The association between fibroblast growth factor receptor 1 gene amplification and lung cancer: a meta-analysis

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Abstract

Introduction: Identifying target oncogenic alterations in lung cancer represents a major development in disease management. We examined the association of fibroblast growth factor receptor 1 (*FGFR1*) gene amplification with pathological characteristics and geographic region.
Material and methods: We conducted a meta-analysis of studies published between January 2010 and October 2016. Relative risks (RR) and corresponding 95% confidence intervals (CI) were calculated regarding the rate of *FGFR1* amplification in different lung cancer types and geographic region.
Results: Twenty-three studies (5252 patients) were included. There was heterogeneity between studies. However, in subgroup analyses for squamous cell carcinoma (SCC), small cell lung cancer (SCLC), studies using the same definition of *FGFR1* amplification, and those from Australia, no significant heterogeneity was detected. The prevalence of *FGFR1* amplification in these studies ranged from 4.9% to 49.2% in non-small cell lung cancer (NSCLC), 5.1% to 41.5% in SCC, 0% to 14.7% in adenocarcinoma, and 0% to 7.8% in SCLC. The prevalence of *FGFR1* amplification was significantly higher in SCC than in adenocarcinoma (RR = 5.2) and SCLC (RR = 4.2). The prevalence of *FGFR1* amplification ranged from 5.6% to 22.2% in Europe, 4.1% to 18.2% in the United States, 7.8% to 49.2% in Asia, and 14.2% to 18.6% in Australia. The rate of *FGFR1* amplification was higher in Asians than in non-Asians (RR = 1.9) in NSCLC.
Conclusions: These results suggest that *FGFR1* amplification occurs more frequently in SCC and in Asians. *FGFR1* amplification may be a potential new therapeutic target for specific patients and lung cancer subtypes.

Key words: fibroblast growth factor receptor 1, gene amplification, lung cancer.

Introduction

Lung cancer is the most common cause of cancer-related deaths worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for 75% of all lung cancers and has two predominant subtypes, adenocarcinoma (ADC) and squamous cell carcinoma (SCC), which constitute 40% and 25% of NSCLC cases, respectively [2, 3]. Small cell lung cancer (SCLC) is a well-recognized histologic variant of lung cancer with a distinct histologic appearance and unique biology. SCLC accounts for approximately 16–18% of all newly diagnosed lung cancers in the United States,

which translates into approximately 30,000 new cases annually [4–6]. Because of the lack of specific symptoms, most cases of lung cancer are diagnosed in the middle or late stages. Methods that may improve earlier detection include positron emission tomography, autofluorescence bronchoscopy, and molecular biomarkers [7]. Although diagnostic strategies, treatment techniques, and surgical approaches for lung cancer management have improved significantly in recent years, most patients with lung cancer still have a poor prognosis, with a 5-year survival rate of approximately 15% [8]. In comparison with NSCLC, SCLC features a shorter doubling time, higher growth fraction, and earlier development of widespread metastases [4–6]. The ability to identify target oncogenic alterations in lung cancer has been a major improvement in disease management. To translate knowledge of these molecular alterations into clinical practice, it is important to develop assays that can quickly and reliably identify specific aberrations in clinical specimens. Thus, identifying factors that contribute to lung cancer prognosis is highly relevant for optimizing treatments and improving the prognosis of patients.

Fibroblast growth factor receptor 1 (*FGFR1*) is an emerging molecular target for the treatment of SCC of the lung [9–11], and several clinical trials of *FGFR* inhibitors in NSCLC are currently underway [12–14]. Amplification of the *FGFR* gene has been found in epithelial malignancies, such as gastric, breast, oral squamous cell, ovarian, and bladder carcinomas [15, 16], and more recently, in lung SCC. The *FGFR1* gene is amplified in lung cancer at varying frequencies and has been shown to be a driving oncogenic factor in lung cancer [17–20]. Thus, *FGFR* is a promising and novel therapeutic target for the treatment of these tumors.

Previous studies of *FGFR1* amplification in lung cancer have focused on SCC [21, 22], several of which have investigated the relationship between *FGFR1* amplification and clinical characteristics such as smoking status, disease stage, and sex; however, findings have been inconsistent across studies and meta-analyses [19, 22]. Additionally, published reviews lack data for Chinese patients. To perform an updated comprehensive quantitative evaluation of the relationship between *FGFR1* amplification and the clinical characteristics of lung cancer, we conducted an updated meta-analysis of the published literature in this area. This study summarizes the current knowledge on *FGFR1* amplification in the main subtypes of lung cancer and comprehensively reports the relationship between *FGFR1* gene amplification and the clinicopathological characteristics of lung cancer.

Material and methods

Search strategy and selection criteria

We searched MEDLINE, EMBASE, Web of Science, and CNKI for articles published in English or Chinese between January 1991 and October 2016. The following search terms were used alone or in combination: Lung Neoplasms OR Pulmonary Neoplasms OR Lung Cancer OR Cancer, Lung OR Pulmonary Cancer OR Cancer, Pulmonary OR Cancer of Lung AND Receptor, Fibroblast Growth Factor, Type 1 OR Fibroblast Growth Factor Receptor 1 OR FGFR1 Protein.

The eligibility of all studies was evaluated and determined by two authors (JM and RL), who scored each study independently. Inclusion criteria were (1) *FGFR1* amplification was measured in lung cancer; (2) when the same group of patients was included in more than one article, the most recent or the most informative report was utilized; (3) only articles published as full-text papers in English or Chinese were included; and (4) test methods included reverse transcription polymerase chain reaction (RT-PCR), fluorescent in situ hybridization (FISH), or silver *in situ* hybridization (SISH). Exclusion criteria were (1) reviews or case-only studies, (2) studies lacking sufficient data for pooling analysis, and (3) duplication of previous publications or replicated samples.

Data extraction and methodological assessment

The following clinical characteristics for patients and other study data were extracted from each study: surname of the first author, year of publication, patient geographic region, histology, *FGFR1* gene copy number, test method, the definition of *FGFR1* amplification, and number of cases and controls. The two reviewers assessed study quality independently using the following factors: (1) a clear definition of the study population and the type of carcinoma, (2) a clear definition of the measurement method and the cut-off value of *FGFR1* gene amplification, (3) sample size larger than 10, and (4) a clear definition of the outcome assessment (if applicable). Studies lacking any of these elements were excluded from the final analysis.

The two reviewers independently read and scored each study according to the NEWCASTLE-OTTAWA scale [23]. The quality score was assessed according to three main categories: (1) patient selection, (2) comparability between the case and control groups, and (3) exposure assessment method. The maximum score was 9 points, and a high-quality study in our analysis was defined as a study with ≥ 7 points (7.42 ±0.98). Any disagreement was resolved by consensus.

Statistical analysis

The statistical heterogeneity was estimated with Cochran's Q (reported as χ^2 and *p*-values) and the I^2 statistic, which indicates the percentage of variation between studies that is due to heterogeneity rather than chance. Unlike Q, I^2 does not inherently depend on the number of studies included; values of 25%, 50%, and 75% indicate low, moderate, and high degrees of heterogeneity, respectively. If the heterogeneity was high ($p < 0.1$) [24], a random-effects model was used; otherwise, a fixed-effects model was used [25]. Subgroup analyses were performed to explore heterogeneity. Sensitivity analyses were performed to assess the stability of the results, and Begg's funnel plots were used to assess publication bias [26]. All *p*-values were two-sided, with $p < 0.05$ considered statistically significant, except in the Q-test. Results are reported in a forest plot, with 95% CI. Statistical analyses were conducted using STATA version 11.0 (StataCorp LP, College Station, TX, USA). In addition, relative risks (RRs) were estimated for the rate of *FGFR1* amplification in different types of lung cancer and different geographic regions using χ^2 tests. The mean and 95% CI were estimated using SPSS Statistics 17.0.

Results

Selection of studies and trial flow

Figure 1 shows the results of the literature search. A total of 4032 potentially relevant abstracts were identified, and 3940 inappropriate studies were removed after reading the title and abstract. Eight were found to be duplicates and were excluded. Another four conference articles were excluded. Fifty-seven studies were excluded because they did not meet the inclusion criteria, including 55 reviews and two meta-analyses. Twenty-three studies met the eligibility criteria and were included in this systematic review.

Study characteristics

In total, 5252 patients participated in the 23 studies included in this analysis. Six studies were conducted in Asia, eight in Europe, seven in the United States, and two in Australia. The gene copy number for *FGFR1* was evaluated using FISH in 16 studies [10, 11, 18, 21, 27–38], RT-PCR in three studies [39–41], SISH in two studies [42, 43], single-nucleotide polymorphism in one study [9], and DNA in one study [44]. Based on data shown in Tables I and II, we concluded that the prevalence of *FGFR1* amplification in these studies ranged from 4.9% to 49.2% in NSCLC, 5.1% to 41.5% in SCC (mean = 19.8%, 95% CI: 15.8–23.8), 0% to 14.7% in ADC (mean = 5.4%, 95% CI: 1.7–9.1), and 0% (0/9) [42] to 7.8% in SCLC (mean = 6.1%, 95% CI: 4.3–8.0). The prevalence of *FGFR1* amplification in lung cancer ranged from 5.6% to 22.2% in Europe [10, 18, 21, 27, 31, 34, 35, 37] (mean = 12.4%, 95% CI: 8.5–16.3), 4.1% to 18.2% in the United States [9, 11, 29, 30, 36, 39, 44] (mean = 12.5%, 95% CI: 5.6–19.4), 7.8% to 49.2% in Asia [28, 32, 38, 40, 41, 43] (mean = 21.1%, 95% CI: 8.7–33.5),

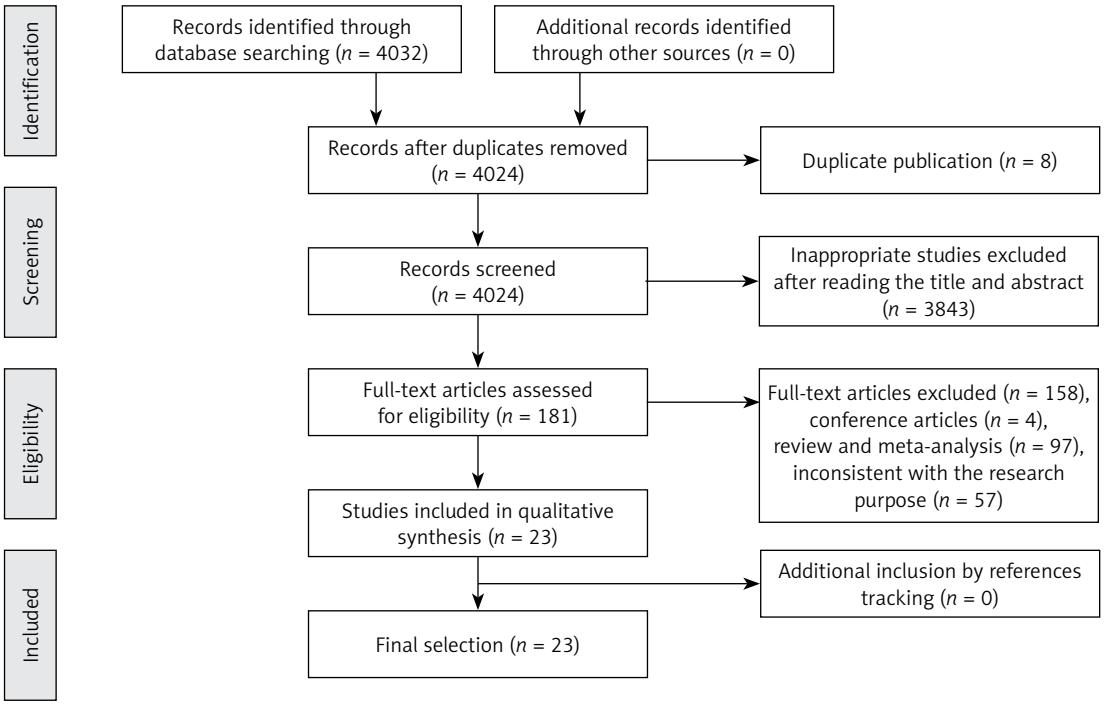

Figure 1. Flow diagram of search results

Table I. Clinical characteristics of the studies

Author	Year	Race	NP	FGFR1+, *n* (%)	Histology	Method	Cut-off
Sousa [10]	2016	Portugal	76	15 (19.7)	NSCLC	FISH	FGFR1/CEN8 ratio ≥ 2.0
Cihoric [31]	2014	Switzerland	329	41 (12.5)	NSCLC	FISH	FGFR1/CEP8 ratio ≥ 2.0
Toschi [11]	2014	United States	445	74 (16.6)	NSCLC	FISH	≥ 4 gene copies/cell
Seo [32]	2014	Korea	369	32 (8.7)	NSCLC	FISH	Gene copy number ≥ 6.2
Russell [33]	2014	Australia	352	50 (14.2)	LC	FISH	FGFR1/CEN8 ratio ≥ 2.0; tumor cell percentage with ≥ 15 signals ≥ 10%; or average number of signals/tumor cell nucleus ≥ 6
Tran [42]	2013	Australia	264	49 (18.6)	NSCLC	SISH	FGFR1/CEP8 ratio ≥ 2.0; mean FGFR1 signals per tumor cell ≥ 6.0; or percentage of tumor cells containing FGFR1 clusters ≥ 10%
Kim [28]	2013	Korean	262	34 (15.3)	SCC	FISH	Gene copy number ≥ 9
Craddock [29]	2013	Canada	121	22 (18.2)	SCC	FISH	Mean FGFR1 copy number per cell > 5.0
Gadgeel [39]	2013	United States	345	17 (4.9)	NSCLC	RT-PCR	Copy number variations > 3.5
Ren [41]	2013	China	59	29 (49.2)	NSCLC	RT-PCR	> 2-fold compared with their adjacent normal counterparts
Schildhaus [27]	2012	Germany	400	60 (15.0)	NSCLC	FISH	(1) FGFR1/CEN8 ratio ≥ 2.0; (2) average number of FGFR1 signals per tumor cell nucleus ≥ 6; (3) percentage of tumor cells containing ≥ 15 FGFR1 signals or large clusters ≥ 10%
Heist [30]	2012	United States	226	37 (16.4)	SCC	FISH	FGFR1/CEP8 ratio ≥ 2.2
Goke [21]	2012	Germany	72	12 (16.7)	SCC	FISH	Gene copy number ≥ 9
Kohler [35]	2012	Germany	260	20 (7.7)	LC	FISH	Gene copies ≥ 4
Sasaki [40]	2012	Japan	100	32 (32.0)	NSCLC	RT-PCR	> 4 copies
Dutt [9]	2011	United States	732	44 (6.0)	NSCLC	SNP	> 3.25 copies
D Wang [38]	2014	China	142	24 (16.9)	SCC	FISH	FGFR1/CEP8 ratio ≥ 2.0 or FGFR1 signals per tumor cell nucleus ≥ 6
Weiss [34]	2010	Germany	153	34 (22.2)	SCC	FISH	Gene copy number > 9
LP Zhang [43]	2015	China	77	6 (7.8)	SCLC	SISH	FGFR1 copies of ≥ 6 or FGFR1/CEN8 ratio ≥ 2
Thomas [36]	2014	United States	68	5 (7.4)	SCLC	FISH	FGFR1/CEN8 ratio > 2
Schultheis [18]	2014	Germany	251	14 (5.6)	SCLC	FISH	(1) FGFR1/CEN8 ratio ≥ 2.0; (2) FGFR1 gene count per tumor cell ≥ 6.0; (3)percentage of tumor cells containing ≥ 15 FGFR1 gene copies ≥ 10%; (4) percentage of tumor cells containing ≥ 5 FGFR1 gene copies ≥ 50%
Peifer [37]	2012	Germany	51	3 (5.9)	SCLC	FISH	Copy number ≥ 3.5
Ross [44]	2014	United States	98	4 (4.1)	SCLC	DNA	N/A

FISH – fish in situ hybridization, FGFR1+ – fibroblast growth factor receptor 1 amplification, CEN8 – centromere 8, SNP – single-nucleotide polymorphism, LC – lung cancer, N/A – not available.

Table II. *FGFR1* amplification in different pathological subtypes

Author	Country	FGFR1 amplification, *n* (%)	
		SCC	ADC
Sousa	Portugal	5 (20.8)	5 (14.7)
Cihoric	Switzerland	35 (20.7)	3 (2.2)
Toschi	United States	39 (28.3)	28 (11.5)
Seo	Korea	25 (18.0)	7 (3.0)
Russell	Australia	40 (22.5)	0 (0)
Tran	Australia	25 (24.8)	13 (11.3)
Gadgeel	United States	7 (5.1)	7 (4.1)
Schildhaus	Germany	58 (20.0)	0 (0)
Kohler	Germany	14 (10.5)	3 (4.7)
Sasaki	Japan	27 (41.5)	N/A
Dutt	United States	12 (21.0)	20 (3.4)

and 14.2% to 18.6% in Australia [33, 42] (mean = 12.5%, 95% CI: 6.7–18.4). The main characteristics of the included studies are shown in Tables I and II.

Test of heterogeneity

There was some heterogeneity among studies regarding the prevalence of *FGFR1* amplification (I^2 = 89.3%, p < 0.001) (Figure 2).

Subgroup analyses according to geographic region, pathologic type, test method, and definition of *FGFR1* amplification revealed the following findings regarding heterogeneity from the same geographic region (Europe: I^2 = 83.3%, p < 0.001; United States: I^2 = 89.9%, p < 0.001; Asia: I^2 = 91.9%, p < 0.001; Australia: I^2 = 52.5%, p = 0.147; Figure 3 A), the same pathologic type (SCC: I^2 = 0.0%, p = 0.677; SCLC: I^2 = 0.0%, p = 0.843; NSCLC: I^2 = 93.6%, p < 0.001; Figure 3 B), the same test method (FISH: I^2 = 79.2%, p < 0.001; SISH: I^2 = 87.1%, p = 0.005; Figure 3 C); the same definition of *FGFR1* amplification (ratio ≥ 2.0: I^2 = 53.4%, p = 0.143; gene copy number > 9: I^2 = 0.0%, p = 0.776; Figure 3 D). Thus, these results show no significant heterogeneity among studies for SCC, SCLC, the same definition of *FGFR1* amplification, and Australia (Figure 3).

Prevalence of *FGFR1* gene amplification

RRs were estimated for the rate of *FGFR1* amplification in different types of lung cancer. There were 2285 SCC, 1860 ADC, and 545 SCLC patients

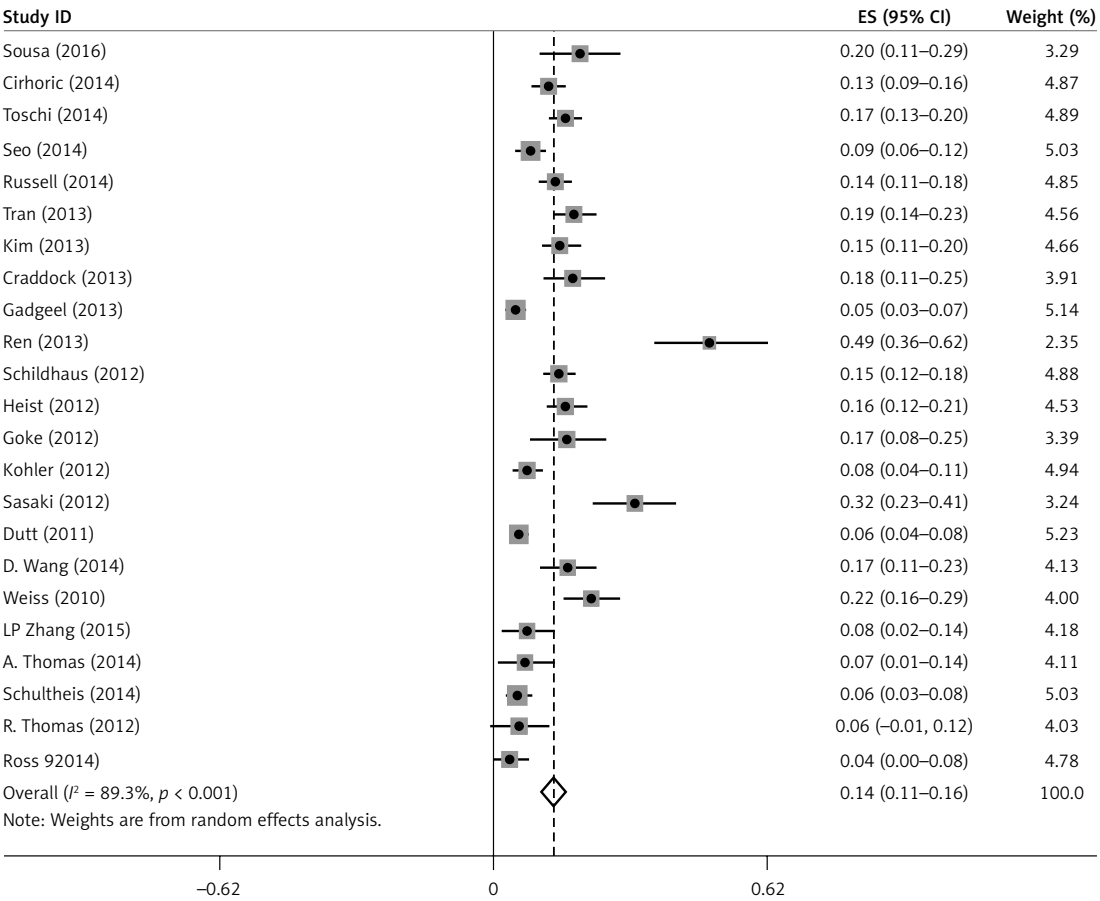

Figure 2. Meta-analysis of *FGFR1* amplification rate in all studies

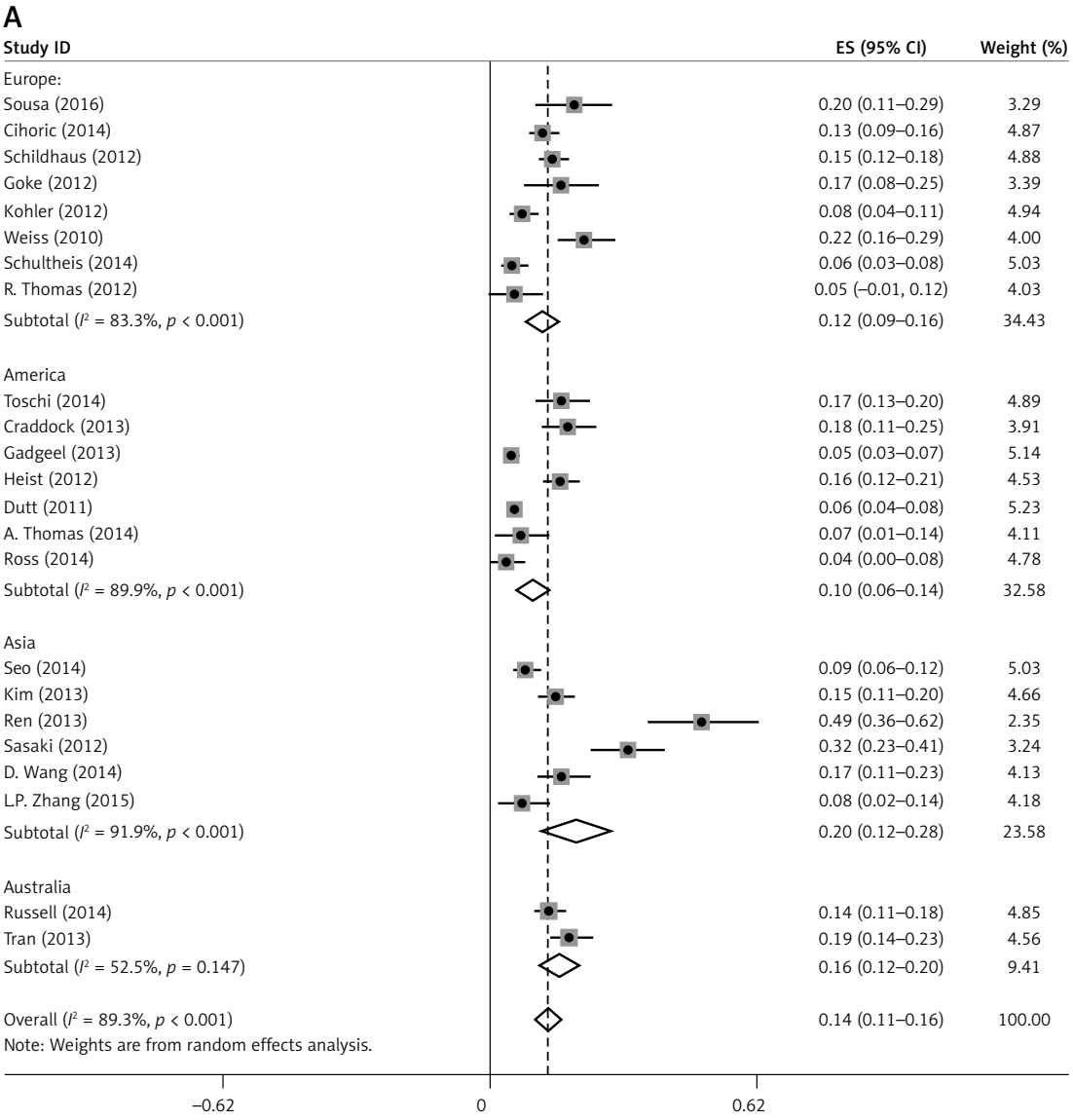

Figure 3. Subgroup Analysis of *FGFR1* Amplification Rate. Meta-analysis of *FGFR1* amplification rate in studies using the same geographic region (**A**)

who participated in the 23 studies included in this analysis; of these, there were 450, 87, and 32 patients, respectively, who exhibited *FGFR1* amplification. The prevalence of *FGFR1* amplification was significantly higher in SCC than that in ADC (RR = 5.2, 95% CI: 4.1–6.7) and SCLC (RR = 4.2, 95% CI: 2.9–6.1); it was also significantly higher in ADC than that in SCLC (RR = 0.8, 95% CI: 0.6–1.3). Of 3731 NSCLC patients who participated in the 12 studies, 463 exhibited *FGFR1* amplification (93 in Asia and 370 in other geographic regions). The mean *FGFR1* amplification rate was 30.0% (95% CI: –0.2 to 0.84) in Asia, 13.7% (95% CI: 0.1–0.2) in Europe, 10.8% (95% CI: –0.6 to 0.9) in the United States, and 12.9% (95% CI: –0.6 to 0.9) in Australia. The rate of *FGFR1* amplification was higher in Asians than that in non-Asians (RR = 1.9, 95% CI: 1.5–2.4).

Publication bias and sensitivity analyses

Begg's funnel plot and Egger's regression test were applied to detect publication bias in the meta-analysis. In all included studies, funnel plot asymmetry was found (p = 0.006), with a 95% CI of –0.03 to 6.96 in Egger's test. Therefore, publication bias was evident from the analysis (Figure 4). Sensitivity analyses were performed to assess the impact of individual studies on the results. As shown in Figure 5, we found no significant difference among the 23 studies.

Discussion

This meta-analysis indicated that the prevalence of *FGFR1* amplification ranged from 4.9% to 49.2% in NSCLC, 5.1% to 41.5% in SCC, 0% to

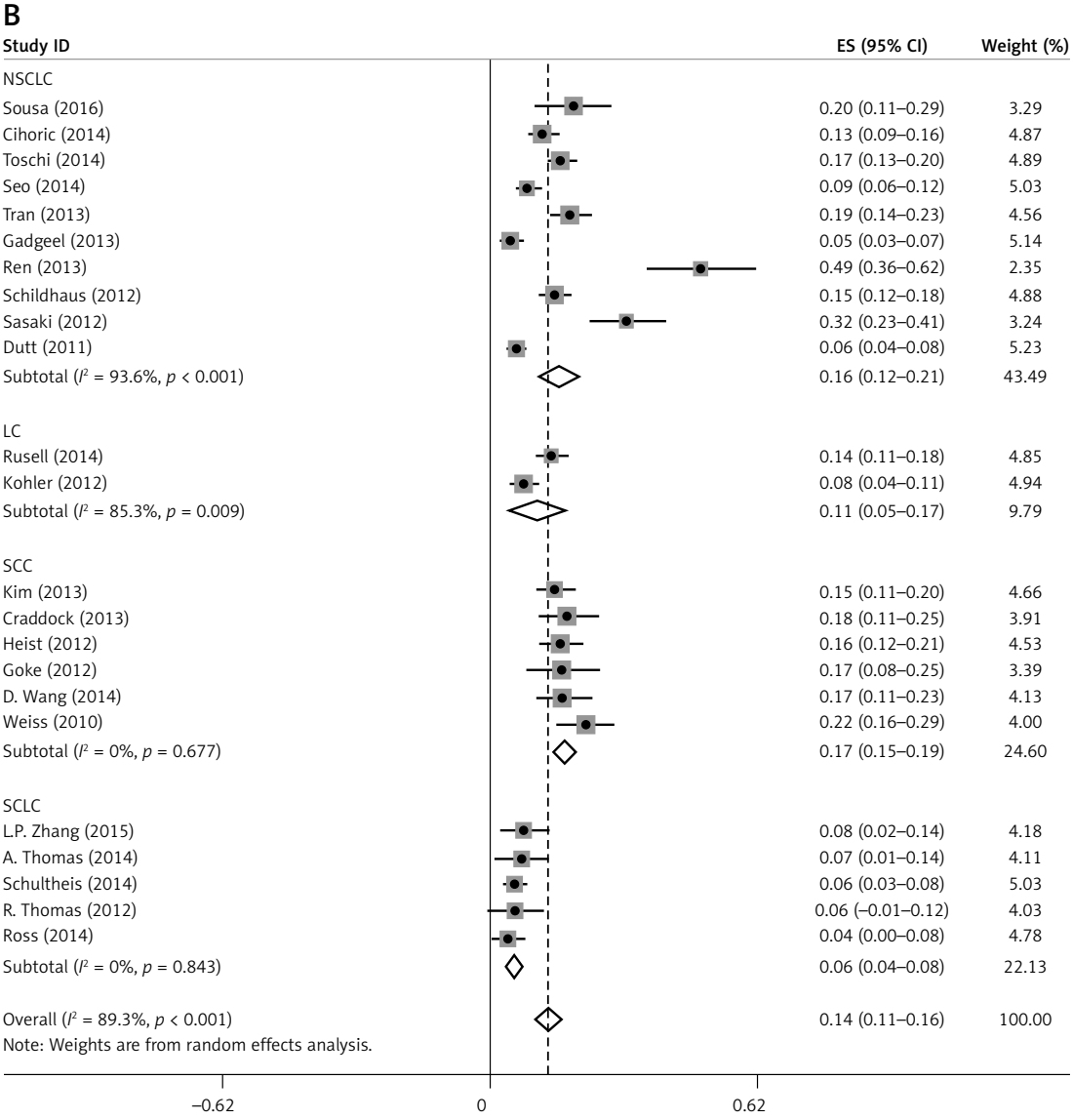

Figure 3. Cont. Same pathologic type (**B**)

14.7% in ADC, and 0% to 7.8% in SCLC. In addition, we found that *FGFR1* amplification occurs more frequently in SCC than in ADC and SCLC. In the subgroup analyses, no significant heterogeneity was detected for SCC, SCLC, and Australia. We also found that the prevalence of *FGFR1* amplification was higher in Asians than in non-Asians.

Wang *et al*. [22] reviewed a total of 12 studies involving 3178 lung SCC patients and suggested that *FGFR1* amplification occurs more frequently in male patients, SCC, and smokers and that *FGFR1* amplification is a risk factor for poor prognosis among Asian patients with SCC. In contrast, Jiang *et al*. [19] reviewed a total of 13 studies involving 1798 lung SCC patients and suggested that sex, stage, ethnicity, and test methods have no influence on *FGFR1* amplification. The conclusions were therefore inconsistent; however, these reviews involved only patients with SCC.

We sought to examine the association between *FGFR1* gene amplification, pathological characteristics, and ethnicity in lung cancer. This meta-analysis was performed with a total of 23 studies involving 5252 lung cancer patients and included data on Chinese patients. However, our systematic review with meta-analysis has some limitations that should be acknowledged. Firstly, the number of included studies was relatively small; thus more data with patients from different ethnicities are needed to conduct a thorough analysis. Secondly, it is possible that there is some degree of publication bias in this area of research.

To identify the source of heterogeneity, we performed subgroup analyses for lung cancer type and ethnicity and found that heterogeneity was

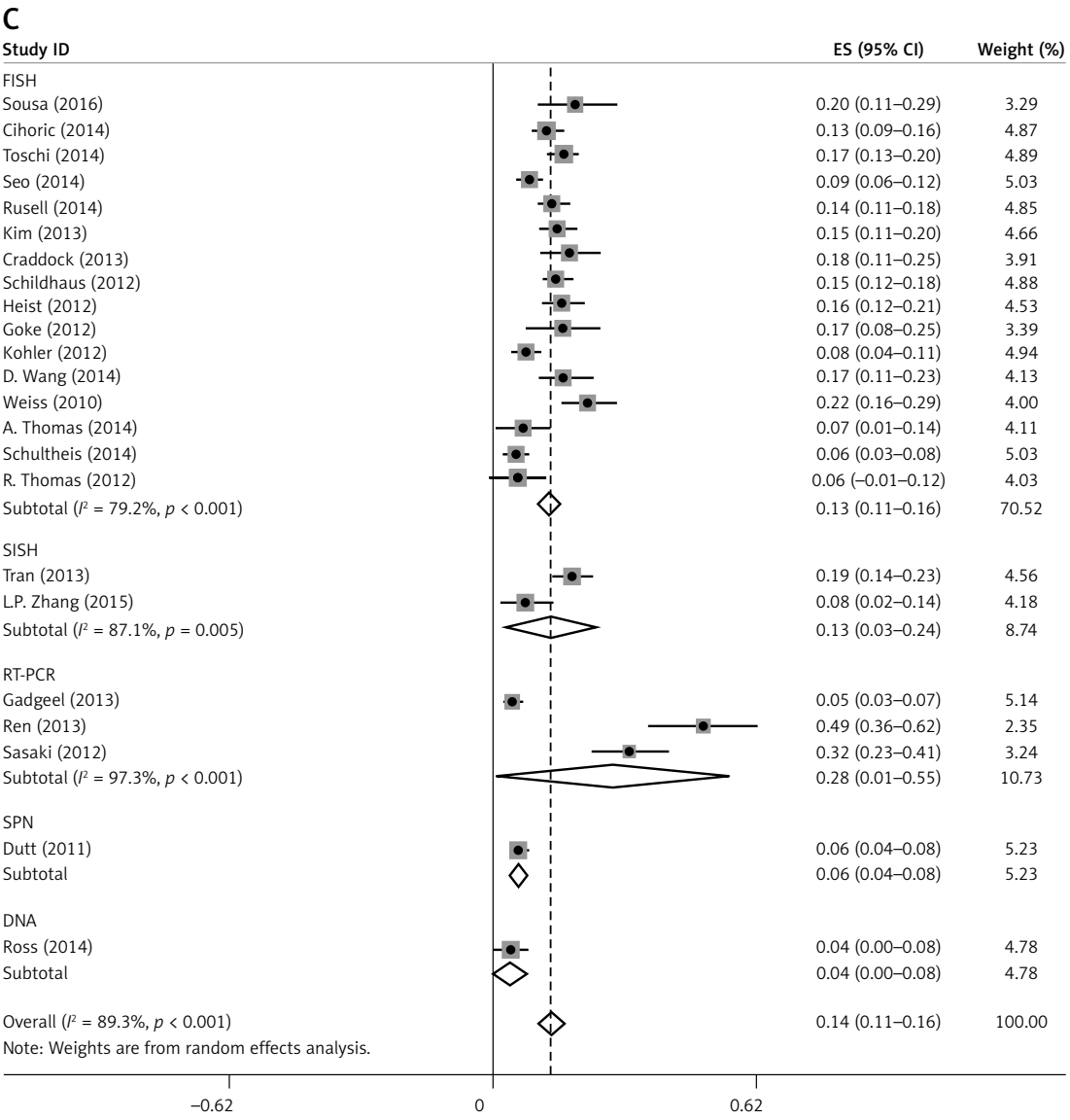

Figure 3. Cont. Same test method (**C**)

non-existent for studies using the same ethnicity and lung cancer type. Subgroup analysis for the *FGFR1* amplification rate evaluated using the same method showed that studies performed using FISH were approximately heterogeneous. However, after pooling the data from studies using the same definition of *FGFR1* amplification, there was no heterogeneity. To encourage the widespread evaluation of *FGFR1* amplification in clinical diagnostics and research laboratories, the definition and test methods should be standardized.

To determine the association between *FGFR1* gene amplification and pathological characteristics, as well as ethnicity in lung cancer, RRs and the corresponding 95% CIs were calculated for the rate of *FGFR1* amplification. The prevalence of *FGFR1* amplification was significantly higher in SCC than in ADC and SCLC, and it was higher in Asians than in non-Asians. More studies are needed to determine whether there is a significant difference between the rates of *FGFR1* amplification in different ethnicities.

For the treatment of NSCLC, the late provision of palliative care to patients limits improvements in the quality of life [45]. Furthermore, targeted therapy is also important. The current study is an updated comprehensive meta-analysis of *FGFR1* amplification in lung cancer and indicates that *FGFR1* amplification may become a potential new therapeutic target for specific patient populations and cancer subtypes. Because patients with SCC of the lung have limited options in terms of systemic therapies, they might benefit from targeted therapy. Currently, treatment with dovitinib, which inhibits *FGFR*, has demonstrated modest efficacy in patients with advanced SCC and *FGFR1* amplification [46]. However, in contrast to targeted therapy in ADC, the results of trials targeting

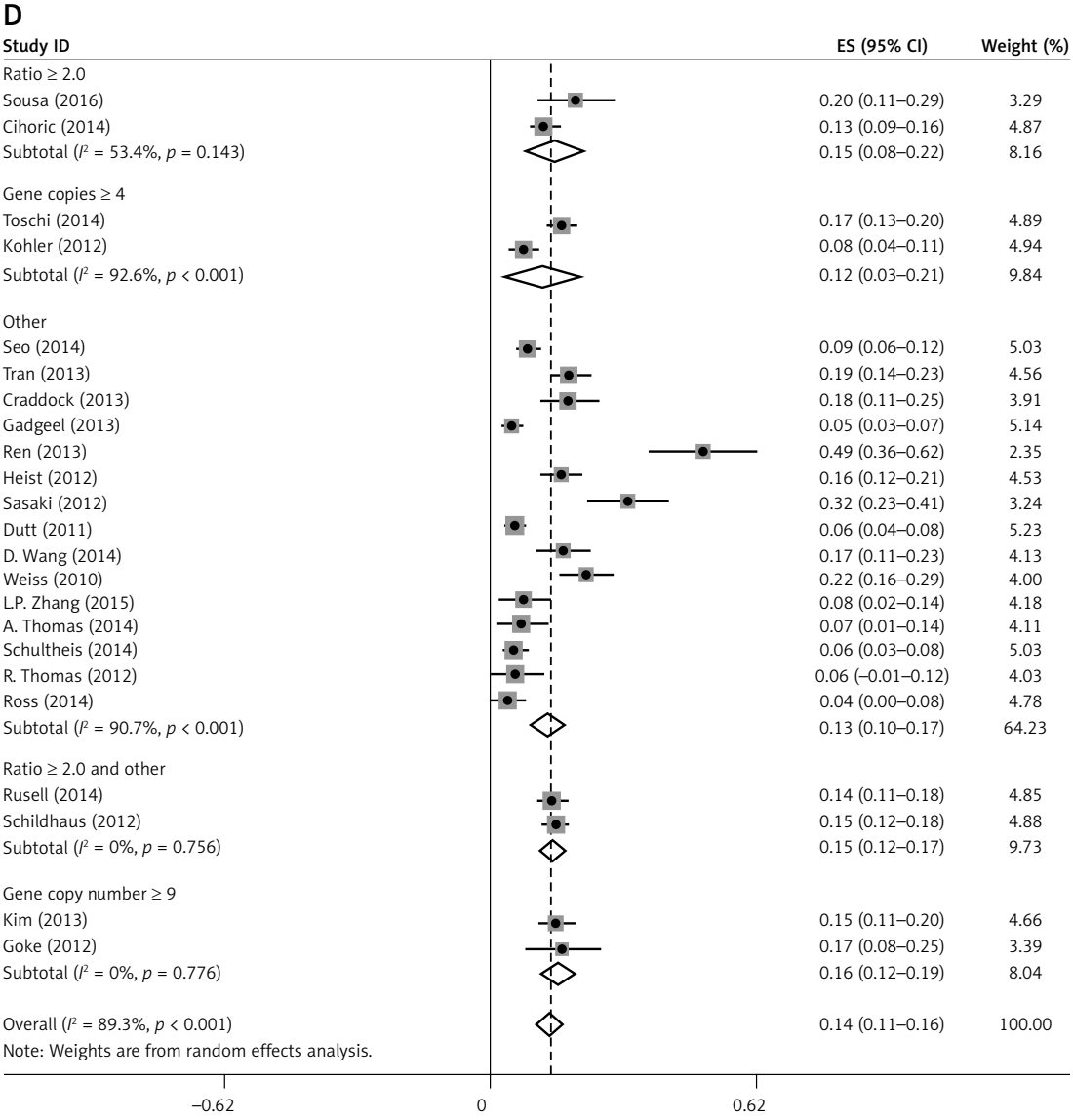

Figure 3. Cont. Same definition of *FGFR1* amplification (**D**)

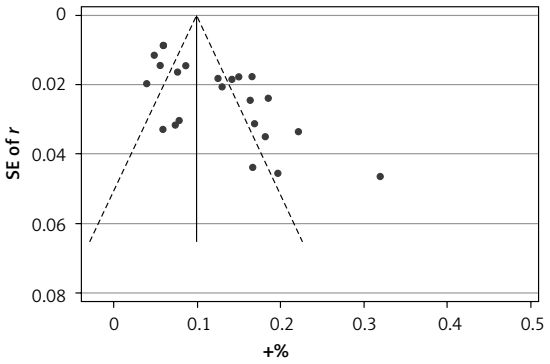

Figure 4. Begg's funnel plot with pseudo 95% confidence limits

FGFR1 in squamous cell lung cancers have generally been disappointing. Gene amplification or overexpression of *FGFR1* may not be a sufficiently robust predictor of the efficacy of *FGFR1* inhibitors [14]. Therefore, the value of *FGFR1* amplification in lung cancer treatment needs to be further investigated.

Conflict of interest

The authors declare no conflict of interest.

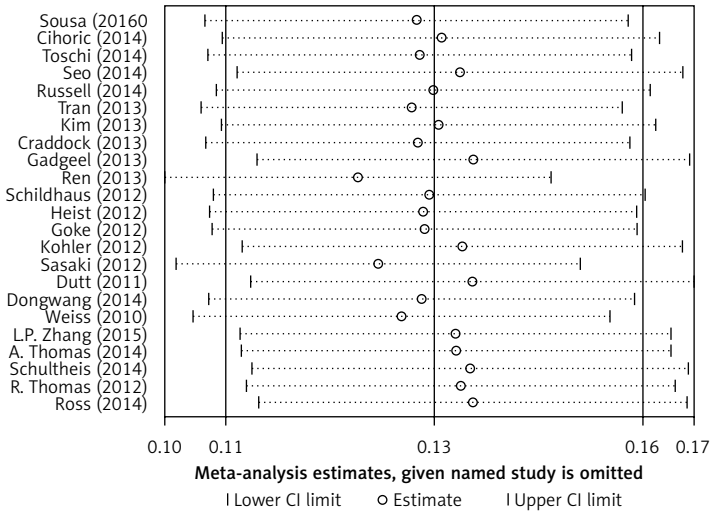

Figure 5. Sensitivity analyses

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics. CA Cancer J Clin 2014; 64: 9-29.
2. Minna JD, Roth JA, Gazdar AF. Focus on lung cancer. Cancer Cell 2002; 1: 49-52.
3. Wistuba II. Genetics of preneoplasia: lessons from lung cancer. Curr Mol Med 2007; 7: 3-14.
4. Sørensen M, Pijls-Johannesma M, Felip E; ESMO Guidelines Working Group. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 (Suppl 5): v120-5.
5. van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. Lancet 2011; 378: 1741-55.
6. Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 2006; 24: 2038-43.
7. Sharma D, Newman TG, Aronow WS. Lung cancer screening: history, current perspectives, and future directions. Arch Med Sci 2015; 11: 1033-43.
8. 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.
9. Dutt A, Ramos AH, Hammerman PS, et al. Inhibitor-sensitive FGFR1 amplification in human non-small cell lung cancer. PLoS One 2011; 6: 20351.
10. Sousa V, Reis D, Silva M, 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.
11. Toschi L, Finocchiaro G, Nguyen TT, 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.
12. Rooney C, Geh C, Williams V, et al. Characterization of FGFR1 locus in sqNSCLC reveals a broad and heterogeneous amplicon. PLoS One 2016; 11: e0149628.
13. Reck M, Kaiser R, Eschbach C, 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.
14. Lim SH, Sun JM, Choi YL, 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.
15. Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. Nat Rev Cancer 2010; 10: 116-29.
16. Wesche J, Haglund K, Haugsten EM. Fibroblast growth factors and their receptors in cancer. Biochem J 2011; 437: 199-213.
17. Wynes MW, Hinz TK, Gao D, et al. FGFR1 mRNA and protein expression, not gene copy number, predict FGFR TKI sensitivity across all lung cancer histologies. Clin Cancer Res 2014; 20: 3299-309.
18. Schultheis AM, Bos M, Schmitz K, et al. Fibroblast growth factor receptor 1 (FGFR1) amplification is a potential therapeutic target in small-cell lung cancer. Modern Pathol 2014; 27: 214-21.
19. 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.
20. Berger W, Setinek U, Mohr T, et al. Evidence for a role of FGF-2 and FGF receptors in the proliferation of non-small cell lung cancer cells. Int J Cancer 1999; 83: 415-23.
21. Göke F, Franzen A, Menon R, et al. Rationale for treatment of metastatic squamous cell carcinoma of the lung using FGFR inhibitors. Chest 2012; 142: 1020-6.
22. Wang Y, Gao W, Xu J, 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.
23. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
24. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-48.
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-88.
26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.

27. Schildhaus HU, Heukamp LC, Merkelbach-Bruse S, 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.
28. Kim HR, Kim DJ, Kang DR, 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.
29. 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.
30. Heist RS, Mino-Kenudson M, Sequist LV, et al. FGFR1 amplification in squamous cell carcinoma of the lung. J Thorac Oncol 2012; 7: 1775-80.
31. Cihoric N, Savic S, Schneider S, et al. Prognostic role of FGFR1 amplification in early-stage non-small cell lung cancer. Br J Cancer 2014; 110: 2914-22.
32. Seo AN, Jin Y, Lee HJ, et al. FGFR1 amplification is associated with poor prognosis and smoking in non-small-cell lung cancer. Virchows Arch 2014; 465: 547-58.
33. Russell PA, Yu Y, Young RJ, 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.
34. Weiss J, Sos ML, Seidel D, et al. Frequent and focal FGFR1 amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer. Sci Transl Med 2010; 2: 62ra93.
35. Kohler LH, Mireskandari M, Knosel T, et al. FGFR1 expression and gene copy numbers in human lung cancer. Virchows Arch 2012; 461: 49-57.
36. Thomas A, Lee JH, Abdullaev Z, et al. Characterization of fibroblast growth factor receptor 1 in small-cell lung cancer. J Thorac Oncol 2014; 9: 567-71.
37. Peifer M, Fernández-Cuesta L, Sos ML, et al. Integrative genome analysis identify key somatic driver mutations of small cell lung cancer. Nat Genet 2012; 44: 1104-10.
38. Wang D, Wang Z. The study of biological significance of fibroblast growth factor receptor 1 amplification in lung and esophageal squamous cell carcinoma. Shan Dong University Dissertation for Doctoral Degree. 2014; 1-132.
39. Gadgeel SM, Chen W, Cote ML, et al. Fibroblast growth factor receptor 1 amplification in non-small cell lung cancer by quantitative real-time PCR. PLoS One 2013; 8: e79820.
40. Sasaki H, Shitara M, Yokota K, et al. Increased FGFR1 copy number in lung squamous cell carcinomas. Mol Med Rep 2012; 5: 725-8.
41. Ren M, Hong M, Liu G, et al. Novel FGFR inhibitor ponatinib suppresses the growth of non-small cell lung cancer cells over-expressing FGFR1. Oncol Rep 2013; 29: 2181-90.
42. Tran TN, Selinger CI, Kohonen-Corish MR, 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.
43. Zhang L, Yu H, Badzio A, et al. Fibroblast growth factor receptor 1 and related ligands in small-cell lung cancer. J Thorac Oncol 2015; 10: 1083-90.
44. Ross JS, Wang K, Elkadi OR, et al. Next-generation sequencing reveals frequent consistent genomic alterations in small cell undifferentiated lung cancer. J Clin Pathol 2014; 67: 772-6.
45. Nowicki A, Farbicka P, Krajnik M. Late palliative care of patients with lung cancer may have a limited effect on quality of life – a pilot observational study. Arch Med Sci Civil Dis 2016; 1: e1-9.
46. Schoenborn CA, Adams PF, Peregoy JA. Health behaviors of adults. United States, 2008–2010. Vital Health Stat 2013; 257: 1-184.