years) age-standardized incidence rate of SQC by age group. For the age group 35–64 years, the rate continued to decrease in males (APC = −1.0%; 95% CI, −1.3% to −0.8%), while it remained stable in females. For the age group 65–74 years and ≥75 years, the rate significantly decreased for both genders. eFigure 2 and eTable 2 show trends in ADC. Among all age groups in males and females, except the age group 65–74 years and ≥75 years, the rate significantly decreased for both genders. eFigure 2 and eTable 2 show trends in ADC. Among all age groups in males and females, except the age group 65–74 years and ≥75 years, the rate significantly increased. The rate among the age group 65–74 years in males levelled off in 1997–2008. eFigure 3 and eTable 3 show trends in SMC by age group. Among the male age groups 35–64 years and 65–74 years and female age groups 65–74 years and ≥75 years, the rate decreased recently. However, the rate levelled off among the male age group ≥75 years and female age group 35–64 years.
Kinoshita FL, et al. 581

Table 1. Characteristics of patients stratified by sex, diagnostic period, histological type, stage, and age group

| Stage | Year | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
|-------|------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Localised | 1975–79 | 454 | 21.6 | 584 | 20.0 | 801 | 19.7 | 936 | 18.3 | 1058 | 16.3 | 1241 | 15.4 | 981 | 13.0 | 6056 | 16.7 |
| Regional | 1975–79 | 1269 | 60.4 | 1748 | 59.7 | 2420 | 59.5 | 3128 | 61.3 | 4295 | 66.0 | 5472 | 68.0 | 5275 | 70.1 | 21367 | 65.1 |
| Distant | 1975–79 | 5164 | 61.8 | 4357 | 43.4 | 4105 | 32.8 | 4884 | 29.9 | 5129 | 27.2 | 4209 | 24.0 | 26303 | 29.8 |
| Squamous cell carcinoma | 1975–79 | 544 | 21.0 | 778 | 29.2 | 1097 | 30.1 | 1324 | 35.1 | 1635 | 35.1 | 1939 | 39.7 | 12333 | 30.0 | 75250 | 27.2 |
| Adenocarcinoma | 1975–79 | 1038 | 18.6 | 1953 | 25.3 | 2664 | 25.8 | 2997 | 23.9 | 3936 | 25.1 | 4487 | 23.8 | 3853 | 22.0 | 20928 | 23.7 |
| Small cell carcinoma | 1975–79 | 913 | 16.3 | 1702 | 22.0 | 2556 | 24.8 | 3023 | 24.1 | 4645 | 29.6 | 5909 | 31.3 | 5859 | 33.5 | 24607 | 27.9 |
| Others | 1975–79 | 321 | 5.7 | 754 | 9.8 | 1124 | 10.4 | 1395 | 11.1 | 1794 | 11.4 | 2134 | 11.3 | 1843 | 10.5 | 9365 | 10.6 |
| Missing | 1975–79 | 221 | 4.0 | 480 | 6.2 | 700 | 6.8 | 669 | 5.3 | 760 | 5.0 | 1028 | 5.4 | 1333 | 7.6 | 5211 | 5.9 |

**DISCUSSION**

Although trends in incidence and mortality rates steeply increased in parallel from 1975 to the 1980s, the incidence rate increased slightly and the mortality rate decreased slightly from 1980s onwards. The latest APC of incidence rates was higher for females than males (0.3% vs 1.1%). Histologically specific analysis showed a continuous increase in ADC and a decrease in SQC and SMC since around 1990.

**Trends in the incidence and mortality rates for all histological types**

Changes in incidence and mortality rates in the 1980s may be due to the decline in smoking prevalence because smoking habits are closely related to the incidence and mortality of lung cancer and other comorbidities. The increasing widespread use of computed tomography (CT) might in part have contributed to the slight increase in incidence and the slight decrease in mortality observed from the late 1980s.
It has been reported that the detection rate of CT scanning is higher than that of x-ray or sputum cytology, and cases detected by CT are likely to be early stage and peripherally located ADC.\textsuperscript{16,17} These cancers can be easily treated by surgery, which might have led to the decrease in mortality. However, low-dose CT screening, which was introduced in the 1990s in Japan, is experimentally conducted only in some specific areas, while CT scanning has been widely used in various clinical scenarios, such as chest pain, hemoptysis, fever, faint abnormal shadow in chest x-ray, and screening for metastasis from other organ cancers. Therefore, it is difficult to evaluate the effects of CT scanning on the trends in lung cancer. The introduction and diffusion of tyrosine kinase inhibitors, such as gefitinib, which is an effective drug for advanced ADC with epidermal growth factor receptor (EGFR) mutations,\textsuperscript{18} might also have partially contributed to the decrease in mortality.

To better understand these incidence and mortality trends, we also confirmed trends in the proportion of early stage cancer diagnosed as a localized cancer. In population-based
cancer registries in Japan, stage at diagnosis is classified into three categories: localized, regional metastases (regional lymph nodes and adjacent organs), and distant metastasis. The proportion of patients with localized cancer slightly increased from the 1990s, especially in females. Moreover, the proportion of patients with ADC was higher in females than males (Table 1). The gender differences in the distribution of histological type and stage of lung cancer might reflect different trends in incidence and mortality between genders.

Cigarette smoking and trends in the incidence rates of SQC and SMC
It is known that the incidence of SQC and SMC is more closely related to smoking behaviors than that of ADC. Japanese smoking prevalence decreased from the 1960s for both genders (from 82.3% in 1965 to 38.9% in 2009 for males, and from 15.7% in 1965 to 11.9% in 2009 for females) (eFigure 4). The continuous decrease in the incidence of SQC and SMC is thought to be due to the decline in smoking prevalence.

Table 3. Trends in age-standardized incidence rates of lung cancer by histological type with jointpoint analysis in Osaka, Japan

| Histological type       | Trend 1                  | Trend 2                  | Trend 3                  | Trend 4                  |
|-------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                         | Years | APC (95% CI)         | Years | APC (95% CI)         | Years | APC (95% CI)         | Years | APC (95% CI)         |
| Males                   |        |                       |        |                       |        |                       |        |                       |
| Squamous cell carcinoma | 1975–1985 | 2.7a (1.7, 3.7) | 1985–1996 | 0 (−0.8, 0.7) | 1996–2008 | −1.9a (−2.4, −1.5) |        |                       |
| Adenocarcinoma          | 1975–1987 | 3.4a (2.7, 4.1) | 1987–1991 | −0.4 (−4.8, 4.3) | 1991–1996 | 4.0a (1.4, 6.6) | 1996–2008 | 1.1a (0.8, 1.5) |
| Small cell carcinoma    | 1975–1985 | 6.0a (4.5, 7.6) | 1985–1992 | 1.7 (−0.6, 4.1) | 1992–2008 | −0.9a (−1.3, −0.4) |        |                       |
| Females                 |        |                       |        |                       |        |                       |        |                       |
| Squamous cell carcinoma | 1975–1986 | 3.1a (1.4, 4.8) | 1986–2008 | −1.3a (−1.7, −0.9) |        |                       |        |                       |
| Adenocarcinoma          | 1975–2008 | 2.3a (2.1, 2.5) |        |                       |        |                       |        |                       |
| Small cell carcinoma    | 1975–1988 | 5.8a (3.9, 7.8) | 1988–2008 | −1.3a (−1.9, −0.7) |        |                       |        |                       |

APC, annual percentage change; CI, confidence interval.

aAPC is statistically significantly different from zero (P < 0.05).
Although the incidence rates of SQC and SMC decreased for both genders, the rates among females in the younger age group (35–64 years) levelled off (eFigure 1 and eFigure 3). Smoking prevalence among females in their 20s and 30s increased from 1965 and almost levelled off at about 17–23% in 1990–2008.21 It was reported that the prevalence of ever smoking by birth cohort among Japanese females continuously increased from the 1930s birth cohort and exceeded 20% by the 1973 birth cohort. Moreover, it was also reported that the mean age of smoking initiation among females declined noticeably during this period.22 The high smoking prevalence among females who were born after the 1960s is possibly related to the stable trends of SQC and SMC among females in the younger age group (35–64 years). The above findings suggest that it is necessary to monitor the incidence rates of SQC and SMC and to reduce smoking prevalence, especially in younger females.

Smoking prevalence for males in Osaka is almost the same as for Japan as a whole (Osaka: 48.1% in 2001 and 33.6% in 2010; Japan as a whole: 48.4% in 2001 and 33.1% in 2010), while it is a little higher among females in Osaka (Osaka: 15.7% in 2001 and 12.3% in 2010; Japan as a whole: 14.0% in 2001 and 10.4% in 2010).23 It is possible that the impact of smoking on lung cancer incidence is greater for females in Osaka.

Trends in the incidence rates of ADC

The incidence rate of ADC showed an increasing trend among all the age groups for both genders except for males in the 65–74 years age group (eFigure 2). An increase in incidence of ADC has been reported worldwide, especially for females in developed countries. However, the determining factor for the increase in ADC remains unclear.24 It has been suggested the switching from non-filtered cigarettes to filtered cigarettes in the 1960s is related to the increase in ADC and decrease in SQC and SMC.25 However, smoking prevalence has decreased since the 1960s, except among younger females, and cigarette consumption per capita has levelled off and then decreased since the late 1970s (eFigure 4).21,26 Therefore, it is difficult to explain the increase in ADC incidence by smoking trends alone. One study has estimated the latency period between exposures to filter cigarettes and ADC development to be about 25 years,25 while another study suggested that it could be more than 30 years if cigarette consumption played a major role in development of ADC.27 If the latency period was about 30 years, the incidence rate of ADC in Osaka would be expected to have begun to level off or decrease from the 2000s.

On the other hand, ADC is the most common type of lung cancer in lifelong non-smokers.28,29 Specific gene mutations, such as EGFR mutations, might be related to the relationship between ADC and never smokers. It has been reported that EGFR mutations are more frequent in females, patients with ADC, never smokers, and people of East Asian ethnicity.30 The higher percentage of never smokers among females than males is probably one reason why the incidence of ADC increased more steeply for females than males. Passive smoking is also considered to be a risk factor for lung cancer.31 and an association has been clearly identified for ADC incidence (HR 2.03; 95% CI, 1.07–3.86).32 It is necessary to monitor trends in ADC and investigate the association between smoking and ADC incidence, with consideration of various factors, such as different distributions of EGFR mutations between ethnicities, smoking patterns, and genders.

Another possible risk factor for lung cancer is air pollution.33 Long-term exposure to NOx has been reported as a possible cause for a temporal increase in ADC incidence in the United States.34 According to a survey by the Japanese government, annual average concentrations of SO2 and SPM have decreased since the 1970s, while NO2 concentration has levelled off and slightly decreased from the 2000s (eFigure 4).35 Therefore, air pollution is not likely to be a major reason for the increased incidence rates of ADC.

Comparison with the results of other studies

Our study confirmed the increase in incidence of ADC and the decrease in incidence of SQC and SMC in Osaka, which has already been shown by a previous study.6 According to a study of nine population-based prefectural cancer registries in Japan,25 incidence rates of SQC have recently decreased for both genders, which is consistent with our results in Osaka. However, the incidence of ADC in males has levelled off (APC 0.2%; 95% CI, −1.6% to 1.9%) since 1998, which is different from the results in Osaka. It seems that there are some differences in trends for lung cancer incidence between Osaka and other prefectures, especially for ADC.

According to lung cancer trends by histological type in other countries,36 incidence rates of SQC and SMC decreased for males and incidence of ADC increased for females in North America, Australia, and several European countries. Nevertheless, there were some differences. In North America, Australia, Denmark, and Iceland, incidence rates of ADC for males and lung cancer for all histological types for females levelled off, while in the other European countries, as in Osaka, incidence of ADC in males and lung cancer of all histological types in females increased. This is probably because smoking prevalence for both genders in North America, Australia, Denmark, and Iceland was lower and declined more sharply between 1980 and 2012 than in other countries, including Japan.37,38 Regarding trends in Hong Kong and Tianjin, China,39,40 incidence rates of lung cancer significantly decreased for both genders after the 1980s and 1990s, respectively. In these two regions, ADC incidence levelled off or decreased and SQC incidence has decreased recently for both genders. However, male smoking prevalence in China among adults aged 15 or above was high and has decreased slowly (61% in 1984 and 52.9% in 2010).41,42
Although smoking is closely associated with lung cancer incidence, it appears that we cannot fully understand trends in lung cancer by trends in smoking prevalence alone. Interpreting these trends more accurately requires that we also study the influence of the spread of cancer screening or exposure to other risk factors on lung cancer incidence.

Limitations
There are several limitations to the present study. The OCR included cases with unspecified histological diagnosis. Although the percentage of cases without histological diagnosis decreased over the years, about one-third of the cases had an unspecified histological diagnosis in 2005–2008 (Table 1). We used the MI approach to solve this problem. However, when we use the MI approach, the mechanism of missingness should be missing at random, where the chance of data being missing is independent of unsee values. Although we assumed that this was the case for the data from OCR, it is difficult to test whether or not this assumption is valid.

The quality of cancer registry data is usually determined using the proportion of death certificate only (DCO) cases and microscopic verified (MV) cases (DCO% and MV%). For the OCR, DCO% and MV% of all cancers are as follows: DCO% in 1987, 1997, and 2007 were 24%, 15%, and 11.6% for males and 21.1%, 14%, and 11.8% for females, respectively; MV% in 1992, 1997, and 2007 were 70%, 70%, and 77.6% for males and 73%, 72%, and 75.8% for females, respectively. DCO% of the OCR has improved over these periods, which might have influenced trends in incidence rates of lung cancer. It was difficult to evaluate the influence of these factors in our analysis.

Conclusion
In this study, we investigated trends in incidence and mortality rates of lung cancer and incidence rates by histological type and age group. The incidence rates of SQC and SMC decreased with the decline in smoking prevalence, which probably led to the change in trends in lung cancer incidence rates from the mid-1980s. It was difficult to explain why the incidence rates of ADC continued to increase for both males and females. Therefore, subsequent studies should carefully monitor trends in lung cancer incidence by histological type, especially trends for ADC. The relationship between the incidence of ADC and its possible risk factors also warrants clarification.

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