Original Article

Association between thyroid cancer and epidermal growth factor receptor mutation in female with nonsmall cell lung cancer

Seo Yun Kim, Hye-Ryoun Kim, Cheol Hyeon Kim, Jae Soo Koh[1], Hee Jong Baek[2], Chang-Min Choi[3,4], Joon Seon Song[5], Jae Cheol Lee[4], Im Il Na[6]

Department of Internal Medicine, Division of Pulmonology, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Departments of [1]Pathology and [2]Thoracic Surgery, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Departments of [3]Pulmonology and Critical Care Medicine, [4]Oncology and [5]Pathology, Asan Medical Center, College of Medicine, University of Ulsan, Ulsan, [6]Department of Internal Medicine, Division of Hematology/Oncology, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, Republic of Korea

Address for correspondence:
Dr. Im Il Na, Department of Internal Medicine, Korea Cancer Center Hospital, 75, Nowon-gil, Nowon-gu, Seoul 139-706, Republic of Korea.
E-mail: hmona71@gmail.com

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Abstract:

BACKGROUND: The aim of this study was to investigate the association between epidermal growth factor receptor (*EGFR*) mutation and thyroid cancer in female patients with nonsmall-cell lung cancer (NSCLC).

METHODS: In a retrospective study, we examined 835 female patients who were diagnosed with NSCLC and underwent an *EGFR* mutation test between June 2003 and August 2013. The associations of *EGFR* mutation with thyroid cancer and a family history of thyroid cancer were evaluated using logistic regression models.

RESULTS: *EGFR* mutation was found in 378 of 835 patients. In addition to adenocarcinoma ($P < 0.001$), *EGFR* mutations were positively associated with a personal history of thyroid cancer (5.8% versus 2.6%; $P = 0.020$), while showing a trend toward inverse association with a personal history of nonthyroid cancer (5.8% vs. 9.0%; $P = 0.086$). Likewise, the incidence of *EGFR* mutations was associated with a family history of thyroid cancer (2.9% vs. 0.9%; $P = 0.028$), while showing a trend toward inverse association with a family history of nonthyroid cancer (27.8% vs. 33.7%; $P = 0.066$). Multivariate logistic regression showed that the incidence of *EGFR* mutations was different in women with thyroid or nonthyroid cancer ($P = 0.035$) and in women with a family history of thyroid or nonthyroid cancer ($P = 0.023$).

CONCLUSIONS: Our data suggest that thyroid cancer and a family history of thyroid cancer are associated with *EGFR*-mutated NSCLC in female patients. The differences in the incidence of thyroid cancer and a family history of thyroid cancer by *EGFR* mutational status provide new insight into pathogenesis of this genetic change.

Key words:

Epidermal growth factor receptor, female, nonsmall cell lung carcinoma, thyroid neoplasm

Lung cancer is the leading cause of cancer-related death worldwide, with 159,260 expected deaths in the United States in 2014.[1] It is estimated that 72,330 women will die from progressive lung cancer, accounting for 26% of all cancer-related deaths among women in the United States.[1] Lung cancer incidence has increased 4-fold in women over the past thirty years, until 2000.[1] Epidemiological data demonstrated sex-specific differences in lung cancer.[2] In Asian populations, 60%–80% of women with lung cancer have never smoked, in contrast to 10%–15% of men with lung cancer.[2]

Epidermal growth factor receptor (*EGFR*) has been one of the targets in the era of individualized therapy for nonsmall cell lung cancer (NSCLC), leading to improvements in survival outcomes and quality of life for patients with tumors harboring *EGFR* mutations,[3] which are predominantly found in women. Other factors associated with *EGFR* mutation are adenocarcinoma histology, no history of smoking, and Asian background.[4-6] Recently, a Chinese group reported that multiple primary malignancies occurred more frequently in lung adenocarcinoma patients with *EGFR* mutations.[7] However, the cohort has included men, whose patterns of cancer history are different from those in women. In the previous study,[7] exclusion of recurred lung cancer has remained uncertain.

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Thus, in female lung cancer patients, the association between the *EGFR* mutations and history of malignancies is unknown.

Thyroid cancer, one of the predominant malignancies in women, is the most common cancer of the endocrine system, and its incidence has been increasing rapidly worldwide.[8] It is estimated that approximately 47,790 new cases of thyroid cancer will be diagnosed in women in the United States in 2014.[1] Epidemiologic studies have reported that the risk of secondary primary lung cancer after thyroid cancer is significantly increased in women.[9,10] The *EGFR* pathway has been proposed to be important for thyroid cancer proliferation and metastasis.[11-13] In laboratory studies, *EGFR* mutation and overexpression have been detected in thyroid cancer.[11,12,14] In addition, Masago *et al*. showed that *EGFR* mutations commonly found in pulmonary adenocarcinoma were also detected in 7 (30.4%) of 23 patients with Japanese papillary thyroid cancer.[12]

Previously, in addition to aggregation of cancer in first relatives of lung cancer patients,[15] the association between family history of cancer and *EGFR* mutational status has been investigated.[16,17] Recent studies have suggested the increased incidence of *EGFR* mutations in patients with family history of all kinds of cancer.[16,17] However, the prevalence of *EGFR* mutation according to family history of thyroid cancer has not been reported.

Based on these findings, we conducted this retrospective study to investigate the association between *EGFR* mutation and thyroid cancer in terms of patient's personal history as well as familial history in female NSCLC.

Methods

Patients

This retrospective study included female patients who were diagnosed with NSCLC histologically or cytologically and underwent an *EGFR* mutation test between June 2003 and August 2013 at the Korea Cancer Center Hospital and the Asan Medical Center. To be eligible for inclusion, patients needed to have a documented EGFR status at the time of diagnosis, which was identified from the NSCLC pathology database of each institution. Informed consent for genetic tests was also required.

The demographic and clinical characteristics, including age at diagnosis of lung cancer, smoking status, and subtype of NSCLC histology, were reviewed from the medical records. We included patients with NSCLC, whose pathological findings were complemented with additional immunohistochemical staining when appropriate. We routinely asked patients about personal and family history of malignancy when patients were admitted for workup of lung cancer. The personal history of nonpulmonary malignancy and the family history of cancers among first-degree relatives of the patients were collected from the medical records retrospectively. To exclude the impact of sex and previous lung cancer, this study was confined to female patients who received an initial diagnosis with NSCLC during the study period. Primary lung cancer was confirmed by pathology review with additional immunohistochemistry staining and clinical review, especially in patients who were diagnosed with other cancer concurrently with the diagnosis of lung cancer.[18,19] This study was approved by our Institutional Review Board.

Epidermal growth factor receptor genotyping

Genomic DNA was extracted from paraffin-embedded tissues, as described previously.[20] In patients whose only available tissue was the cytological sample at initial diagnosis, methanol-fixed cytological specimens were used for DNA extraction.[21] *EGFR* mutation analysis was carried out by direct sequencing ($n = 571$) or pyrosequencing ($n = 264$), using previously described methods.[20,22,23] The presence of *EGFR* mutations was determined by evaluating exons 18, 19, 20, and 21.

Statistics

The associations between *EGFR* mutation status and clinicopathological parameters, such as age, smoking status, histology, *EGFR* mutation status, personal history of other cancer, and family history of cancer were compared using the χ^2 test for categorical variables and *t*-test for continuous variables. The odds ratios for the risk of *EGFR* mutation were analyzed using a multivariate logistic regression model, including age, smoking status, histology (adenocarcinoma vs. nonadenocarcinoma), stage, personal history of thyroid and nonthyroid cancer, and family history of thyroid and nonthyroid cancer. A two-sided alpha level of 0.05 was used to indicate statistical significance. All statistical analyses were carried out using SPSS software (version 18.0; SPSS, Inc., Chicago, IL, USA).

Results

Epidermal growth factor receptor mutation and clinical features

A total of 835 female patients who satisfied the inclusion criteria were identified in the study. The clinical characteristics of the study population are summarized in Table 1. The mean age was 60.0 ± 11.7 years, and most individuals had never been smokers (93.4%). The major histologic type was adenocarcinoma (744 cases), followed by squamous (38), adenosquamous (9), large cell (4), and other (39) carcinoma types.

Three hundred and seventy-eight (45.3%) of the 835 patients had *EGFR* mutations. The most prevalent *EGFR* mutations were in-frame deletions of exon 19 (263 patients, 69.8%), followed by L858R substitution in exon 21 (105 patients, 27.9%). The remaining ten patients (2.6%) had a G719X mutation in exon 18.

The frequency of *EGFR* mutation was significantly higher in patients with adenocarcinoma than in those with nonadenocarcinoma tumors (48.0% vs. 23.1%, $P < 0.001$). *EGFR* mutation was more common in never-smokers than ever-smokers, but the difference was not statistically significant (46.2% vs. 32.7%; $P = 0.053$). The differences in age (mean age ± standard deviation, 60.6 ± 11.0 years vs. 59.4 ± 12.2 years, $P = 0.126$) according to *EGFR* mutation did not reach statistical significance. A different incidence of *EGFR* mutation according to stage was observed (51.5% [I/II] vs. 35.4% [III] vs. 44.8% [IV], $P = 0.013$).

Table 1: Relationship between epidermal growth factor receptor mutation and clinical factors

	All patients (*n*=835)	EGFR mutation		*P*
		Positive (*n*=378)	Negative (*n*=457)	
Age, year (mean±SD)	60.0±11.7	60.6±11.0	59.4±12.2	0.126
Smoking history (%)				0.053
Ever smoker	55 (6.6)	18 (32.7)	37 (67.3)	
Never smoker	782 (93.4)	360 (46.2)	420 (53.8)	
Histology (%)				<0.001
Adenocarcinoma	744 (89.1)	357 (48.0)	387 (52.0)	
Nonadenocarcinoma	91 (10.9)	21 (23.1)	70 (76.9)	
Squamous cell carcinoma	38	4	34	
Adenosquamous carcinoma	9	5	4	
Large cell carcinoma	4	2	2	
Other	39	9	30	
EGFR mutation (%)		378 (45.3)		
Exon 21 L858R		105 (27.9)		
Exon 19 deletion		263 (69.8)		
Exon 18 G719X		10 (2.6)		
Stage (%)				0.013
I/II	237 (28.4)	122 (51.5)	115 (48.5)	
III	127 (15.2)	45 (35.4)	82 (64.6)	
IV	471 (56.4)	211 (44.8)	260 (55.2)	
History of cancer (%)	98 (11.7)	44 (11.6)	54 (11.8)	0.937
Thyroid cancer[a]	34 (4.1)	22 (5.8)	12 (2.6)	0.020
Nonthyroid cancer[b]	63 (7.5)	22 (5.8)	41 (9.0)	0.086
Family history of cancer[c] (%)	282 (34.1)	122 (32.4)	160 (35.3)	0.385
Thyroid cancer	15 (1.8)	11 (2.9)	4 (0.9)	0.028
Nonthyroid cancer	259 (31.0)	105 (27.8)	154 (33.7)	0.066

[a]Including two patients with triple primary cancer, [b]Including four patients with triple primary cancer, [c]Information on the family history of cancer was missing for six patients. SD=Standard deviation, EGFR=Epidermal growth factor receptor

Association of epidermal growth factor receptor mutation with thyroid cancer and a family history of thyroid cancer

Ninety-eight (11.7%) of the 835 patients had a personal history of cancer. Of these, 34 (4.1%) had thyroid cancer and 63 (7.5%) nonthyroid cancers. Of the 63 patients with nonthyroid cancers, 22 (2.6%) had cervical cancers, 16 (1.9%) breast cancers, 9 (1.1%) colon cancers, 6 (0.7%) gastric cancers, and 16 (1.9%) other cancers. Of the 34 thyroid cancer patients, 17 (50%) were diagnosed with thyroid cancer concurrently with the diagnosis of lung cancer, while 10 (29.4%) were diagnosed with thyroid cancer within 5 years before the diagnosis of lung cancer. The median time from the diagnosis of thyroid cancer to the diagnosis of lung cancer was 6 months (range: 0–40 years), and was not associated with *EGFR* mutations (data not shown). Two hundred and eighty-two (34.1%) of the 835 patients had a family history of cancer among first-degree relatives. Of these, 15 (1.8%) had thyroid cancer and 259 (31.0%) nonthyroid cancers. Of the 259 patients with nonthyroid cancers, 72 (8.6%) had lung cancer, 68 (8.4%) gastric cancer, 49 (6.0%) hepatocellular carcinoma, 30 (3.7%) colon cancer, 27 (3.3%) cervical cancer, 20 (2.4%) breast cancer, and 72 (8.9%) other cancers.

The presence of *EGFR* mutations was positively associated with a personal history of thyroid cancer (5.8% vs. 2.6%; $P = 0.020$) [Table 1], while it showed a trend toward inverse association with personal history of nonthyroid cancer (5.8% vs. 9.0%; $P = 0.086$). Interestingly, the incidence of *EGFR* mutations was associated with a family history of thyroid cancer (2.9% vs. 0.9%; $P = 0.028$), while it showed a trend toward inverse association with a family history of nonthyroid cancer (27.8% vs. 33.7%; $P = 0.066$).

When we evaluated the association of thyroid cancer on *EGFR* mutations using a multivariate model including age, smoking history, histology and stage, overall different effect between personal history of thyroid and nonthyroid cancers on *EGFR* mutation was maintained [$P = 0.035$, Table 2]. In further statistical evaluation, *EGFR* mutation was positively related with thyroid cancer and inversely associated with nonthyroid cancer like as univariate analysis. However, analysis of each variable did not reach statistical significance ($P = 0.050$ for thyroid cancer and $P = 0.118$ for nonthyroid cancer, respectively). In addition, the statistical difference in the incidence of *EGFR* mutations in patients with a family history of thyroid versus nonthyroid cancer remained significant ($P = 0.023$). There were also similar trends between family history of thyroid cancer and nonthyroid cancer on *EGFR* mutation like as univariate analysis, but they did not show significant difference ($P = 0.067$ for thyroid cancer and $P = 0.060$ for nonthyroid cancer, respectively).

Discussion

This is the first study to evaluate the possibility of an association of *EGFR* mutations with thyroid cancer and a family history of thyroid cancer in female patients with NSCLC. The

Table 2: Multivariate analysis for epidermal growth factor receptor mutation in female nonsmall-cell lung cancer

	OR	95% CI	*P*
Age (years)[a]	1.01	0.99-1.02	0.110
Never smoker	Reference		
Ever smoker	0.64	0.35-1.19	0.156
Nonadenocarcinoma	Reference		
Adenocarcinoma	2.97	1.74-5.05	<0.001
Stage			0.029[b]
I/II	Reference		
III	0.54	0.34-0.85	
IV	0.77	0.56-1.07	
History of cancer			0.035[b]
No history	Reference		
Thyroid cancer	2.11	1.00-4.45	0.050
Nonthyroid cancer	0.64	0.36-1.12	0.118
Family history of cancer			0.023[b]
No history	Reference		
Thyroid cancer	3.03	0.93-9.94	0.067
Nonthyroid cancer	0.74	0.55-1.01	0.060

[a]1-year increase in age, [b]*P* value for Wald test. OR=Odds ratio, CI=Confidence interval

frequency of *EGFR* mutation was consistent with previous reports.[3,6] Association of smoking history with histology has also been observed in recent studies of female lung cancer.[24,25] Interestingly, *EGFR* mutations were more prevalent in patients with thyroid cancer or a family history of thyroid cancer. These associations remained significant in a multivariate analysis.

Recent studies supported the idea of a high likelihood of *EGFR* mutations in female patients with thyroid cancer. An epidemiological study investigated the incidence and types of second primary malignancies in Korean patients with thyroid cancer. Among 178,844 patients with thyroid cancer from the Korea Central Cancer Registry database, the overall risk of lung cancer calculated by the standardized incidence ratio (SIR) according to the number of cancer events was elevated (SIR = 1.35, 95% confidence interval [CI]: 1.22–1.50). The risk of lung cancer events among women with thyroid cancer was significantly increased (SIR = 1.58, 95% CI: 1.40–1.78), whereas it was not increased in male patients (SIR = 0.95; 95% CI: 0.77–1.17).[9] In another population-based study based on the Taiwan Cancer Registry, a significantly elevated risk of lung cancer was found after thyroid cancer was observed in women (SIR = 1.80, 95% CI: 1.37–2.34), but not in men (SIR = 1.24, 95% CI: 0.82–1.80).[10] Interestingly, a trend toward inverse association with *EGFR* mutation was observed in nonthyroid cancer, which is inconsistent with a previous study, which reported that *EGFR* mutations were frequently found in multiple primary cancers.[7] This discrepancy may be caused by the different study population. Our study population was sex-specific, dealing with only female patients, while previous studies included both male and female patients.

It is uncertain how thyroid cancer affects *EGFR* mutation in female patients with NSCLC. However, there are several explanations for the association between *EGFR* mutation and thyroid cancer. First, recent studies suggest that estrogen is involved in the pathogenesis of thyroid cancer and lung cancer in females.[26,27] Estrogen is a potent growth factor both for benign and malignant thyroid cells that may explain the sex difference in the prevalence of thyroid nodules and thyroid cancer. Estrogen is also involved in the regulation of angiogenesis and metastasis that are critical for the outcome of thyroid cancer.[26] Laboratory studies of lung cancer suggest that estrogen receptor may act in conjunction with *EGFR* in carcinogenesis.[28] Furthermore, strong nuclear expression of estrogen receptor beta has been detected in *EGFR* mutated tumors.[29] Second, we suggest that thyroid transcription factor 1 (TTF-1) might play a certain role. Parental cells of lung and thyroid cancer have similar developmental properties. The progenitor cells of lung and thyroid originate from the embryonic foregut endoderm,[30] and the process of organogenesis requires NK2 homeobox 1 (NKX2-1), also known as TTF-1.[31,32] Several studies showed that NKX2-1 is amplified in lung cancer, implying that NKX2-1 is likely functionally relevant to the pulmonary tumorigenic process.[33] It should be noted that TTF-1 was predominantly expressed in *EGFR* mutated lung adenocarcinoma.[34] Interestingly, altered expression of TTF-1 was observed in thyroid tumors.[35]

This study is the first to report the association of *EGFR* mutations in lung cancer cells with a family history of thyroid cancer in women. Inconsistent results with previous studies could be attributed to heterogeneous populations, as well as different accuracies in reporting family cancer history between men and women.[36,37] The mechanism of the impact of family history of thyroid or of any cancer on the incidence of *EGFR* mutation is still unknown. A recent report described a family with multiple cases of NSCLC associated with germ line transmission of *EGFR* T790M gene mutation.[38] The presence of this mutation in a case of familial clustering of NSCLC could have a role in the inherited susceptibility to NSCLC. However, its significance in thyroid cancer is unknown. Rather, inherited single nucleotide polymorphisms of NKX2-1, a potential genetic risk factor for papillary thyroid cancer,[39] may play a role in the pathogenesis of *EGFR*-mutated tumors.

The current study has several limitations. First, all studies relied on self-report of family history and thus had the potential for a recall bias. The limited knowledge or errors of their family history of cancer will result in a false family history. Second, in some patients diagnosed with thyroid cancer before the diagnosis of lung cancer, the histologic type (papillary thyroid carcinoma, follicular thyroid carcinoma, and anaplastic thyroid carcinoma, and others) was unknown. Third, the detailed information on age and the number of first-degree relatives could not be analyzed in this retrospective study. Finally, because of retrospective nature, our findings about the relation between thyroid cancer and the incidence of *EGFR* mutation need external validation through further studies.

Conclusions

We found that thyroid cancer and a family history of thyroid cancer are common in female NSCLC patients with *EGFR* mutation. Although the pathogenesis of *EGFR* mutated NSCLC has not been understood yet, the fact that thyroid cancer

relates to *EGFR* mutation in NSCLC might provide a clue to the pathogenesis of this genetic change.

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Conflicts of interest
There are no conflicts of interest.

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