Incidence and survival of non-small cell lung cancer in Shanghai: a population-based cohort study

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ABSTRACT

Objectives: Large population-based studies on the incidence and outcome of non-small cell lung cancer (NSCLC) are lacking in mainland China. This study aimed to investigate the NSCLC incidence, demographic features and survival as well as factors affecting survival of patients with NSCLC in Shanghai.

Design: Prospective observational cohort study.

Setting: Baseline information was collected from Shanghai Health Information Network, which is based on the Health Information Systems from all the comprehensive hospitals and specialist hospitals qualified for cancer diagnosis in the Shanghai metropolitan area.

Participants: All NSCLC cases identified from the database between 2011 and 2013 were recruited (15 020 patients).

Main results: The crude and age-adjusted incidences of NSCLC were 54.20 per 100 000 people (55.90 per 100 000 for men, 52.39 per 100 000 for women) and 39.05 per 100 000 people (41.43 per 100 000 for men and 37.13 per 100 000 for women), respectively. The median survival time was 22.7 months (95% CI 21.8 to 24.2 months) with an overall 1-year survival rate of 71.8% (95% CI 69.8% to 73.8%). The 1-year survival rate was 96.5% (95% CI 94.0% to 98.6%) in patients with stage I NSCLC, 78.8% (95% CI 74.1% to 83.5%) in patients with stage II NSCLC, 70.8% (95% CI 66.7% to 74.9%) in patients with stage III NSCLC, 78.8% (95% CI 74.1% to 83.5%) in patients with stage IIA NSCLC and 58.9% (95% CI 56.1% to 61.7%) in patients with stage IIIB/IV NSCLC. Multivariate analysis showed surgical resection (HR=0.607, 95% CI 0.511 to 0.722) and chemotherapy (HR=0.838, 95% CI 0.709 to 0.991) significantly improved survival. Factors associated with poor survival included older age, male sex, larger tumour size, lymph node metastasis, distant metastasis and squamous cell carcinoma.

Conclusions: A higher incidence and better survival rates for patients with NSCLC were identified when compared with previously published studies, which may provide evidence on the incidence and survival of NSCLC in China.

INTRODUCTION

Lung cancer remains the most frequently diagnosed cancer worldwide and the leading cause of cancer-related death in China. Non-small cell lung cancer (NSCLC) accounts for about 85% of lung cancer. According to the Surveillance, Epidemiology and End Results (SEER) registry, the incidence of NSCLC is 42.6 per 100 000 people (49.7 per 100 000 for men and 37.2 per 100 000 for women; adjusted to the US standard population, 2011). In contrast to the decreasing trend of lung cancer incidence in developed countries, its incidence continues to increase in developing countries, especially in China. For patients with early-stage NSCLC, including stage I and II and a subset of stage III disease, the standard and potentially curative treatment is radical resection. In a majority of patients, NSCLC is usually diagnosed at an advanced stage, and curative surgical resection is often impossible. Large population-based studies in Western countries have indicated that the overall 1-year survival rate of NSCLC is 30–46%. The SEER registry reports the 5-year survival rate of NSCLC as being 19%.

Although some population-based studies on the epidemiology and prognosis of NSCLC in Western countries have been published, few studies have been conducted to investigate the characteristics of NSCLC in China. Available Chinese studies on NSCLC are mainly based on the national or local
cancer registry of China, such as National Central Cancer Registry (NCCR) and Sihui Cancer Registry, which analyse lung cancer as a whole (including small cell lung cancer), and only report the incidence and mortality.\textsuperscript{2,9} To the best of our knowledge, population-based studies in the Chinese population have never been conducted to estimate the NSCLC incidence and overall survival (OS) as well as the demographic features and prognostic factors of NSCLC.

In this population-based study, information was collected from Shanghai Health Information Network. The epidemiological features, and survival and prognostic factors of OS were investigated in patients with NSCLC.

**MATERIALS AND METHODS**

**Ethics statement**

Written informed consent was not obtained from patients as it was not required, since a unique ID was allocated to each patient to replace identifiable personal information by the source database administrator before analysis, and also since it was specifically waived by the Institutional Review Board.

**Data source**

Data analysed in this study were obtained from the Shanghai Health Information Network, which is organised and funded by the Shanghai Municipal Commission of Health and Family Planning (former Shanghai Municipal Bureau of Health).\textsuperscript{10} This network automatically and dynamically integrates the data of Health Information Systems (HIS) from all the public healthcare facilities of Shanghai, aiming to facilitate a comprehensive utilisation of health records by patients, healthcare professionals and health management organisations. Therefore, comprehensive healthcare data including demographic, diagnostic and treatment information for each patient are available from this network database. This network was initiated in 2011 and it has covered all the comprehensive hospitals and specialist hospitals qualified for cancer diagnosis in the Shanghai metropolitan area in 2013. Only the network database administrator, as a third party, is authorised to extract information from the database.

NSCLC cases were identified using the primary site coding system of the International Classification of Disease for Oncology 3rd Revision (ICD-10) from the WHO and the pathological findings in the medical records. The diagnosis of NSCLC was confirmed by tissue diagnosis.

Age, sex, histological subtype, treatments, and tumour, node and metastasis (TNM) score were also collected from the database. Clinical as well as pathological TNM information was accepted and coded to the TNM classification based on the TNM classification of malignant tumours (seventh edition).\textsuperscript{11} We prioritised the coded TNM stage where coded stage and recorded stage were both available.

The deadline of the follow-up was set on 31 January 2015. The end point mortality data were matched using the municipal death registration system. The population demographics in this study were obtained from the Shanghai Statistical Yearbook 2012 and 2013 of Shanghai Statistics Bureau.\textsuperscript{12} Incidence was age-standardised (per 100 000 person-years) using the World Standard Population as proposed by Segi,\textsuperscript{13} and modified by Doll and Cook.\textsuperscript{14}

**Case selection and inclusion criteria**

From 1 January 2011 to 31 December 2013, 15 020 patients with NSCLC were identified in Shanghai. All of these patients were recruited to depict the epidemiological features of NSCLC at diagnosis.

Since this network was established in 2011, but covered all the qualified hospitals for cancer diagnosis in Shanghai in 2013, most patients identified in the database were diagnosed in 2013 (n=12 996). Patients who were diagnosed in 2013 were selected to calculate the yearly incidence of NSCLC.

In survival analysis, patients were excluded if the following conditions were present: (1) patients had missing vital status before 31 January 2015; (2) patients had unspecified T, N or M stage, while patients with stage specified as ‘X’ or ‘cannot be accessed’ were included; (3) patients had incomplete baseline information (gender, age or histological subtype). Survival time was calculated by subtracting the date of diagnosis from the date of death or the deadline of the study. Finally, 2013 patients were included in survival analysis (figure 1).

**Statistical analysis**

The incidence of NSCLC in 2013 was calculated by dividing the number of newly diagnosed patients with NSCLC identified from the inpatients database by the number of Shanghai permanent residents in the Shanghai Statistical Yearbook. The \( \chi^2 \) test was employed to compare the baseline characteristics between patients with and without surgical resection. Kaplan-Meier method was used to evaluate the survival rate of NSCLC by cancer stage and treatment (surgical resection vs no surgical resection). To investigate the factors affecting the OS, the following clinicopathological factors were included in the univariate Cox proportional hazard model analysis: age, gender, tumour size (T), regional lymph node status (N), metastasis (M), TNM stage, histology, surgery and chemotherapy. Since TNM stage is basically a combination of T, N and M scores, TNM stage was excluded from the multivariable Cox model while T, N and M scores were still included as potential prognostic factors. To further explore the influence of surgery on the survival, patients were stratified by TNM stage. The proportional hazard hypothesis was visually checked with log–log curves. A value of two-sided \( p<0.05 \) was considered statistically significant. Statistical analysis was conducted using SAS V9.4 (SAS Institute, Inc, Cary, North Carolina, USA).

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RESULTS

Incidence of NSCLC

There were 12,996 newly identified NSCLC cases in Shanghai in 2013, with a crude NSCLC incidence of 54.20 per 100,000 people. The crude incidence of NSCLC in males was higher than that in females (55.90 and 52.39 per 100,000 people, respectively). The age-adjusted incidence was 39.05 per 100,000 people overall, 41.43 per 100,000 people in males and 37.13 per 100,000 people in females, based on the World Standard Population (table 1).

Demographic and tumour characteristics and treatments

From 1 January 2011 to 31 December 2013, 15,020 patients with NSCLC were identified. Approximately 53.3% of patients were men. The mean age at diagnosis was 61.9±10.9 years (range 15–98 years), and half of the patients were aged between 55 and 69 years on diagnosis. Tumour stages were available in 34% of patients (n=5099). Among patients with known tumour stage, 17.9% had stage I NSCLC, 5.7% stage II NSCLC, 12.9% stage IIIa NSCLC and 63.5% stage IIIb/IV NSCLC. In addition, adenocarcinoma was found in 70.6% of patients, while 27.7% were diagnosed with squamous cell carcinoma, among patients with known histological type. Patients undergoing surgical resection were younger, had lower TNM score on tumour size, lymph node metastasis and distant metastasis (table 2).

Among 15,020 patients, 33.7% underwent a surgical resection (n=5069), and this proportion ranged from 94% in patients with stage I NSCLC to 20.8% in patients with stage IIIb/IV NSCLC. The proportion of patients receiving chemotherapy was 52.5%, and ranged from 55.5% in patients with stage I NSCLC to 82.9% in patients with stage IIIa NSCLC (table 3).

OS and prognostic factors

In our study, 2013 patients with NSCLC had complete information from the date of diagnosis until death or 31 January 2015, of whom 1009 patients (50.1%) died during this period.

The median OS is shown in table 4; plots of the survival rate were independently depicted by stage and surgical resection (figures 2 and 3). The median duration of follow-up for all patients with NSCLC was 21.5 months (95% CI 21.2 to 21.8 months). The median survival time for all patients with NSCLC was 22.7 months (95% CI 21.8 to 24.2 months) and the 1-year survival rate was 71.8% (95% CI 69.8% to 73.8%). The median survival time was unavailable for patients with stages I and II NSCLC. For patients with stages IIIa and IIIb/IV NSCLC, the median survival time was 24.3 months (95% CI 21.4 to 26.2 months) and 16.0 months (95% CI 14.8 to 16.7 months). The 1-year survival rate was 96.5% (95% CI 94.0% to 98.6%) in patients with stage I NSCLC, 89.1% (95% CI 83.3% to 94.9%) in patients with stage II NSCLC, 78.8% (95% CI 74.1% to 83.5%) in patients with stage IIIa NSCLC and 58.9% (95% CI 56.1% to 61.7%) in patients with stage IIIb/IV NSCLC (table 4 and figure 2).

Patients who had undergone surgical resection had better survival rates than those without surgical intervention, with median survival time of 34.4 months (95% CI 29.5 to 38.1 months) vs 15.4 months (95% CI 14.1 to 16.5 months) and 1-year survival rate of 87.8% (95% CI 85.7% to 89.9%) vs 57.9% (95% CI 55.0% to 60.8%) (table 4).

Univariate analysis showed that patients who were female or younger and had smaller tumour size, no

Table 1

| Age group, years | Gender | N   | Crude rate (1/10^5) | ASR* (1/10^5) |
|-----------------|--------|-----|-------------------|---------------|
| <55             | Both   | 2958| 15.93             | 15.94         |
|                 | Male   | 1307| 13.46             | 13.35         |
|                 | Female | 1651| 18.64             | 18.85         |
| ≥55, <70        | Both   | 6904| 187.91            | 204.23        |
|                 | Male   | 3762| 200.77            | 219.86        |
|                 | Female | 3142| 174.54            | 187.93        |
| ≥70             | Both   | 3134| 180.60            | 199.59        |
|                 | Male   | 1834| 239.97            | 250.99        |
|                 | Female | 1300| 133.87            | 156.96        |
| Overall         | Both   | 12 996| 54.20          | 39.05         |
|                 | Male   | 6903| 55.90             | 41.43         |
|                 | Female | 6093| 52.39             | 37.13         |

*ASR, age-standardised rates by world standard population; NSCLC, non-small cell lung cancer.
lymph node metastasis, no distal metastasis, lower stage, and had received surgical resection or had adenocarcinoma, showed a longer survival time than their counterparts, while chemotherapy failed to benefit patients on survival rates. However, after adjustment for the demographic factors and tumour characteristics in multivariate analysis, patients receiving chemotherapy showed a significantly longer survival time (HR=0.838, 95% CI 0.709 to 0.991). Patients receiving surgical resection also had improved survival (HR=0.607, 95% CI 0.511 to 0.722) as compared with those without surgical intervention. In this multivariable Cox proportional hazard model, factors associated with a poor survival rate included male sex (HR=1.751, 95% CI 1.521 to 2.015), older age at diagnosis (age ≥70 vs <55 years: HR=1.727, 95% CI 1.426 to 2.091), larger tumour size (T4 vs T1: HR=1.385, 95% CI 1.083 to 1.772), lymph node metastasis (N3 vs N0: HR=3.527, 95% CI 2.762 to 4.504), distant metastasis (HR=1.722, 95% CI 1.456 to 2.037) and squamous cell carcinoma (HR=1.172, 95% CI 1.003 to 1.369) (table 4).

In order to further evaluate the prognostic role of surgery in patients with NSCLC, additional multivariable analysis was performed according to TNM stages. T, N

### Table 2 Demographics, tumour characteristics and treatments of newly identified NSCLC cases in Shanghai between 2011 and 2013 (n=15 020)

| Characteristics               | All subjects (n=15 020) | Surgical resection (n=5069) | No surgical resection (n=9951) | p Value |
|-------------------------------|-------------------------|----------------------------|-------------------------------|---------|
| Sex                           |                         |                            |                               |         |
| Male                          | 8002 (53.3%)            | 2457 (48.5%)               | 5545 (55.7%)                  | <0.0001 |
| Female                        | 7018 (46.7%)            | 2612 (51.5%)               | 4406 (44.3%)                  |         |
| Age groups, years             |                         |                            |                               |         |
| <55                           | 3396 (22.6%)            | 1213 (23.9%)               | 2183 (21.9%)                  | <0.0001 |
| 55–70                         | 7935 (52.8%)            | 2831 (55.8%)               | 5104 (51.3%)                  |         |
| ≥70                           | 3689 (24.6%)            | 1025 (20.2%)               | 2664 (26.8%)                  |         |
| TNM tumour                    |                         |                            |                               |         |
| T1                            | 570 (3.8%)              | 393 (19.6%)                | 177 (6.6%)                    | <0.0001 |
| T2                            | 1630 (10.9%)            | 1052 (52.4%)               | 578 (21.4%)                   |         |
| T3                            | 646 (4.3%)              | 254 (12.6%)                | 392 (14.5%)                   |         |
| T4                            | 1771 (11.8%)            | 286 (14.2%)                | 1485 (55.1%)                  |         |
| Tx                            | 88 (0.6%)               | 24 (1.2%)                  | 64 (2.4%)                     |         |
| Unspecified/unknown           | 10 315 (68.7%)          | 3060 (--)                  | 7255 (--)                     |         |
| TNM node                      |                         |                            |                               |         |
| N0                            | 1395 (9.3%)             | 1141 (56.7%)               | 254 (9.4%)                    | <0.0001 |
| N1                            | 563 (3.7%)              | 213 (10.6%)                | 350 (13.0%)                   |         |
| N2                            | 1590 (10.6%)            | 465 (23.1%)                | 1125 (41.7%)                  |         |
| N3                            | 1020 (6.8%)             | 151 (7.5%)                 | 869 (32.2%)                   |         |
| Nx                            | 144 (1.0%)              | 44 (2.2%)                  | 100 (3.7%)                    |         |
| Unspecified/unknown           | 10 308 (68.6%)          | 3055 (--)                  | 7253 (--)                     |         |
| TNM metastasis                |                         |                            |                               |         |
| M0                            | 2390 (15.9%)            | 1672 (75.4%)               | 718 (24.4%)                   | <0.0001 |
| M1                            | 2671 (17.8%)            | 523 (23.6%)                | 2148 (73.1%)                  |         |
| Mx                            | 95 (0.6%)               | 22 (1.0%)                  | 73 (2.5%)                     |         |
| Unspecified/unknown           | 9864 (65.7%)            | 2852 (--)                  | 7012 (--)                     |         |
| Stage                         |                         |                            |                               |         |
| Ia/ib                         | 912 (6.1%)              | 857 (39.5%)                | 55 (1.9%)                     | <0.0001 |
| IIa/Ilb                       | 292 (1.9%)              | 253 (11.6%)                | 39 (1.3%)                     |         |
| IIIa                          | 659 (4.4%)              | 389 (17.9%)                | 270 (9.2%)                    |         |
| IIIb/IV                       | 3236 (21.5%)            | 673 (31.0%)                | 2563 (87.6%)                  |         |
| Unspecified/unknown           | 9921 (66.1%)            | 2897 (--)                  | 7024 (--)                     |         |
| Histology                     |                         |                            |                               |         |
| Adenocarcinoma                | 2976 (19.8%)            | 1408 (70.0%)               | 1568 (71.1%)                  | <0.0001 |
| Squamous cell carcinoma       | 1168 (7.8%)             | 545 (27.1%)                | 623 (23.8%)                   |         |
| Other (adenosquamous carcinoma and large cell carcinoma) | 73 (0.4%) | 59 (2.9%) | 14 (0.7%) |
| Unspecified/unknown           | 10 803 (70.3%)          | 3057 (--)                  | 7746 (--)                     |         |
| Chemotherapy                  |                         |                            |                               |         |
| Yes                           | 7134 (47.5%)            | 2182 (43.0%)               | 4952 (49.8%)                  | <0.0001 |
| No                            | 7886 (52.5%)            | 2887 (57.0%)               | 4999 (50.2%)                  |         |

NSCLC, non-small cell lung cancer; TNM, tumour, node and metastasis score.
DISCUSSION

Incidence

To the best of our knowledge, this was the first population-based study to describe the epidemiological characteristics of NSCLC in mainland China. Our results showed the crude incidence of NSCLC in 2013 was 54.20 per 100,000 people (55.90 per 100,000 for men and 52.39 per 100,000 for women) with an age-adjusted incidence of 39.05 per 100,000 people (41.43 per 100,000 for men and 37.15 per 100,000 for women). Compared with the SEER registry, a population-based national cancer registry covering approximately 28% of the population in the USA and 50% of Asians in the USA, the crude incidence in our study was higher than that of all races in the SEER registry (42.6 per 100,000 people, adjusted to the US standard population). One possible explanation for the higher crude NSCLC incidence in our study could be the ageing of the Chinese population, as an older age has been identified as an independent risk factor for NSCLC. Population ageing is especially obvious in Shanghai, where 27% of the population was older than 60 years of age in 2013, while a mere 16.5% of the US population was older than 60 years of age in 2000.

Most available population-based studies investigate lung cancer as a whole, including both NSCLC and small cell lung cancer. GLOBOCAN database, which is from population-based cancer registries worldwide and referenced by WHO, reports an incidence of lung cancer of 37.98 per 100,000 people overall, 60.26 per 100,000 for men and 20.29 per 100,000 for women, between 2007 and 2011, based on the local cancer registry. Both examples are adjusted by Segi’s World Standard Population. Estimating the NSCLC incidence as 85% of lung cancer incidence, the NSCLC incidence in our study was slightly higher than those listed above, which was largely due to the higher incidence in women in our study. According to the National Central Cancer Registry 2010 in China, the incidence of lung cancer in China was 36.39 per 100,000 people. When compared with the estimated NSCLC incidences, there was an 8% increase in NSCLC incidence per year from 2010 to 2013. This was consistent with previous findings that the incidence of lung cancer is increasing in China.

For example, in the Sihui study, a 6% increase was reported in the annual incidence of lung cancer for women and an 11% increase for men, from 2005 to 2010. Except for the effect of population ageing, several other factors may contribute to this higher and increased NSCLC incidence in our study. First, the smoking prevalence in China has dramatically increased in the past two decades. Although the cigarette smoking rate has peaked and decreased in the USA and several other areas in recent years, the prevalence of smoking in China remains at a high level, and China has become one of those countries with the highest smoking prevalence in the world. According to the 2010 report of China Global Adults Smoking Survey (GATS), 53% of men aged 15 years and above are current smokers. Considering that smoking is the main risk factor of NSCLC, this high smoking prevalence in the past three decades in China is closely related to the increasing prevalence of lung cancer. The relationship between smoking and lung cancer is also confirmed in a study by Gomez et al. Gomez et al found a significant decline in the incidence of squamous cell lung cancer among foreign-born Chinese Americans from 1900 to 2004, accompanied by a temporal decline in current smoking prevalence within the same group, while the incidence was stable for adenocarcinoma, which is less closely associated with tobacco smoke than squamous cell lung cancer. Another factor related to this higher incidence is the higher diagnosis rate due to improved oncology services in Shanghai, as it is one of the most developed cities in China.

Of note, a higher ratio of NSCLC incidence was observed in women as compared to men in this study.

| Stage       | n       | Surgical resection (n=5069) |   |   | No surgical resection (n=9951) | Surgical resection (%) | No chemotherapy (%) | Chemotherapy (%) |
|-------------|---------|---------------------------|---|---|-----------------------------|-------------------------|----------------------|------------------|
| Ia/lb       | 912 (100%) | 465 (51.0%) | 392 (43.0%) | 41 (4.5%) | 14 (1.5%) | 94.0 | 55.5 |
| IIa/lb      | 292 (100%) | 184 (63.0%) | 69 (36.6%) | 27 (9.2%) | 12 (4.1%) | 86.6 | 72.3 |
| Ila         | 659 (100%) | 317 (48.1%) | 72 (10.9%) | 229 (34.7%) | 41 (6.2%) | 59.0 | 82.9 |
| IIb/IV      | 3236 (100%) | 508 (15.7%) | 165 (5.1%) | 1980 (61.2%) | 583 (18.0%) | 20.8 | 76.9 |
| Unknown     | 9921 (100%) | 1413 (14.2%) | 1484 (15.0%) | 2722 (27.4%) | 4302 (43.4%) | 29.2 | 41.7 |
| Total       | 15020   | 2887         | 2182         | 4999         | 4952         | 33.7 | 52.5 |

In Table 3, proportions and rates of surgical resection and chemotherapy, grouping by stage.
While this ratio was 0.75 and 0.40 in the SEER study and GLOBLECAN report, respectively. The higher risk for lung cancer in Chinese women after considering smoking status was also found by Boffetta and Parkin, and Epplein et al. The reasons for the higher incidence of lung cancer among Chinese women are unclear, but might be partly ascribed to household air pollution due to cooking fumes and unventilated coal-fuelled heating stoves. Besides, considering the high overall smoking prevalence in China, secondhand smoke may also be a critical risk factor for NSCLC in non-smokers, typically women.

**Survival**

A better survival rate (overall and stage-specified) was observed in this study as compared to that in previously published population-based studies on groups of non-Asian ethnicity, though different population-based lung cancer databases showed different outcomes.

### Table 4 Median overall survival and prognostic factors of newly diagnosed NSCLC cases in Shanghai, between 2011 and 2013 (n=2013)

| Characteristics   | Median (95% CI)* | Crude HR (95% CI)† | Adjusted HR (95% CI)‡ | p Value‡ |
|-------------------|------------------|---------------------|------------------------|----------|
| Surgery           |                  |                     |                        |          |
| Yes               | 34.4 (29.5 to 38.1) | 0.276 (0.240 to 0.318) | 0.607 (0.511 to 0.722) | 0.000    |
| No                | 15.4 (14.1 to 16.5) | 1.00                | 1.00                   |          |
| Chemotherapy      |                  |                     |                        |          |
| Yes               | 22.2 (21.2 to 23.2) | 1.145 (0.974 to 1.347) | 0.838 (0.709 to 0.991) | 0.039    |
| No                | 26.9 (23.2 to 32.1) | 1.00                | 1.00                   |          |
| Gender            |                  |                     |                        |          |
| Male              | 19.2 (17.7 to 20.4) | 1.721 (1.508 to 1.964) | 1.751 (1.521 to 2.015) | 0.000    |
| Female            | 26.2 (25.7 to 29.1) | 1.00                | 1.00                   |          |
| Age, years        |                  |                     |                        |          |
| <55               | 24.9 (22.7 to 26.2) | 1.00                | 1.00                   |          |
| 55–70             | 25.1 (23.7 to 26.0) | 1.048 (0.885 to 1.241) | 1.111 (0.936 to 1.318) | 0.228    |
| ≥70               | 16.1 (14.6 to 18.3) | 1.850 (1.539 to 2.224) | 1.727 (1.426 to 2.091) | 0.000    |
| T                 |                  |                     |                        |          |
| T1                | 30.3 (28.7 to 48.2) | 1.00                | 1.00                   |          |
| T2                | 27.5 (25.9 to 33.9) | 1.437 (1.122 to 1.841) | 1.214 (1.045 to 1.561) | 0.129    |
| T3                | 18.4 (15.5 to 21.5) | 2.847 (2.186 to 3.707) | 1.461 (1.111 to 1.920) | 0.007    |
| T4                | 16.3 (14.5 to 16.9) | 3.545 (2.807 to 4.477) | 1.385 (1.083 to 1.772) | 0.009    |
| Tx                | 10.3 (6.8 to 16.3) | 3.715 (2.400 to 5.751) | 1.571 (0.872 to 2.830) | 0.133    |
| N                 |                  |                     |                        |          |
| N0                | –                 | 1.00                | 1.00                   |          |
| N1                | 21.6 (19.0 to 24.2) | 3.890 (3.022 to 5.007) | 1.949 (1.483 to 2.563) | 0.000    |
| N2                | 17.1 (15.8 to 19.0) | 5.221 (4.240 to 6.428) | 2.845 (2.263 to 3.576) | 0.000    |
| N3                | 13.6 (11.8 to 15.4) | 6.927 (5.567 to 8.620) | 3.527 (2.762 to 4.504) | 0.000    |
| Nx                | 12.0 (8.4 to 18.3) | 5.898 (4.073 to 8.541) | 2.482 (1.489 to 4.139) | 0.000    |
| M                 |                  |                     |                        |          |
| 0                 | 30.3 (27.6 to 35.1) | 1.00                | 1.00                   |          |
| 1                 | 15.6 (14.3 to 16.7) | 3.000 (2.627 to 3.427) | 1.722 (1.456 to 2.037) | 0.000    |
| X                 | –                 | 3.223 (1.920 to 5.411) | 1.458 (0.859 to 2.476) | 0.162    |
| Stage             |                  |                     |                        |          |
| Ia/Ib             | –                 | 1.00                |                        |          |
| Ila/Ilb           | –                 | 3.578 (2.144 to 5.971) |                        |          |
| Illa              | 24.3 (21.4 to 26.2) | 8.094 (5.508 to 11.892) |                        |          |
| Ilb/IV            | 16.0 (14.8 to 16.7) | 14.594 (10.247 to 20.785) |                        |          |
| Histological subtype |                |                     |                        |          |
| Adenocarcinoma    | 24.4 (23.1 to 25.7) | 1.00                | 1.00                   |          |
| Squamous cell carcinoma | 19.0 (16.8 to 21.1) | 1.370 (1.195 to 1.571) | 1.172 (1.003 to 1.369) | 0.045    |
| Other             | 25.3 (22.7 to 38.6) | 0.768 (0.468 to 1.262) | 1.058 (0.639 to 1.752) | 0.827    |

*Median and 95% CI were estimated using the Kaplan-Meier method.
† Crude HR and 95% CI were estimated using the univariate Cox regression model.
‡Adjusted HR, 95% CI and p value were estimated using the multiple Cox regression model adjusted by surgical resection, chemotherapy, sex, age group, TNM score and histology.
NSCLC, non-small cell lung cancer; TNM, tumour, node and metastasis score.

(0.90), while this ratio was 0.75 and 0.40 in the SEER study and GLOBLECAN report, respectively. The higher risk for lung cancer in Chinese women after considering smoking status was also found by Boffetta and Parkin, and Epplein et al. The reasons for the higher incidence of lung cancer among Chinese women are unclear, but might be partly ascribed to household air pollution due to cooking fumes and unventilated coal-fuelled heating stoves. Besides, considering the high overall smoking prevalence in China, secondhand smoke may also be a critical risk factor for NSCLC in non-smokers, typically women. A nationwide cross-sectional survey conducted in 15,540 Chinese adults showed that, in 2000–2001, more than 49.2% of adult female non-smokers reported exposure to tobacco smoke, while this proportion was only 35% according to international data from 192 countries in 2004. This suggests an additional risk for lung cancer in Chinese women.

**Survival**

A better survival rate (overall and stage-specified) was observed in this study as compared to that in previously published population-based studies on groups of non-Asian ethnicity, though different population-based lung cancer databases showed different outcomes.
According to the databases from Australia, Canada, Denmark, Norway, Sweden and the UK, the 1 year OS of NSCLC in 2004–2007 ranged from 30% to 46%, with stage-specified 1-year survival rate of 71.1–86.2% for stage I NSCLC, 58.6–79.0% for stage II NSCLC, 34.4–37.1% for stage III NSCLC and 15.5–25.9% for stage IV NSCLC. A lower survival rate was also observed in the SEER registry (overall 1-year survival rate of 46.6% in 2011; 1-year survival rate of 15.9% for stage IV NSCLC in 1998–2003) and the study of Rasco et al. However, the Asian population shows improved survival. Lin et al. reported the 2-year survival rate was 80.0–96.2%, 64.4–80.2% and 57.5–67.4% for patients with stages I, II and IIIa NSCLC, respectively, among 30 069 Taiwanese patients, between 2004 and 2007. In a study on 4622 Korean patients between 1998 and 2005, the median OS for stages I, II, III and IV NSCLC was 100, 41, 14 and 7 months, respectively. No population-based study has been conducted to investigate the characteristics of NSCLC in mainland China.

The better survival outcome observed in this study may be related to several factors. First, Asian ethnicity has been recognized as an independent favourable prognostic factor for OS among patients with NSCLC. Asian patients with NSCLC showed distinct response to cytotoxic chemotherapy when compared with white patients. For example, Gandara et al. reported a 3-month increase in the median OS of Japanese patients over white patients receiving chemotherapy with the same paclitaxel plus carboplatin regimen; this regimen is also one of the routine regimens for chemotherapy for advanced NSCLC in China. At the same time, epidermal growth factor receptor (EGFR) mutation confers survival benefit independent of treatment in NSCLC, while the East Asian population has the highest incidence of EGFR mutation. Meanwhile, advances in treatment in recent years, such as the introduction of target agents and adjuvant chemotherapy after complete resection, may improve the survival of patients with NSCLC.

Similar to previous studies, our results showed that female gender, younger age, smaller tumour size, no lymph node metastasis and no distant metastasis, were related to a better survival rate. The evaluation of impact of surgery on the survival of patients at different TNM stages showed that patients with stage IIIa or IIIb/IV NSCLC who underwent surgical resection had improved survival. This suggests surgical intervention may improve the survival, even for patients with advanced NSCLC, though the details of therapeutic modality still need to be investigated. Currently, there are controversies on the role of surgery in stage IIIa NSCLC. According to the Chinese guidelines for lung cancer, surgical resection is the current standard treatment for patients with stage I to stage IIIa NSCLC; some patients with stage IV NSCLC with single metastasis are also suitable for surgery. Goldstraw et al. proposed that “current evidence supports an expansion in surgery as part of multimodality management of patients with N2 disease, and greater uptake in patients who are willing to accept higher risks,” which may be ascribed to the improvements in diagnostic imaging and endoscopic techniques. In multivariate analysis, chemotherapy was also shown as a protective prognostic factor, suggesting that a confounding factor does exist in the univariate analysis.

Our study had several strengths. First, this was the first study, to the best of our knowledge, to evaluate the incidence, survival and prognostic factors of NSCLC, based on a large population in mainland China. Existing Chinese studies, mainly the national and local annual cancer registry reports, investigate lung cancer as a whole, and only report incidence and mortality, because limited information is offered by the cancer registration report cards used by the registry system. By contrast, based on the HIS system within the Shanghai Health Information Network, not only can NSCLC cases be specifically identified, but clinicopathological information and treatments are also available. At the same time, our study offered a higher but comparable incidence to that of the existing cancer registration systems, with consistent constitutions of gender and TNM staging in NSCLC cases with other studies, which confirms the reliability of our findings. Furthermore, this study was based on data through 2013, whereas the most recently NSCLC population-based studies from other Asian countries or districts recruited data of 2010. Last, our study reported a higher incidence of and better survival rates for NSCLC as compared to previous studies, which may provide a fresh and meaningful perspective for the evaluation of NSCLC diagnosis and treatment.
considering the ethnic difference, smoking prevalence and treatment improvement.

However, this study also had several limitations. First, as a retrospective study, some important features of patients with NSCLC, such as performance status, body weight and details of treatment, were not available in the database. Specifically, patients' smoking status was unavailable. As a known prognostic factor, its absence may lead to residual confounding. In addition, since the network database is newly established, though important variables such as diagnosis and demographic information are available, the TNM classification and histological subtype were still unavailable in several patients. Therefore, it was difficult to calculate the incidence stratified by or adjusted for these variables. Non-availability of detailed records of diagnosis and treatment also handicapped us in conducting further analysis. However, selection bias can be considerably diminished in the survival analysis as only patients with known potential prognostic factors were included. At last, the duration of follow-up time was short (median: 21.5 months) because the network database has been newly established. Thus, long-term follow-up is required to determine the survival of patients with NSCLC, especially of those with early-stage NSCLC.

Table 5  Multivariate HR of overall survival according to surgical resection by stage (n=2013)

| Stage | Surgical resection vs no surgical resection (ref) | n=2013 | Adjusted HR (95% CI)* | p Value* |
|-------|-------------------------------------------------|-------|-----------------------|---------|
| Ia/Ib | 451                                             | 0.360 (0.104 to 1.237) | 0.105 |
| IIa/IIb | 110                                            | 0.723 (0.205 to 2.542) | 0.613 |
| IIIa  | 288                                             | 0.513 (0.352 to 0.748) | 0.001 |
| IIIb/IV | 1164                                         | 0.646 (0.536 to 0.779) | 0.000 |

*Adjusted HR, 95% CI and p value were estimated using the multiple Cox regression model adjusted by sex, age group and histology type.
CONCLUSION
The present study shows a higher incidence and a better survival rate for Chinese patients with NSCLC. High smoking prevalence and the consequent high environment tobacco exposure may be related to the higher NSCLC incidence both overall and in women. In addition to female gender and younger age, surgical resection is found as a protective prognostic factor for NSCLC at stage IIIa and above.

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Contributors
N-QZ, G-YQ and Z-YS conceived and designed the study; HF, Z-YS, Y-YX, Z-HX, WG and CX conducted this study; HF analysed the data. HF, Y-YX and Z-YS drafted the paper; N-QZ and G-YQ revised the paper.

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Competing interests
None declared.

Ethics approval
The present study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the School of Public Health, Fudan University, Shanghai, China.

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No additional data are available.

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REFERENCES
1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
2. Chen W, Zheng R, Zeng H, et al. Annual report on status of cancer in China, 2011. Chin J Cancer Res 2013;27:2–12.
3. Oser MG, Niederst MJ, Sequist LV, et al. Prognostic significance of baseline and oral epidermal growth factor receptor tyrosine kinase inhibitor era. J Thorac Oncol 2015;10:866–72.
4. Surveillance, Epidemiology, and End Results (SEER) Program. May 2015. http://seer.cancer.gov/
5. Youlend DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. J Thorac Oncol 2008;3:819–31.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. V. 2. Dec 2014. http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf
7. Walters S, Maringe C, Coleman MP, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study., 2004–2007. Thorax 2013;68:551–64.
8. Coleman MP, Forman D, Bryant H, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (The International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. Lancet 2011;377:127–38.
9. Du JL, Lin X, Zhang LF, et al. Secular trend analysis of lung cancer incidence in Shihui City, China between 1987 and 2011. Chin J Cancer 2013;5:34–33.
10. Shanghai Health Information Network. May 2015. http://www.shhs.org.cn
11. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007;2:706–14.
12. Shanghai Statistical Year Book (2013). Dec 2014. http://www.stats-sh.gov.cn/data/toTsnj.html?xt=2013e
13. Segi M. Cancer mortality for selected sites in 24 Countries (1950–57). Japan: Department of Public Health, Tohoku University of Medicine, 1960.
14. Doll R, Cook P. Summarizing indices for comparison of cancer incidence data. Int J Cancer 1967;2:699–709.
15. Gomez SL, Noonoe AM, Lichtensztajn DY, et al. Cancer incidence trends among Asian American populations in the United States, 1990–2008. J Natl Cancer Inst 2013;105:1096–110.
16. Gerontological Society of Shanghai. Dec 2014. http://www.shanghaiage.org.cn
17. Standard Populations—19 Age Groups, Surveillance, Epidemiology, and End Results Program. Dec 2014. http://seer.cancer.gov/stdpopulations/stdpop19ages.html
18. Chen W, Zheng R, Zeng H, et al. Epidemiology of lung cancer in China. Thorac Cancer 2015;6:1–15.
19. Yang L, Parkin DM, Li L, et al. Time trends in cancer mortality in China: 1987–1999. Int J Cancer 2003;106:771–83.
20. Molina JR, Yang P, Cassivi SD, et al. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83:933–43.
21. Zhang H, Cai B. The Impact of tobacco on lung health in China. Respirrology 2003;8:17–21.
22. Zhang J, Oi JX, Bai CX. Tobacco smoking in China: prevalence, disease burden, challenges and future strategies. Respirrology 2011;16:1165–72.
23. Gomez SL, Yang J, Lin SW, et al. Incidence trends of lung cancer by immigration status among Chinese Americans. Cancer Epidemiol Biomarkers Prev 2015;24:1157–64.
24. Yang LL, Zhang XC, Yang XN, et al. Lung cancer treatment disparities in China: a question in need of an answer. Oncologist 2014;19:1084–90.
25. Boffetta P, Parkin D. Cancer in developing countries. CA Cancer J Clin 1994;2:81–90.
26. Eplee PM, Schwarz, SM, Potter JD, et al. Smoking-adjusted lung cancer incidence among Asian-Americans (United States). Cancer Causes Control 2005;16:1085–90.
27. Cancer IAFR. Personal habits and indoor combustions. In. IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: IARC Press, 2010–15.
28. Wang BY, Huang JY, Cheng CY, et al. Lung cancer and prognosis in Taiwan: a population-based cancer registry. J Thorac Oncol 2013;8:1128–35.
29. Feng G, Jiayang, Zhao L, et al. [Degree of exposure to secondhand smoking and related knowledge, attitude among adults in urban China]. Zhonghua Liu Xing Bing Xue Za Zhi 2014;35:998–1001.
30. Gu D, Wu X, Reynolds K, et al. Cigarette smoking and exposure to environmental tobacco smoke in China: the International Collaborative Study of Cardiovascular Disease in Asia. Am J Public Health 2004;94:1972–6.
31. Oberg M, Jaakola MS, Woodward A, et al. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. Lancet 2011;377:139–46.
32. Cetin K, Ettinger DS, Hei YJ, et al. Survival by histologic subtype in stage IV nonsmall cell lung cancer based on data from the surveillance, epidemiology and end results program, Clin Epidemiol 2011;3:139–48.
33. Rasco DW, Yan J, Xie Y, et al. Looking beyond surveillance, epidemiology, and end results: patterns of chemotherapy administration for advanced non-small cell lung cancer in a contemporary, diverse population. J Thorac Oncol 2010;5:1529–35.
34. Lin ZZ, Shao WY, Shao YY, et al. Survival following surgery with or without adjuvant chemotherapy for stage I-IIA non-small cell lung cancer: an East Asian population-based study. Oncologist 2012;17:1294–302.
35. Ahn MJ, Lee J, Park YH, et al. Korean ethnicity as compared with white ethnicity is an independent favorable prognostic factor for overall survival in non-small cell lung cancer before and after the oral epidermal growth factor receptor tyrosine kinase inhibitor era. J Thorac Oncol 2010;5:1185–96.
36. Ou SH, Zilagis 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.
37. Tannenbaum SL, Koru-Sengul T, Zhao W, et al. Survival disparities in non-small cell lung cancer by race, ethnicity, and socioeconomic status. Cancer J 2014;20:237–45.
38. Gandara DR, Kawaguchi T, Crowley J, et al. Japanese-US common-arm analysis of pacitaxel plus carboplatin in advanced
non-small-cell lung cancer: a model for assessing population-related pharmacogenomics. *J Clin Oncol* 2009;27:3540–6.

39. Bell DW, Lynch TJ, Hasserlat SM, et al. Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials. *J Clin Oncol* 2005;23:8081–92.

40. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005;23:5900–9.

41. Lynch TJ, Bell DW, Sordella R, 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.

42. Calvo E, Baselga J. Ethnic differences in response to epidermal growth factor receptor tyrosine kinase inhibitors. *J Clin Oncol* 2006;24:2158–63.

43. XY Z, YK S, JM Y. Standards for the diagnosis and treatment of primary lung cancer (2015 Version) in China. *Chin J Oncol* 2015;37:67–78.

44. Goldstraw P, Ball D, Jett JR, et al. Non-small-cell lung cancer. *Lancet* 2011;378:1727–40.

45. Ebbert JO, Yang P, Vachon CM, et al. Lung cancer risk reduction after smoking cessation: observations from a prospective cohort of women. *J Clin Oncol* 2003;21:921–6.