Review Article

Fibroblast Growth Factor Receptor 1 Gene Amplification in Nonsmall Cell Lung Cancer

Jian-Long Miao[1], Rui-Juan Liu[1], Jin-Hua Zhou[1], Shu-Hua Meng[2]

[1]Department of Respiratory Medicine, Shandong Jining No. 1 People's Hospital, Jining, Shandong 272000, China
[2]Zouping County Institute for Tuberculosis Prevention and Control, Binzhou, Shandong 256200, China

Abstract

Objective: To review the prevalence and prognostic significance of fibroblast growth factor receptor 1 (*FGFR1*) amplification and to establish an association between *FGFR1* amplification and the clinical characteristics of nonsmall cell lung cancer (NSCLC).
Data Sources: We searched PubMed for English-language studies published between January 2010 and May 2016.
Study Selection: We included all relevant articles, with no limitation of study design.
Results: *FGFR1* amplification was reported in 8.7–20.0% of NSCLC cases and was significantly more frequent in squamous cell carcinomas (SCCs) (9.7–28.3%) than in adenocarcinomas (ADCs) (0–15.0%). The rates of *FGFR1* amplification were as follows: males, 13.9–22.1%; females, 0–20.1%; Stage I NSCLC, 9.3–24.1%; Stage II NSCLC, 12.9–25.0%; Stage III NSCLC, 8.2–19.5%; Stage IV NSCLC, 0–12.5%; current smokers, 13.3–29.0%; former smokers, 2.5–23.0%; and nonsmokers, 0–22.2%. Overall survival was 43.9–70.8 months in patients with *FGFR1* amplification and 42.4–115.0 months in patients with no *FGFR1* amplification; disease-free survival was 22.5–58.5 months and 52.4–94.6 months, respectively.
Conclusions: *FGFR1* amplification is more frequent in SCCs than in ADCs. The association between *FGFR1* amplification and clinical characteristics (gender, smoking status, and disease stage) and the prognostic significance of *FGFR1* amplification in NSCLC remain controversial.

Key words: Fibroblast Growth Factor Receptor 1; Gene Amplification; Lung Cancer; Prognosis

Introduction

Lung cancer is the most common cancer worldwide and the leading cause of cancer-related mortality despite improved diagnosis and therapy.[1] Nonsmall cell lung cancer (NSCLC) accounts for 75% of all lung cancers and includes two predominant subtypes, adenocarcinoma (ADC) and squamous cell carcinoma (SCC), which comprise 40% and 25% of NSCLCs, respectively. Due to the lack of specific symptoms, most lung cancer patients are in the mid or late stage of the disease when they were diagnosed. Although diagnostic approaches, treatment techniques, and surgical levels toward lung cancer treatment have been improved greatly in recent years, most lung cancer patients still have bad prognosis, with 5-year survival rates fluctuating around 15%.[2] It is of great significance in treatment selection and patient survival rate increase to look for factors relevant to lung cancer prognosis.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.194649

Fibroblast growth factor receptor 1 (FGFR1) has been identified as one of the emerging molecular targets for the treatment of SCC of the lung,[3-5] and several early-phase clinical trials of FGFR1 inhibitors are currently being undertaken in NSCLC.[6-8] Alterations of the *FGFR* gene have been recognized in many epithelial malignancies, including amplifications in gastric, breast, oral squamous cell, ovarian, and bladder carcinomas,[9,10] and more recently in squamous NSCLC. Previous studies of *FGFR1* amplification in lung cancer have focused on SCC.[11-13] This review summarizes the current knowledge of *FGFR1*

Address for correspondence: Dr. Rui-Juan Liu, Department of Respiratory Medicine, Shandong Jining No. 1 People's Hospital, Jining, Shandong 272000, China
E-Mail: mqb_6@163.com

Received: 31-08-2016 **Edited by:** Qiang Shi
How to cite this article: Miao JL, Liu RJ, Zhou JH, Meng SH. Fibroblast Growth Factor Receptor 1 Gene Amplification in Nonsmall Cell Lung Cancer. Chin Med J 2016;129:2868-72.

amplifications in the main subtypes of NSCLC. The next sections describe the prevalence and prognostic significance of *FGFR1* amplification and report the clinical characteristics associated with *FGFR1* amplification in NSCLC.

Role of Fibroblast Growth Factor Receptor 1 in Oncogenesis

FGFR1 is a member of the Type 4 family of receptor tyrosine kinases, which consists of the closely related and highly conserved *FGFRs* 1–4. All these proteins are transmembrane receptors composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular part that contains the functionally relevant tyrosine kinase domain. Constitutive activation of *FGFR1* occurs basically by three major mechanisms: gene amplification, translocation, or activating mutations. Compared to *FGFR* gene mutation and translocation, gene amplification of *FGFR* is most well studied. *FGFR1* amplification is associated with poor prognosis[14] and one of the most frequent genetic changes in breast cancer.[15,16] Amplification of *FGFR1* has additionally been reported in SCC of the head and neck (17%) as well as of the esophagus (28.6%).[17,18] Translocations of *FGFR1* have originally been described in a myeloproliferative hematological disorder which has now been referred to as an "8p11 myeloproliferative syndrome characterized by *FGFR1* translocation" by the current WHO classification system. Very recently, *FGFR1* translocations have been additionally found in a subset of glioblastoma multiforme and in rhabdomyosarcoma.

The important advances achieved over the past decade through identifying oncogenic mutations in lung ADC have led to several efforts to screen for targetable oncogenes in SCC of the lung. *FGFR1* amplification has been detected in SCC of the lung, with lower frequency in lung ADC.[19,20] Lung cancer cells harboring *FGFR1* amplification exhibit a highly tumorigenic phenotype, and *FGFR1* regulates the stem cell-like phenotype of SCC of the lung.[21]

Detection of Fibroblast Growth Factor Receptor 1 Amplification by Fluorescence *In situ* Hybridization

There are currently no validated antibody assays on the market, which could reliably detect *FGFR1* expression levels quantitatively or semiquantitatively using paraffin-embedded tumor samples. Reliable *FGFR1* fluorescence *in situ* hybridization (FISH) probes are now commercially available. In this review, we focused on the detection of *FGFR1* amplification by FISH. In FISH, the *FGFR1* gene locus is labeled with a green fluorochrome and the centromeric reference probe (*CEN8*) is labeled with an orange fluorochrome. Before hybridization, samples are cut into 5-μm sections, deparaffinized, and pretreated with the commercial pretreatment kit Vysis. Hybridization is performed overnight in a humidified chamber at 37°C. Next, slides are washed with Vysis washing solution and counterstained with 4',6-diamidino-2-phenylindole.

We searched PubMed for English-language studies published between January 2010 and May 2016 using the terms "*FGFR1*" OR "fibroblast growth factor receptor 1" and "lung cancer" OR "lung carcinoma" or combinations thereof, and the references cited in the identified studies or reviews were also used to complete the search. The variability of *FGFR1* amplification rates as determined by FISH is related to differences in the definition of a positive result and in interpretation of results. Table 1 shows the results of the literature search about *FGFR1* amplification cutoff values and methods.

Fibroblast Growth Factor Receptor 1 Amplification in Nonsmall Cell Lung Cancer Epidemiology

FGFR1 is one of the most frequently amplified genes in human cancer. Many researchers studied the prevalence of *FGFR1* amplification in patients with NSCLC. Table 2 shows results of our literature search. From January 2010 to May 2016, 11 studies were identified and included in the final analysis. Statistics were not included for three of those studies due to alternative diagnoses focusing on SCC. In those three studies, *FGFR1* amplification rates were 13.0% (34/262), 18.2% (22/121), and 16.0% (37/226).[19,23,24] *FGFR1* amplification was reported in 8.7–20.0% of NSCLC cases. *FGFR1* amplification was significantly more frequent in SCCs (9.7–28.3%) than in ADCs (0–15.0%).

The prevalence of *FGFR1* amplification was 30.0% (3/10) in pleomorphic carcinomas[4] and 13.0% (3/23) in large cell carcinoma (LCC).[25] Russell *et al*.[27] confirmed that

Table 1: *FGFR1* amplification cutoff values and methods

Author	Year	*FGFR1* amplification cut-off	Method
Sousa *et al*.[4]	2016	*FGFR1*/*CEN8* ratio ≥2.0	FISH
Cihoric *et al*.[25]	2014	*FGFR1*/*CEP8* ratio ≥2.0	FISH
Toschi *et al*.[5]	2014	≥4 gene copies/cell	FISH
Seo *et al*.[26]	2014	Gene copy number of 6.2	FISH
Russell *et al*.[27]	2014	*FGFR1*/*CEN8* ratio ≥2.0	FISH
Tran *et al*.[28]	2013	*FGFR1*/*CEP8* ratio ≥2.0	SISH
Kim *et al*.[19]	2013	Gene copy number ≥9	FISH
Craddock *et al*.[23]	2013	Mean gene copies/cell ≥5.0	FISH
Schildhaus *et al*.[22]	2012	(1) *FGFR1*/*CEN8* ratio ≥2.0; or (2) average number of *FGFR1* signals per tumor cell nucleus ≥6; or (3) percentage of tumor cells containing ≥15 *FGFR1* signals or large clusters ≥10%	FISH
Heist *et al*.[24]	2012	*FGFR1*/*CEP8* ratio ≥2.2	FISH
Weiss *et al*.[29]	2010	Gene copy number >9	FISH

FGFR1: Fibroblast growth factor receptor 1; *CEN8*/*CEP8*: Centromere 8; FISH: Fluorescence *in situ* hybridization.

FGFR1 amplification was 16.7% (1/6) and 21.7% (5/23) in pleomorphic carcinomas and LCC, respectively.

Association between Fibroblast Growth Factor Receptor 1 Amplification and Clinical Characteristics

The following clinical characteristics were extracted from each study: gender, smoking status, and disease stage. When referring to smoking status, we defined never smokers as adults who never smoked or smoked fewer than 100 cigarettes in their lifetime; former smokers were those who smoked at least 100 cigarettes but currently do not smoke; current smokers were people who smoked 100 cigarettes in their lifetime and currently smoke. Nonsmokers were defined as both former smokers and never smokers.[30]

Seven studies were identified and included in the final analysis [Table 3]. *FGFR1* amplification was reported in 13.9–22.1% of male NSCLC patients and in 0–20.1% of female NSCLC patients. Cihoric *et al*.[25] and Russell *et al*.[27] found that *FGFR1* amplification was significantly more frequent in male patients (14.8% and 17.1%, respectively) compared with female patients (5.9% and 8.5%, respectively).

FGFR1 amplification occurred in 13.3–29.0% of current smokers, 2.5–23.0% of former smokers, and 0–22.2% of never smokers. Kim *et al*.,[19] Craddock *et al*.,[23] and Russell *et al*.[27] reported that the frequency of *FGFR1* amplification was significantly higher in current smokers than in former smokers and never smokers. As the smoking dosage increased, so did the rate of *FGFR1* amplification. However, the remaining studies considered that there was no significant correlation between *FGFR1*-positive status and other clinicopathological features including smoking history.

FGFR1 amplification occurred in 9.3–24.1% of Stage I (IA and IB), 12.9–25.0% of Stage II (IIA and IIB), 8.2–19.5% of Stage III (IIIA and IIIB), and 0–12.5% of Stage IV NSCLC cases. Cihoric *et al*.[25] found a significant correlation between higher tumor stage and *FGFR1* amplification rate. However, the remaining studies found contradictory results.

Table 2: Prevalence of *FGFR1* amplification in nonsmall cell lung cancer (%)

Author	NSCLC	SCC	ADC
Sousa *et al*.[4]	15/76 (20.0)	5/24 (21.0)	5/34 (15.0)
Cihoric *et al*.[25]	41/329 (12.5)	35/169 (20.7)	3/137 (2.2)
Toschi *et al*.[5]	74/445 (16.6)	39/138 (28.3)	28/243 (11.5)
Seo *et al*.[26]	32/369 (8.7)	25/139 (18.0)	7/230 (3.0)
Russell *et al*.[27]	50/352 (14.2)	40/178 (22.5)	0/99 (0)
Tran *et al*.[28]	49/264 (10.6)	25/101 (24.8)	13/115 (11.3)
Weiss *et al*.[29]	–	15/155 (9.7)	1/77 (01.0)
Schildhaus *et al*.[22]	60/400 (15.0)	58/290 (20.0)	0/97 (0)

FGFR1: Fibroblast growth factor receptor 1; NSCLC: Nonsmall cell lung cancer; SCC: Squamous cell lung cancer; ADC: Adenocarcinoma; –: Not applicable.

Fibroblast Growth Factor Receptor 1 Amplification and Prognosis

Seven studies were identified and included in the final analysis [Table 4]. Overall survival was 43.9–70.8 months in patients with *FGFR1* amplification and 42.4–115.0 months in patients with no *FGFR1* amplification; disease-free survival (DFS) was 22.5–58.5 months and 52.4–94.6 months, respectively. Two studies considered patients with *FGFR1* amplification who died within the first 5 years, thus resulting in a significantly worse overall survival compared with patients with no *FGFR1* amplification. Overall, the results were largely inconsistent across studies.

Discussion

The ability to identify target oncogenic alterations in NSCLC has been a major advance in the management of patients. An important aspect of translating these molecular alterations into clinical practice is to develop assays that can quickly and reliably identify specific aberrations in clinical specimens. *FGFR1* has recently emerged as a promising target in NSCLC. Our review reports that the prevalence of *FGFR1* amplification was 8.7–20.0% in NSCLC and was significantly higher in SCC (9.7–28.3%) than in ADC (0–15.0%). The prevalence of *FGFR1* amplification was 13.0–21.7% in LCCs and 16.7–30.0% in pleomorphic carcinomas.

Table 3: Rate of *FGFR1* amplification according to clinical characteristics of patients with nonsmall cell lung cancer

Author	Sex (%)		Smoking (%)			Disease stage (%)			
	Male	Female	C	F	N	I	II	III	IV
Cihoric *et al*.[25]	14.8	5.9	13.8*	–	5.6	9.3	22.0	–	–
Toschi *et al*.[5]	17.3	13.0	17.8*	–	7.5	16.2†	–	17.0‡	–
Russell *et al*.[27]	17.1	8.5	17.4	15.7	2.9	14.8	17.2	8.2	12.5
Tran *et al*.[28]	15.8	20.1	21.8*	–	0	18.1	18.6	19.5	–
Kim *et al*.[19]	13.9	0	29.0	2.5	0	10.3	16.7	14.1	–
Craddock *et al*.[23]	22.1	11.4	16.3	23.0	0	24.1	12.9	13.8	0
Heist *et al*.[24]	19.5	12.2	13.3	16.9	22.2	14.4	25.0	18.2	7.4

*Former or current smoker; †Stage I or II; ‡Stage III or IV. *FGFR1*: Fibroblast growth factor receptor 1; C: Current smoker; F: Former smoker; N: Never smoker; –: Not applicable.

Table 4: Prognosis of *FGFR1* amplification-positive and *FGFR1* amplification-negative lung cancer patients

Author	OS (months), positive versus negative	DFS (months), positive versus negative
Cihoric *et al*.[25]	43.9 versus 103.1	22.5 versus 52.4
Toschi *et al*.[5]	47.4 versus 42.4	–
Seo *et al*.[26]*	58.6 versus 80.0	58.5 versus 80.0
Kim *et al*.[19]*	51.2 versus 115.0	26.9 versus 94.6
Craddock *et al*.[23]*	51.0 versus 58.0†	34.0 versus 53.0†
Heist *et al*.[24]*	70.8 versus 55.2	–
Tran *et al*.[28]	60.3 versus 48.1	–

*Data from squamous cell lung cancer patients; †5-year OS and DFS rates (%). –: Not applicable; *FGFR1*: Fibroblast growth factor receptor 1; OS: Overall survival; DFS: Disease-free survival.

There was no consistent relationship between *FGFR1*-positive status and clinical characteristics across studies. Most researchers reported that *FGFR1* amplification was significantly more frequent in male patients compared with female patients and that the prevalence of smoking history was higher among patients with *FGFR1* amplification than among those without. However, other researches reported no significant correlation between *FGFR1*-positive status and clinical features including gender, smoking history, and disease stage.

The prognostic significance of *FGFR1* amplification in NSCLC was also inconsistent. Cihoric *et al*.[25] reported that *FGFR1* amplification is common in early-stage SCC of the lung and is an independent and adverse prognostic marker. Kim *et al*.[19] also reported that patients with *FGFR1* amplification had significantly shorter overall survival and DFS than those without *FGFR1* amplification. On the contrary, Russell *et al*.[27] compared overall survival and DFS between surgically radically treated patients with pure SCC and found no significant difference in overall survival in surgically radically treated patients stratified by stage and *FGFR1* amplification status. However, Tran *et al*.[28] reported that *FGFR1* amplification-positive patients show a tendency toward longer overall survival in univariate analysis. These inconsistent results may be caused by a variety of reasons: (1) The sample size in various series was too small to draw definitive conclusions. (2) The studies included patients with different disease stages. (3) The cutoff values were different across studies. Larger, multicenter studies will help clarify the prognostic significance of *FGFR1* amplification in NSCLC.

FGFR1 has been discussed as a possible new therapeutic target. Therefore, *FGFR1* amplification status should be evaluated prospectively in patients with lung SCC, LCC, and ADC. As patients with lung SCC have only limited options regarding systemic therapies, they might profit from a targeted therapy. Now, treatment with dovitinib demonstrated modest efficacy in patients with advanced SCC with *FGFR1* amplification.[30] In contrast to targeted therapy development in lung ADC, trials targeting FGFR1 in lung SCC have been generally disappointing. Gene amplification or overexpression of this target may not be a sufficiently robust predictor of efficacy for FGFR1 inhibitors.[8] Therefore, the value of *FGFR1* amplification in NSCLC has to be determined in further studies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. American Cancer Society. American Cancer Society Cancer Facts and Figures 2014. J Consum Health Internet 2012;16:366-7. doi: 10.1080/15398285.2012.701177.
2. Wistuba II, Gelovani JG, Jacoby JJ, Davis SE, Herbst RS. Methodological and practical challenges for personalized cancer therapies. Nat Rev Clin Oncol 2011;8:135-41. doi: 10.1038/nrclinonc.2011.2141.
3. Dutt A, Ramos AH, Hammerman PS, Mermel C, Cho J, Sharifnia T, *et al.* Inhibitor-sensitive FGFR1 amplification in human non-small cell lung cancer. PLoS One 2011;6:e20351. doi: 10.1371/journal.pone.0020351.
4. Sousa V, Reis D, Silva M, Alarcão AM, Ladeirinha AF, d'Aguiar MJ, *et al*. Amplification of FGFR1 gene and expression of FGFR1 protein is found in different histological types of lung carcinoma. Virchows Arch 2016;469:173-82. doi: 10.1007/s00428-016-1954-5182.
5. Toschi L, Finocchiaro G, Nguyen TT, Skokan MC, Giordano L, Gianoncelli L, *et al.* Increased SOX2 gene copy number is associated with FGFR1 and PIK3CA gene gain in non-small cell lung cancer and predicts improved survival in early stage disease. PLoS One 2014;9:e95303. doi: 10.1371/journal.pone.0095303.
6. Rooney C, Geh C, Williams V, Heuckmann JM, Menon R, Schneider P, *et al.* Characterization of FGFR1 locus in sqNSCLC reveals a broad and heterogeneous amplicon. PLoS One 2016;11:e0149628. doi: 10.1371/journal.pone.0149628.
7. Reck M, Kaiser R, Eschbach C, Stefanic M, Love J, Gatzemeier U, *et al.* A phase II double-blind study to investigate efficacy and safety of two doses of the triple angiokinase inhibitor BIBF 1120 in patients with relapsed advanced non-small-cell lung cancer. Ann Oncol 2011;22:1374-81. doi: 10.1093/annonc/mdq618.
8. Lim SH, Sun JM, Choi YL, Kim HR, Ahn S, Lee JY, *et al.* Efficacy and safety of dovitinib in pretreated patients with advanced squamous non-small cell lung cancer with FGFR1 amplification: A single-arm, phase 2 study. Cancer 2016;122:3024-31. doi: 10.1002/cncr.30135.
9. Turner N, Grose R. Fibroblast growth factor signalling: From development to cancer. Nat Rev Cancer 2010;10:116-29. doi: 10.1038/nrc2780.
10. Wesche J, Haglund K, Haugsten EM. Fibroblast growth factors and their receptors in cancer. Biochem J 2011;437:199-213. doi: 10.1042/BJ20101603.
11. Göke F, Franzen A, Menon R, Goltz D, Kirsten R, Boehm D, *et al.* Rationale for treatment of metastatic squamous cell carcinoma of the lung using fibroblast growth factor receptor inhibitors. Chest 2012;142:1020-6. doi: 10.1016/S0959-8049(12)71447-8.
12. Jiang T, Gao G, Fan G, Li M, Zhou C. FGFR1 amplification in lung squamous cell carcinoma: A systematic review with meta-analysis. Lung Cancer 2015;87:1-7. doi: 10.1016/j.lungcan.2014.11.009.
13. Wang Y, Gao W, Xu J, Chen X, Yang Y, Zhu Y, *et al.* The role of FGFR1 gene amplification as a poor prognostic factor in squamous cell lung cancer: A meta-analysis of published data. Biomed Res Int 2015;2015:763080. doi: 10.1155/2015/763080.
14. Chang J, Liu X, Wang S, Zhang Z, Wu Z, Zhang X, *et al.* Prognostic value of FGFR gene amplification in patients with different types of cancer: A systematic review and meta-analysis. PLoS One 2014;9:e105524. doi: 10.1371/journal.pone.0105524.
15. Khoo BL, Lee SC, Kumar P, Tan TZ, Warkiani ME, Ow SG, *et al.*

Short-term expansion of breast circulating cancer cells predicts response to anti-cancer therapy. Oncotarget 2015;6:15578-93. doi: 10.18632/oncotarget.3903.
16. André F, Bachelot T, Commo F, Campone M, Arnedos M, Dieras V, *et al.* Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: A multicentre, prospective trial (SAFIR01/UNICANCER). Lancet Oncol 2014;15:267-74. doi: 10.1016/S1470-2045(13)70611-9.
17. Freier K, Schwaenen C, Sticht C, Flechtenmacher C, Mühling J, Hofele C, *et al.* Recurrent FGFR1 amplification and high FGFR1 protein expression in oral squamous cell carcinoma (OSCC). Oral Oncol 2007;43:60-6. doi: 10.1016/j.oraloncology.2006.01.005.
18. Bandla S, Pennathur A, Luketich JD, Beer DG, Lin L, Bass AJ, *et al.* Comparative genomics of esophageal adenocarcinoma and squamous cell carcinoma. Ann Thorac Surg 2012;93:1101-6. doi: 10.1016/j.athoracsur.2012.01.064.
19. Kim HR, Kim DJ, Kang DR, Lee JG, Lim SM, Lee CY, *et al.* Fibroblast growth factor receptor 1 gene amplification is associated with poor survival and cigarette smoking dosage in patients with resected squamous cell lung cancer. J Clin Oncol 2013;31:731-7. doi: 10.1200/JCO.2012.43.8622.
20. Kohler LH, Mireskandari M, Knösel T, Altendorf-Hofmann A, Kunze A, Schmidt A, *et al.* FGFR1 expression and gene copy numbers in human lung cancer. Virchows Arch 2012;461:49-57. doi: 10.1007/s00428-012-1250-y.
21. Ji W, Yu Y, Li Z, Wang G, Li F, Xia W, *et al.* FGFR1 promotes the stem cell-like phenotype of FGFR1-amplified non-small cell lung cancer cells through the hedgehog pathway. Oncotarget 2016;7:15118-34. doi: 10.18632/oncotarget.7701.
22. Schildhaus HU, Heukamp LC, Merkelbach-Bruse S, Riesner K, Schmitz K, Binot E, *et al.* Definition of a fluorescence *in-situ* hybridization score identifies high-and low-level FGFR1 amplification types in squamous cell lung cancer. Mod Pathol 2012;25:1473-80. doi: 10.1038/modpathol.
23. Craddock KJ, Ludkovski O, Sykes J, Shepherd FA, Tsao MS. Prognostic value of fibroblast growth factor receptor 1 gene locus amplification in resected lung squamous cell carcinoma. J Thorac Oncol 2013;8:1371-7. doi: 10.1097/JTO.0b013e3182a46fe9.
24. Heist RS, Mino-Kenudson M, Sequist LV, Tammireddy S, Morrissey L, Christiani DC, *et al*. FGFR1 amplification in squamous cell carcinoma of the lung. J Thorac Oncol 2012;7:1775-80. doi: 10.1097/JTO.0b013e31826aed28.
25. Cihoric N, Savic S, Schneider S, Ackermann I, Bichsel-Naef M, Schmid RA, *et al*. Prognostic role of FGFR1 amplification in early-stage non-small cell lung cancer. Br J Cancer 2014;110:2914-22. doi: 10.1038/bjc.2014.229.
26. Seo AN, Jin Y, Lee HJ, Sun PL, Kim H, Jheon S, *et al.* FGFR1 amplification is associated with poor prognosis and smoking in non-small-cell lung cancer. Virchows Arch 2014;465:547-58. doi: 10.1007/s00428-014-1634-2.
27. Russell PA, Yu Y, Young RJ, Conron M, Wainer Z, Alam N, *et al.* Prevalence, morphology, and natural history of FGFR1-amplified lung cancer, including squamous cell carcinoma, detected by FISH and SISH. Mod Pathol 2014;27:1621-31. doi: 10.1038/modpathol.
28. Tran TN, Selinger CI, Kohonen-Corish MR, McCaughan BC, Kennedy CW, O'Toole SA, *et al.* Fibroblast growth factor receptor 1 (FGFR1) copy number is an independent prognostic factor in non-small cell lung cancer. Lung Cancer 2013;81:462-7. doi: 10.1016/j.lungcan.
29. Weiss J, Sos ML, Seidel D, Peifer M, Zander T, Heuckmann JM, *et al.* Frequent and focal FGFR1 amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer. Sci Transl Med 2010;2:357-62. doi: 10.1126/scitranslmed.3001451.
30. Schoenborn CA, Adams PF, Peregoy JA. Health behaviors of adults: United States, 2008-2010. Vital Health Stat 2013;257:1-184.