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Original Research

Association between EGFR mutation and ageing, history of pneumonia and gastroesophageal reflux disease among patients with advanced lung cancer

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KEYWORDS
Lung cancer;
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Ageing;
GERD;
Pneumonia

Abstract ***Background:*** Epidermal growth factor receptor (*EGFR*) mutation is the most frequently encountered oncogenic driver in lung cancer. Risk factors for *EGFR* mutation may help prevention, surveillance and diagnosis strategies of *EGFR*-mutated lung cancer.
Patients and methods: A nationwide, retrospective, longitudinal, cohort study was performed between January 2002 and December 2015. Patient data were collected from the Korean National Health Insurance Database. The lung cancer group included EGFR tyrosine kinase inhibitor (TKI)–treated patients. Controls were randomly selected from people without a history of lung cancer and determined to be four times the number of patients with *EGFR*-mutated advanced lung cancer. The risk model of developing *EGFR*-mutated lung cancer was constructed by multiple logistic regression analysis.
Results: Among the 2010 new cases of lung cancer treated in 2010–2015, 214 cases were classified as *EGFR*-mutated advanced lung cancer. The risk of developing *EGFR*-mutated advanced lung cancer was higher in patients in their 50s (odds ratio [OR]: 3.42; 95% confidence interval [CI]: 1.68–6.93), 60s (OR: 7.04; 95% CI: 3.35–14.77) and 70s (OR: 10.27; 95% CI: 4.73–22.30) and in those aged >80 years (OR: 5.98; 95% CI: 2.25–15.92) than those in their 40s. The risk of developing *EGFR*-mutated lung cancer was also higher in hospitalised patients with a history of pneumonia (OR: 5.22; 95% CI: 1.88–14.46) and those with gastroesophageal reflux disease (OR: 2.02; 95% CI: 1.32–3.07).

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Conclusions: Patients with EGFR-mutated advanced lung cancer were associated with ageing, history of being hospitalised for pneumonia and gastroesophageal reflux disease.

1. Introduction

Therapies targeting somatic mutations in lung cancer have shown remarkable progress in the last 20 years. In adenocarcinomas, the most prominent molecular biologic feature has been cancer growth and progression through the activation of the epidermal growth factor receptor (EGFR) pathway. Hence, tyrosine kinase inhibitors (TKIs) that inhibit the EGFR signalling pathway are very effective in treating tumours with *EGFR*-sensitising mutations [1–4]. Studies are currently ongoing about how somatic mutations occur in normal cells and which mechanisms lead to cancer [5–7].

EGFR mutations occur in about 40% of lung cancer cases in Asians and in 15% of lung cancer cases in the Western population [3,4,8]. The known *EGFR* mutation risk factors include adenocarcinoma, smoking status and female sex [9–11], although these were identified in cross-sectional studies on patients with lung cancer.

A size of 1 cm^3 tumor is considered to contain 1×10^8 cells [12]. Considering the doubling time of adenocarcinoma as half a year [13,14], clonal abnormality should occur after 9–15 years, developing into a 1-cm lung tumour. Therefore, longitudinal studies of patients with a long history from before the occurrence of *EGFR* mutation are necessary to assess the risk factors for *EGFR* mutations. However, there was paucity of epidemiologic investigation of risk factors related with *EGFR* mutation development.

To identify the risk factors for *EGFR* mutation, the general population should be selected as the control group. Accordingly, this study investigated the risk factors associated with causing *EGFR* mutations by analysing closed longitudinal cohorts of the general population and patients with *EGFR*-mutated lung cancer .

2. Materials and methods

2.1. Database

There is only one health insurance system in Korea, with a unique resident registration number for each citizen, thereby avoiding duplication of subjects. The Korean National Health Insurance Service (KNHIS) covers more than 97% of all Korean residents and includes all health claim data such as diagnostic codes, procedures, prescription drugs, patient personal information and hospital information. This study used data from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) 2002–2015, released by the KNHIS in 2015; the data include all medical claims filed from January 2002 to December 2015 for 1,031,392 nationally representative randomly selected subjects, accounting for approximately 2.2% of the entire population in the KNHIS in 2002. The data were produced by the KNHIS using a systematic sampling method to generate a representative sample from all 46,605,433 Korean residents in 2002 [15]. The KNHIS data are linked to the statistics korea (National Statistical Office) data, resulting in accurate identification of deaths via the death certificate record. The present study was approved by the Institutional Review Board (IRB) at Dongsan Hospital, Keimyung University School of Medicine. The IRB waived the requirement for informed consent.

2.2. Patient identification and inclusion

Patients with lung cancer between January 2010 and December 2015 were enrolled (Fig. 1). The International Classification of Diseases, 10th revision (ICD-10) codes were used as a key reference for diagnosing disease and for identifying data within the National Health Insurance (NHI) database. The diagnostic codes for lung cancer cases diagnosed before 2010 were maintained in the NHI database. New lung cancer cases were identified and counted by including new cases registered during the calendar year after excluding preexisting lung cancer. Patients with lung cancer (C34) were included only if the patients were identified with a special code, V193 or V194.

EGFR mutation was identified as an important factor for the response to EGFR-TKIs in the Iressa Pan-Asia Study (IPASS) study in 2009 [3]. Therefore, in Korea, the use of EGFR-TKIs is based on the *EGFR* mutation status in advanced lung cancer (stage IIIb and IV).

To exclude patients using EGFR-TKIs as second-line treatment without *EGFR* mutation [16], patients who used EGFR-TKIs for more than 2 months were defined as having *EGFR*-mutated lung cancer. The number of patients with *EGFR*-mutated lung cancer treated with primary and secondary therapies is presented in Table 1.

Patients with *EGFR*-mutated lung cancer who did not use EGFR-TKIs after recurrence after local treatment,

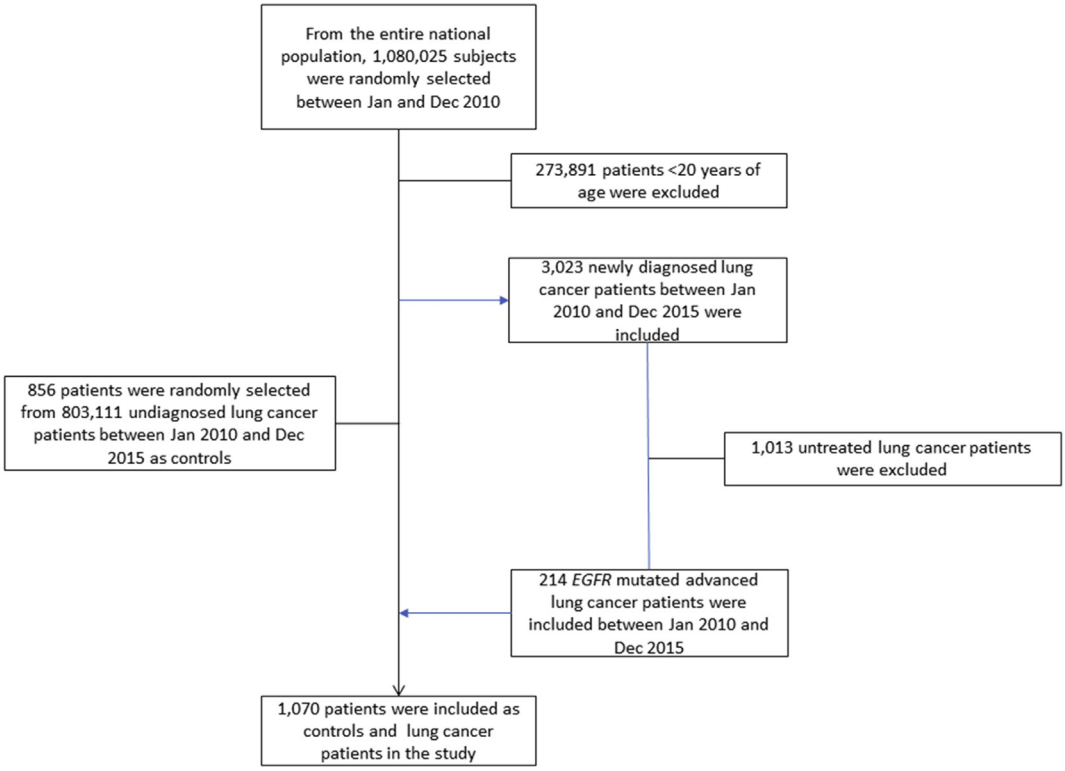

Fig. 1. Flow chart of the study showing the selection of the *EGFR*-mutated lung cancer group and the control group.

such as surgery or concurrent chemoradiation therapy, were not included in the study. However, later on if patients treated with EGFR-TKIs after local treatment, they were included in the advanced *EGFR*-mutated lung cancer group; the number of patients is presented in Table 2. Untreated cases were defined as those who had never undergone surgery, radiation or chemotherapy until death, after the diagnosis of lung cancer. The treated cases were defined by using the medical claim data.

In the NHIS-NSC 2002–2015 database, random sampling was performed to include patients without lung cancer between 2010 and 2015. The number of people in the control group was determined to be four times the number of patients with lung cancer. Data about the total population of the Republic of Korea in 2010, the NHIS-NSC 2002–2015 database, the random sampling control group and the age distribution of these three groups are presented in Table 3.

2.3. Comorbidities

Patient comorbidities—diagnosed and identified using ICD-10 codes since 2002 until the index date—included hypertension, diabetes mellitus, a history of hospitalised pneumonia and gastroesophageal reflux disease (GERD). The Charlson Comorbidity Index (CCI) was also included.

2.4. Data verification

A specific code for lung cancer (C34) has been implemented by the NHI service since 2005. All patients with lung cancer send their documents to the NHI that confirms their diagnosis. All patients with cancer are strictly validated and finally registered in a separate national cancer database maintained by the National Cancer Centre (NCC). Patients whose cancer diagnoses were not validated were excluded. Since 2005, patients with cancer are eligible for payment reduction from the NHI, according to the government's improved policy regarding enhanced support for patients with cancer. The physicians of such patients registered for lung cancer send the necessary eligibility documents to the NHI. The indications for EGFR-TKI use and eligible patients with lung cancer are strictly controlled by the NHI after considering the *EGFR* mutation status.

2.5. Statistical analysis

Baseline characteristics at the initiation date (age, sex, history of hospitalised pneumonia, body mass index, smoking status, comorbidities, residential area and household income) for cases and controls are summarised using descriptive statistics such as proportions. Controls were randomly selected from people without a history of lung cancer and determined to be four times

Table 1
The number of cases treated with epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKI) by year.

EGFR-TKI treatment	2010	2011	2012	2013	2014	2015	Total
First-line EGFR-TKI	3	13	12	15	22	26	91
Second-line EGFR-TKI	32	29	29	15	15	3	123
Total	35	42	41	30	37	29	214

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

the number of patients with EGFR-mutated advanced lung cancer. A chi-squared test was used to compare frequencies of risk factors between the control and the EGFR-mutated advanced lung cancer groups. Logistic regression models were used to evaluate the risk factors for the EGFR-mutated advanced lung cancer. The multivariate logistic regression models were constructed using patient age groups (20–39, 40–49, 50–59, 60–69, 70–79, ≥80 years), sex, history of hospitalised pneumonia, body mass index, smoking status, comorbidities, geographic location (capital, large cities, other) and household income (high, middle, low, very low, Medicaid). The Kaplan-Meier curve was used to calculate the 5-year survival rate between the control and the EGFR-mutated advanced lung cancer groups. *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, North Carolina, USA) and SPSS, version 21 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline characteristics

Table 4 shows the baseline characteristics of the cases included in our study. Sixty-one percent (130 cases) of patients with *EGFR*-mutant lung cancer were female, in contrast to 50.5% of the control group (432 cases).

Among the 2010 new cases of lung cancer diagnosed in 2010–2015, 214 cases (10.6%) were *EGFR*-mutated advanced lung cancer. Until 70s, older patient age was associated with a higher frequency of EGFR mutation. Patients who had EGFR mutation were more likely to have hypertension, diabetes, GERD and a history of hospitalised pneumonia. Moreover, a higher CCI was associated with a higher frequency of EGFR-mutated patients. There was no difference in the frequency of patients with body mass index ≥25 or smoking status between EGFR-mutated patients and controls. Between 2010 and 2015, 35 cases (16.3%), 42 cases (19.6%), 41 cases (19.1%), 30 cases (14.0%), 37 cases (17.3%) and 29 cases (13.5%) of *EGFR*-mutated advanced lung cancer were enrolled each year (Table 5).

3.2. Risk factors associated with EGFR-mutated advanced lung cancer

Table 6 shows the results of multivariate and univariate logistic regression analyses for all the variables. The results revealed a significant association between the risk of *EGFR*-mutated advanced lung cancer and the presence of comorbidities; a history of hospitalised pneumonia resulted in 5.2 times higher risk, and GERD resulted in a 2.0 times higher risk. The most notable risk factor was age. Compared with patients in their 40s, the risk of *EGFR*-mutated advanced lung cancer was 3.4 times higher in patients in their 50s, 7.0 times higher in patients in their 60s, 10.2 times higher in patients in their 70s and 5.9 times higher in patients aged >80 years. Status of smoking and residential area variables changed the direction of the odds ratio between the univariate and the multivariate analyses, although they were not statistically significant. The odds ratio for hypertension, diabetes and CCI reduced after multivariate analysis. For the CCI, the odds ratio on multivariate analysis compared with the univariate analysis was decreased after adding age in the model.

3.3. Survival

The median survival of patients who received EGFR-TKI treatment was 2.32 years (95% confidence interval: 1.80–3.15), and the 5-year survival rate was 18.9% (Fig. 2).

Table 2
The number of patients who started receiving epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI) as first-line and second-line treatment.

Treatment type	First-line treatment (n)	%	EGFR-TKI treatment during follow-up	%
Surgery	469	23.33	11	8.94
Surgery and adjuvant chemotherapy	168	8.36	11	8.94
Definitive radiation therapy	20	1	1	0.81
More than two combinations of surgery, radiation or chemotherapy	617	30.7	60	48.78
Chemotherapy alone	487	24.23	33	26.83
Palliative radiation therapy	158	7.86	7	5.69
EGFR-TKI treatment	91	4.53	0	0
Total	2010	100	123	100

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor

Table 3
Distribution of age and sex in the national population of Korea, the National Health Insurance Service (NHIS) sample database, and the control used in this study in 2010.

Age group (years)	National population, 2010				NHIS-NSC 2002–2015, in 2010				Random Sampling from NHIS-NSC 2002–2015, in 2010–2015			
	Male (n)	%	Female (n)	%	Male (n)	%	Female (n)	%	Male (n)	%	Female (n)	%
20–29	3,428,176	18.97	3,166,193	16.61	58,376	16.64	61,808	15.97	84	19.81	69	15.97
30–39	3,926,630	21.73	3,867,865	20.29	72,303	20.61	77,514	20.02	94	22.17	101	23.38
40–49	4,116,072	22.78	4,088,709	21.45	78,733	22.44	81,724	21.11	93	21.93	89	20.60
50–59	3,248,720	17.98	3,316,106	17.40	70,033	19.96	73,574	19.01	77	18.16	71	16.44
60–69	1,890,277	10.46	2,104,127	11.04	40,381	11.51	44,378	11.46	36	8.49	51	11.81
70–79	1,083,620	6.00	1,566,761	8.22	24,585	7.01	33,930	8.77	29	6.84	31	7.18
≥80	375,480	2.08	953,247	5.00	6473	1.84	14,167	3.66	11	2.59	20	4.63
Total	18,068,975	100	19,063,008	100	350,884	100	387,095	100	424	100	432	100

NSC, national sample cohort.

4. Discussion

The results of this study showed that ageing, a history of hospitalised pneumonia and GERD were the risk factors for *EGFR*-mutated advanced lung cancer. For patients in their 70s, the odds ratio was higher than 10, and as age increased, the odds ratio increased, suggesting that the *EGFR* mutation was significantly associated with ageing. In addition, the odds ratio significantly decreased in the group of patients aged 20–39 years compared with those in their 40s. The odds ratios for pneumonia requiring hospitalisation and GERD were high, 5.2 and 2.0, respectively, suggesting that these two factors were associated with *EGFR* mutation.

In this study, the proportion of EGFR-mutated advanced lung cancer among lung cancer–treated patients was 10.6%. A total of 17 domestic studies have

Table 4
Demographic and clinical characteristics of patients with the EGFR-mutated advanced lung cancer and the control.

Characteristic	EGFR mutated (n = 214)	Control (n = 856)	p-value
Sex			
Male	84 (39.3)	424 (49.5)	0.007
Age (yr)			
20–39	3 (1.4)	348 (40.7)	<0.001
40–49	15 (7.0)	182 (21.3)	
50–59	50 (23.4)	148 (17.3)	
60–69	62 (29.0)	87 (10.2)	
70–79	67 (31.3)	60 (7.0)	
≥80	17 (7.9)	31 (3.6)	
Baseline comorbidity			
Hypertension	109 (50.9)	198 (23.1)	<0.001
Diabetes	89 (41.6)	154 (18.0)	<0.001
GERD	140 (65.4)	287 (33.5)	<0.001
History of hospitalised pneumonia	17 (7.9)	8 (0.9)	<0.001
Charlson Comorbidity Index (CCI)			
CCI 0	27 (12.6)	313 (36.6)	<0.001
CCI 1	34 (15.9)	233 (27.2)	
CCI 2	31 (14.5)	134 (15.7)	
CCI 3	122 (57.0)	176 (20.3)	
Risk factors			
BMI ≥ 25 (missing n = 212)	63 (33.0)	220 (33.0)	1.000
Current or ex-smoker (missing n = 229)	54 (28.7)	232 (35.5%)	0.083
Place of residence			
Seoul, capital city	46 (21.5)	200 (23.4)	0.688
Large cities	51 (23.8)	216 (25.2)	
Small cities and rural area	117 (54.7)	440 (51.4)	
Household income relative to the median (%)			
90–100	74 (34.6)	218 (25.5)	0.011
60–89	71 (33.2)	267 (31.2)	
30–59	34 (15.9)	219 (25.6)	
10–29	29 (13.6)	117 (13.7)	
0–9	6 (2.8)	35 (4.1)	

Values are presented in number (%). GERD, gastroesophageal reflux disease; BMI, body mass index; EGFR, epidermal growth factor receptor.

Table 5
The number of cases according to EGFR-TKI drug by year.

EGFR-TKI treatment	2010	2011	2012	2013	2014	2015	Total
Gefitinib	29	28	29	23	26	19	154
Erlotinib	6	14	12	7	10	4	53
Afatinib	0	0	0	0	1	6	7
Total	35	42	41	30	37	29	214

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

shown that *EGFR* mutation was detected in approximately 43% of lung adenocarcinomas [8]. *EGFR* mutation was observed in 29–34.6% of cases of non-squamous non-small-cell lung carcinoma or adenocarcinoma, except when only surgically resected specimens were included [17,18]. As adenocarcinoma accounted for approximately 50% of lung cancer cases in Korea in 2010 [19], 1005 of 2010 patients were supposed to have adenocarcinoma in the present study. In this study, *EGFR* mutation was probably detected in about 21% of patients with adenocarcinoma. These results seem to be lower than the result shown in previous domestic studies, possibly because of not including patients who had received local treatment.

Advanced age is closely associated with cancer development [20,21]. Recent studies on driver mutations showed age-related expansion of driver gene mutations in oesophageal cancer [5]. The number and size of cells with this driver gene mutation increase with age [5,22]. The results of the present study provide epidemiological support for the molecular biology research results.

GERD is associated with lung cancer [23,24]. The incidence of GERD linearly increases in women, non-smokers and patients with adenocarcinomas [25]. As most *EGFR* mutations occurred in adenocarcinoma [8], we may conclude that the results show good agreement with those of previous studies. In the present study, the incidence of GERD was 33% in the control group, higher than that reported in Western countries, wherein the prevalence of GERD in the US was 18.1–27.8% and that in Europe was 8.8–25.9% [26]. This difference might be because GERD in the present study was identified based on medical claims and the calculated cumulative incidence during the study period.

The relationship between pneumonia and *EGFR*-mutated lung cancer has not yet been established. In the present study, the incidence of patients hospitalised for pneumonia was not high, but the relationship between pneumonia and *EGFR*-mutated lung cancer was significant, even when other variables were controlled. This may suggest a relationship between local inflammation and *EGFR* mutation. However, in this study, the location of previous pneumonia and the location of lung

Table 6
Univariate and multivariate logistic regression analyses for factors associated with the EGFR-mutated advanced lung cancer.

Variables	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Women (reference: men)	1.51 (1.11–2.06)	0.007	1.29 (0.77–2.15)	0.327
Age group (yr)				
20–39	0.10 (0.03–0.36)	<0.001	0.062 (0.008–0.48)	0.008
40–49 (reference)				
50–59	4.09 (2.21–7.59)	<0.001	3.42 (1.68–6.93)	<0.001
60–69	8.64 (4.65–16.06)	<0.001	7.04 (3.35–14.77)	<0.001
70–79	13.54 (7.20–25.49)	<0.001	10.27 (4.73–22.30)	<0.001
≥80	6.65 (3.01–14.68)	<0.001	5.98 (2.25–15.92)	<0.001
Hypertension (reference: no)	3.45 (2.52–4.71)	<0.001	0.89 (0.57–1.40)	0.636
Diabetes (reference: no)	3.24 (2.35–4.48)	<0.001	0.78 (0.47–1.27)	0.326
GERD (reference: no)	3.75 (2.73–5.14)	<0.001	2.02 (1.32–3.07)	0.001
History of hospitalised pneumonia (reference: no)	9.14 (3.89–21.49)	<0.001	5.22 (1.88–14.46)	0.001
BMI ≥ 25 (reference: BMI < 25)	1.00 (0.71–1.40)	1.00	0.78 (051–1.19)	0.25
Current or ex-smoker (reference: never smoker)	0.73 (0.51–1.04)	0.083	1.32 (0.76–2.29)	0.314
Charlson Comorbidity Index (CCI)				
CCI 0 (reference)				
CCI 1	1.69 (0.99–2.88)	0.053	0.97 (0.48–1.94)	0.938
CCI 2	2.68 (1.54–4.66)	<0.001	1.13 (0.54–2.36)	0.727
CCI 3	8.03 (5.09–12.67)	<0.001	2.00 (0.99–4.07)	0.053
Residential area				
Seoul, Capital city (reference)				
Large cities	1.02 (0.65–1.59)	0.908	0.72 (0.41–1.28)	0.275
Small cities and rural area	1.15 (0.79–1.69)	0.454	0.95 (0.57–1.56)	0.850
Household income relative to the median (%)				
90–100 (reference)				
60–89	0.78 (0.54–1.13)	0.198	0.99 (0.61–1.60)	0.979
30–59	0.45 (0.29–0.71)	0.001	0.58 (0.32–1.05)	0.076
10–29	0.73 (0.45–1.18)	0.203	0.90 (0.48–1.68)	0.740
0–9	0.50 (0.20–1.24)	0.139	0.29 (0.07–1.08)	0.066

GERD, gastroesophageal reflux disease; BMI, body mass index.

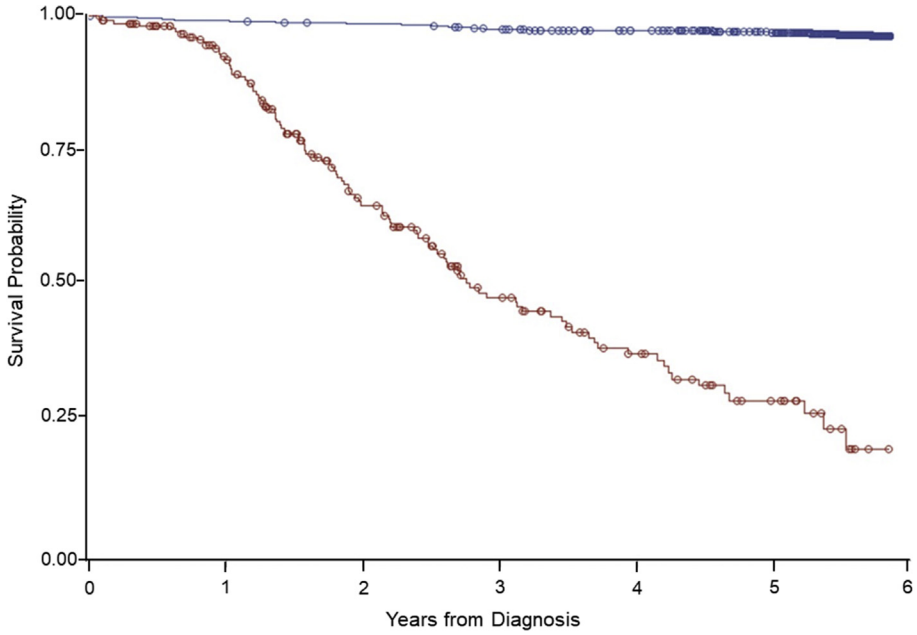

Fig. 2. Survival curve of the *EGFR*-mutated advanced lung cancer group (red line) and the control group (blue line). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

cancer could not be confirmed because the patient data were anonymised.

Previous studies have shown that *EGFR* mutation and female sex are correlated, but there was no significant association in other studies [9–11]. In the present study, there was no significant association between female sex and *EGFR*-mutated advanced lung cancer. We found that GERD and non-smoker were more common in female. When GERD and smoking status are controlled by statistical analysis, female sex would not be the risk factors for EGFR mutation.

This study has several limitations. The study results are not a direct confirmation of *EGFR* mutation results. Therefore, the results of *EGFR* mutation types could not be confirmed. First, owing to the high cost of EGFR-TKI treatment, the NHIS strictly restricts treatment unless the patient is positive for *EGFR* mutation. Therefore, the use of EGFR-TKI treatment in patients without *EGFR* mutation seems to be very rare when *EGFR* mutation types are not identified. Second, the present study did not include patients who were treated with local therapy unless they were progressed to advanced stage, even though they had *EGFR* mutations. This study also did not include patients with occult stage *EGFR*-mutated lung cancer. Third, the comorbidities were defined based on ICD codes, which should have been validated through patient records. However, this database consists of random samples of national insurance claim data without identification numbers. Therefore, it was not possible to validate individual cases through a chart review. Finally, selection bias may have occurred because patients who did not receive any treatment were excluded.

To confirm the cause of *EGFR* mutation, it is necessary to perform representative random sampling of the whole population and to perform the *EGFR* test uniformly. In addition, tracking the *EGFR* mutation at regular intervals in a representative sample may help in understanding the actual genetic epidemiology of *EGFR* mutations.

5. Conclusions

In this observational study of patients with EGFR-mutated advanced lung cancer, compared with those who did not have lung cancer, *EGFR*-mutated advanced lung cancer was associated with ageing, history of being hospitalised for pneumonia and gastroesophageal reflux disease. The findings require confirmation in prospective cohort including genetic information. In addition, a risk-based lung cancer screening model could be considered for the screening and surveillance of EGFR-mutated lung cancer.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.09.010.

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