Influence of Smoking Habits on the Efficacy of EGFR-TKI Therapy in Patients with Advanced NSCLC: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are considered as the first-line treatment for advanced EGFR mutation-positive non-small cell lung cancer (NSCLC). We aimed to analyze the efficacy of EGFR-TKIs treatment in patients with advanced NSCLC of different smoking habits.

METHODS: We conducted a search for meta-analyses and systematic reviews on the PubMed, MEDLINE, Embase, and the Cochrane Library to address this knowledge gap. Patients were divided into 2 groups: (1) experimental group: treated with EGFR-TKIs or EGFR-TKIs combined with chemotherapy, immunotherapy, antiangiogenesis, radiotherapy and (2) control group: treated with chemotherapy. Progressive-free survival (PFS) and total survival (OS) were adopted for evaluating the efficacy of EGFR-TKIs between experimental group and control group.

RESULTS: Eleven studies including 6760 patients were included in the meta-analysis. The results showed that smoking (including previous and current smoking) significantly reduces the PFS and OS in comparison to non-smoking group in the treatment of NSCLC with EGFR-TKIs. In addition, EGFR-TKIs combined with anti-vascular endothelial growth factor therapy can reduce the risk of disease progression in smokers.

CONCLUSIONS: Our study indicated that smoking significantly reduced the PFS and OS in comparison to non-smoking group in the treatment of NSCLC with EGFR-TKIs.

KEYWORDS: Non-small cell lung cancer, epidermal growth factor receptor-tyrosine kinase inhibitors, PFS, OS, smoking

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Introduction

Lung cancer is one of the most common cancers, and the leading cause of cancer-related death, with 80% to 85%, was diagnosed as non-small cell lung cancer (NSCLC) in China.[1] The most common mutations linked to epidermal growth factor receptor (*EGFR*) gene, with different incidence between Asians and Caucasians.[2] Therefore, epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are considered as the first-line treatment for advanced EGFR mutation-positive NSCLC.[3-5] Moreover, the EGFR was recognized as a highly polymorphic and mutation-prone gene; the variants −216G > T were confirmed to affect the efficacy and safety of the total survival (OS) and progressive-free survival (PFS) in gefitinib-treated or erlotinib-treated NSCLC patients.[6] In addition, accumulating evidence indicates that no smoking history is a predictor of a benefit prognosis of EGFR-TKI treatment. It may be that smokers have a lower *EGFR* gene mutation rate and an increased Kirsten Rat Sarcoma Oncogene Homolog (KRAS) gene mutation rate compared with non-smokers, resulting in this part of patients being insensitive to conventional EGFR-TKIs.[7,8] However, the impact of tobacco exposure on the clinical efficacy of EGFR-TKIs has not yet been determined.

In this study, we conducted a meta-analysis of published randomized controlled trials (RCTs) to analyze the efficacy of EGFR-TKIs treatment in patients with advanced NSCLC of different smoking habits.

Data and Methods

Search strategy

A systematic search of clinical study was conducted using PubMed, MEDLINE, Embase, and the Cochrane Library until October 31, 2022. The database search terms were as follows: "Carcinoma, Non-Small-Cell Lung," "Smoking," "EGFR-TKI," "epidermal growth factor receptor-tyrosine kinase inhibitor," "gefitinib," "erlotinib," "icotinib," "dacomitinib," "osimertinib," "afatinib," and "aflutinib." Inclusion criteria were as follows: (1) RCTs; (2) smokers or non-smokers of EGFR mutation for advanced NSCLC patients; (3) the experimental group was treated with EGFR-TKIs or EGFR-TKIs combined with

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chemotherapy, immunotherapy, antiangiogenesis, radiotherapy; the control group was treated with chemotherapy; and (4) progressive-free survival (PFS) and/or total survival (OS). Studies were excluded if (1) conference papers; (2) no necessary sample data; and (3) study reported insufficient details and other outcomes.

Risk of bias assessment

Rev Man 5.4 software was performed to evaluate the quality of the included RCTs. The quality of the included studies was evaluated based on whether random sequence generated in the study, allocation concealment, double blinding of the implementer and participant, blind methods for outcome evaluation, incomplete outcome data, bias in selective presentation, and the corresponding basis was explained. In addition, red indicates high risk, yellow indicates unknown risk, and green indicates low risk.

Statistical analysis

Rev Man 5.4 software was used for statistical analysis, and I^2 was used to statistically evaluate the heterogeneity. If $I^2 > 50\%$, a random-effects model was used for the analysis, or the data were analyzed on fixed-effects model to calculate the combined PFS and OS risks, obtain a 95% confidence interval (95% CI) of the effect amount, and test the level $\alpha = 0.05$.

Results

Literature search and study selection

Through the initial search, a total of 1267 records were retrieved. After examining the titles and abstracts, 57 studies were selected for full-text scrutiny. In all, 11 studies were included in the meta-analysis (Figure 1).

A total of 6760 patients were included in this study, and the basic characteristics of the included study are shown in Table 1. According to the different medication conditions of patients, the literature was divided into 3 groups for analysis: EGFR-TKIs and placebo group, EGFR-TKIs and chemotherapy group, and EGFR-TKIs combined with vascular endothelial growth factor (VEGF) and EGFR-TKIs monotherapy.

Effect of epidermal growth factor receptor-tyrosine kinase inhibitors on progressive-free survival in patients with advanced non-small cell lung cancer

Three studies reported the effects of EGFR-TKIs and placebo on PFS in patients with advanced NSCLC. Heterogeneity testing indicates heterogeneity among studies ($I^2 = 72\%$), so a random-effect model was used. The results suggested that EGFR-TKIs can shorten the median (similarly hereinafter) PFS in patients with advanced NSCLC, with a statistically significant difference (odds ratio = [OR] [95% CI] = 0.80 [0.65-0.99], $Z = 2.07$, $P = .04$) compared with the placebo group. Subgroup analysis based on different smoking habits suggested that EGFR-TKIs could shorten the median PFS of patients with advanced NSCLC who had never smoked, with a statistically significant difference (OR [95% CI] = 0.70 [0.50-0.98], $Z = 2.07$, $P = .04$). However, patients with advanced NSCLC who smoked, there was no significant difference in the efficacy between the 2 treatments ($P = .36$) (Figure 2A).

Three studies indicated the effects of EGFR-TKIs and chemotherapy on PFS in patients with advanced NSCLC. Heterogeneity test indicated that there was no heterogeneity among the studies ($I^2 = 0\%$), so a fixed-effect model was used for analysis. The results suggested that there was no significant difference between EGFR-TKIs and chemotherapy in reducing the median PFS in patients with advanced NSCLC ($P = .15$). According to subgroup analysis based on different smoking habits, both EGFR-TKIs and chemotherapy can reduce the median PFS in patients with advanced NSCLC who have never smoked (OR [95% CI] = 0.61 [0.44-0.84], $Z = 3.00$, $P = .003$) and smoked (OR [95% CI] = 0.54 [0.27-1.08], $Z = 1.74$, $P = .08$), with statistically significant differences (Figure 2B).

Two studies showed the effects of EGFR-TKIs combined with anti-VEGF therapy and EGFR-TKIs monotherapy on PFS in patients with advanced NSCLC. Heterogeneity testing indicates heterogeneity among studies ($I^2 = 65\%$), so a random-effect model was used. The results suggested that there was no significant difference between EGFR-TKIs combined with anti-VEGF therapy and EGFR-TKIs monotherapy in reducing the median PFS in patients with advanced NSCLC ($P = .14$). Subgroup analysis based on different smoking habits showed that EGFR-TKIs combined with anti-VEGF therapy could significantly reduce the median PFS in patients with advanced NSCLC who smoked, with a statistically significant difference (OR [95% CI] = 0.60 [0.40-0.89], $Z = 2.52$, $P = .01$), whereas there was no significant impact on the median PFS in patients who had never smoked ($P = .69$) (Figure 2C).

Effect of epidermal growth factor receptor-tyrosine kinase inhibitor on total survival in patients with advanced non-small cell lung cancer

Five studies showed the effects of EGFR-TKIs and placebo on PFS in patients with advanced NSCLC. Heterogeneity test indicated heterogeneity among studies ($I^2 = 64\%$), so a random-effect model was used for analysis. The results suggested that EGFR-TKI can reduce the median OS in patients with advanced NSCLC, with a statistically significant difference (OR [95% CI] = 0.81 [0.70-0.95], $Z = 2.66$, $P = .008$) compared with the placebo group. Subgroup analysis based on different smoking habits suggested that EGFR-TKIs could reduce the median OS in patients with advanced NSCLC who had never smoked, with a statistically significant difference (OR [95% CI] = 0.61 [0.49-0.77], $Z = 4.30$, $P < .001$). However, in patients with advanced NSCLC who smoked, there was no significant difference in the efficacy of the 2 treatments ($P = .20$) (Figure 3A).

Three studies showed the effects of EGFR-TKIs and chemotherapy on PFS in patients with advanced NSCLC.

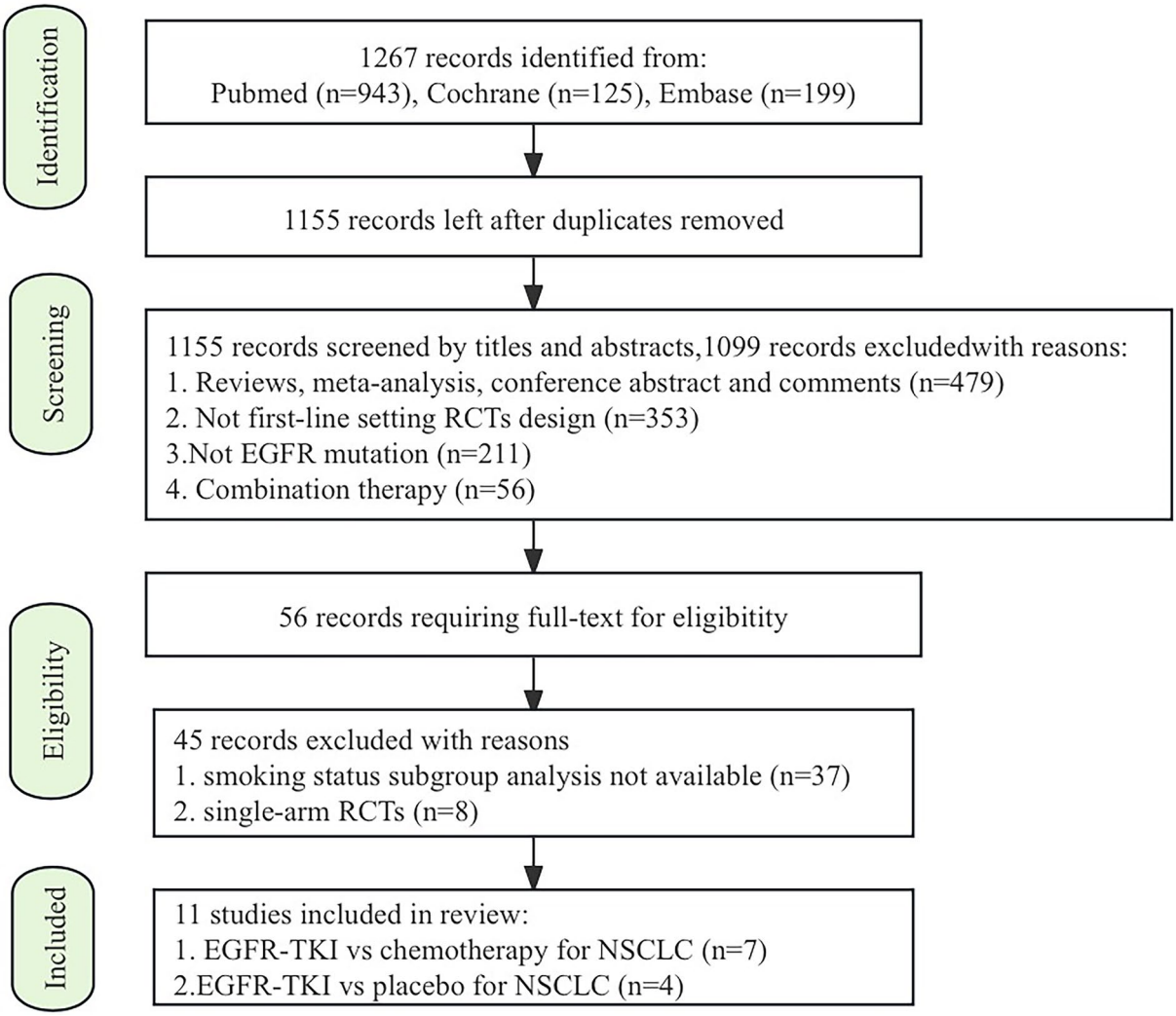

Figure 1. Literature review PRISMA flowchart.
EGFR indicates epidermal growth factor receptor; NSCLC, non-small cell lung cancer; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor.

Heterogeneity test indicated that there was no heterogeneity among the studies ($I^2 = 0\%$), so a fixed-effect model was used for analysis. The results suggested that there was no significant difference between EGFR-TKIs and chemotherapy in reducing the median OS in patients with advanced NSCLC ($P = .15$). A subgroup analysis based on different smoking habits showed that there was no significant difference in the impact of the 2 treatments on the median PFS between smoking and non-smoking patients with advanced NSCLC ($P = .11$ and $P = .98$) (Figure 3B). Only 1 study showed the impact of EGFR-TKIs combined with anti-VEGF therapy and EGFR-TKIs monotherapy on OS in patients with advanced NSCLC, and no analysis was conducted.

Discussion

This study explored the differences in the efficacy of EGFR-TKIs in NSCLC patients with different smoking habits. The results suggested that smoking (including previous and current smoking) significantly reduces the PFS and OS in comparison to non-smoking group in the treatment of NSCLC with EGFR-TKIs. In addition, EGFR-TKIs combine with anti-VEGF therapy can reduce the risk of disease progression in smokers, which suggested that this treatment mode has greater clinical benefits for smokers.

All data in this study were obtained in the II/III clinical trials. The methods used in testing EGFR variants for NSCLC patients were mostly polymerase chain reaction (PCR) and sequencing, which have been proved to be sensitive and specific for EGFR variants detection and indicated that our study was reliable.[18] The impact of EGFR-TKIs alone or EGFR-TKIs combined with other treatments in 6760 patients for advanced NSCLC with different smoking habits was evaluated. Progressive-free survival was evaluated in 4301 patients, and OS was evaluated in 6229 patients, with reliable results. According to the comparative grouping of patients according to different treatment methods. (1) In the 5 studies comparing the efficacy of EGFR-TKI with placebo, the conclusion that the PFS and OS of the non-smoker group after EGFR-TKI treatment are significantly better than those in the placebo group. In the smoker group, 2 studies suggest that the PFS and OS of

Table 1. The main summary of included studies.

STUDY	INTERVENTION	SAMPLE SIZE	ONLY ASIAN	AGE		MEN	ECOG PERFORMANCE STATUS		III-IV NSCLC	SMOKE STATUS		COMMON ADVERSE EVENTS	EGFR ANALYSIS METHODS
				MEAN	SD		0-1	⩾2		EVER-SMOKER	NON-SMOKER		
Mok et al[3]	Gefitinib vs carboplatin/ paclitaxel	1217	Yes	57.00	9.91	252	1091	126	1175	77	1140	Rash or acne, diarrhea, dry skin	Amplification refractory mutation system
Zhou et al[5]	Erlotinib vs gemcitabine/ carboplatin	152	Yes	57.94	7.14	63	144	10	16	138	109	Rash, increased ALT, diarrhea	PCR-based direct sequencing
Ciuleanu) et al[9]	Erlotinib vs docetaxel/ pemetrexed	424	No	59.00	8.52	321	339	85	424	350	74	Rash, diarrhea, nausea	DNA sequencing
Shi et al[10]	Icotinib vs cisplatin/ pemetrexed	296	Yes	56.00	7.06	85	271	14	285	61	224	Increased AST, increased ALT, leukopenia	Amplification refractory mutation system
Saito et al[11]	Erlotinib vs bevacizumab	224	Yes	67.5	1.98	80	222	2	182	95	129	Rash, proteinuria, increased aminotransferase	Not mentioned
Soo et al[12]	Osimertinib vs bevacizumab	155	No	67.01	7.83	59	146	9	154	62	93	Diarrhea, rash acneiform, fatigue	ctDNA analysis
Thatcher et al[13]	Gefitinib vs placebo	1692	No	61.67	10.02	1139	1126	561	1533	1316	375	Rash, diarrhea, nausea	Not mentioned
Chang et al[14]	Gefitinib vs placebo	343	Yes	61.00	9.00	204	247	30	315	141	201	Rash, diarrhea, dry skin	Not mentioned
Cappuzzo et al[15]	Erlotinib vs placebo	1060	No	60.00	8.41	659	889	0	889	152	737	Rash, diarrhea, anorexia	Amplified PCR
Lee et al[16]	Erlotinib vs placebo	670	No	77.00	55.95	409	106	564	670	453	37	Fatigue, diarrhea, anorexia	Sequenom OncoCarta panel PCR
Lee et al[17]	Erlotinib vs placebo	527	No	77.09	6.66	315	89	438	527	498	29	Rash	Sequenom OncoCarta panel PCR

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; SD, standard deviation.

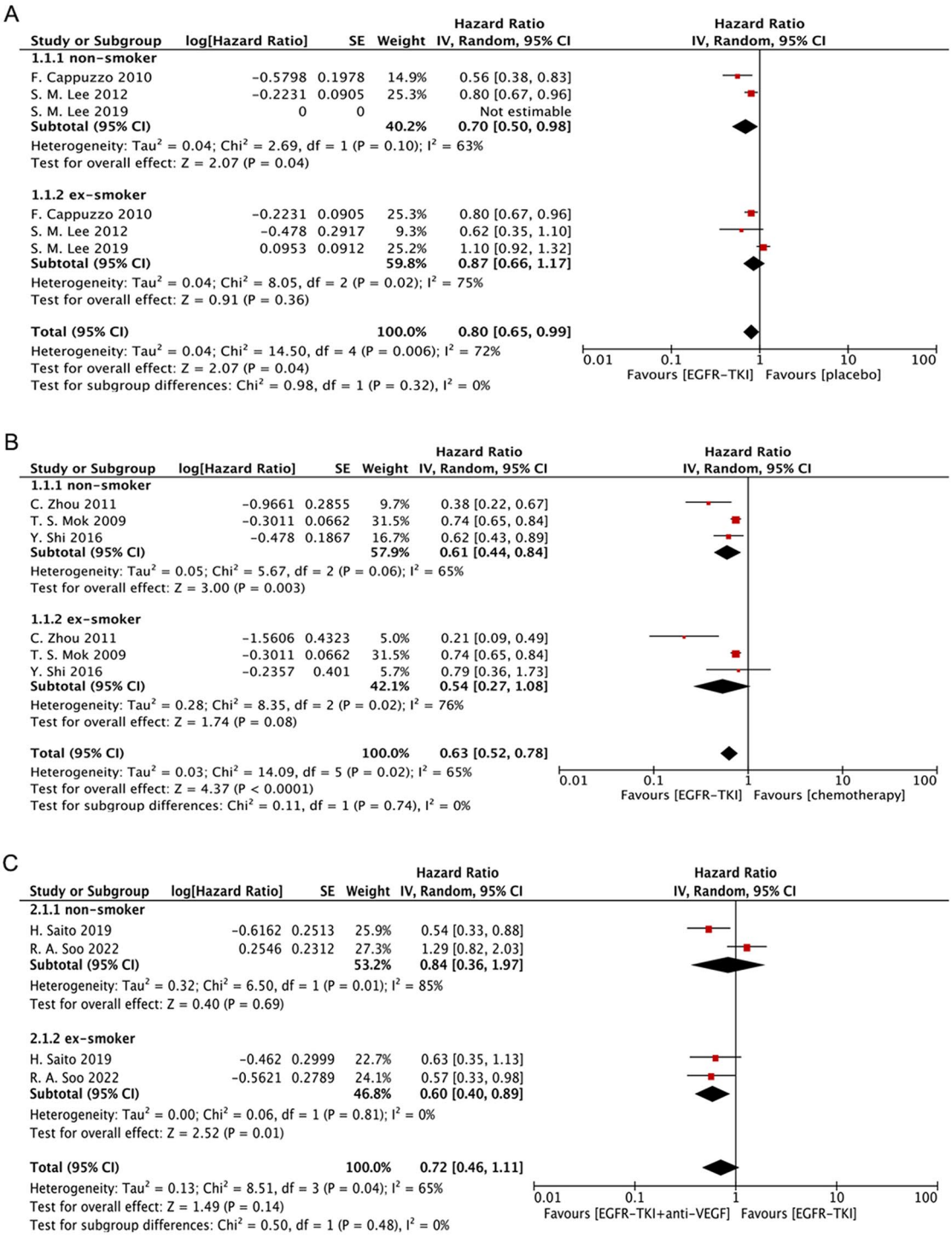

Figure 2. Effects of EGFR-TKIs and placebo on improving PFS in patients with advanced NSCLC. (A) Comparison of EGFR-TKIs with placebo; (B) comparison between EGFR-TKIs and chemotherapy group; and (C) comparison of EGFR-TKIs combined with anti-VEGF therapy and EGFR-TKIs monotherapy.

CI indicates confidence interval; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progressive-free survival; SE, standard error; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

patients in the EGFR-TKI treatment have a trend of being better than those in the placebo group, whereas the study by Lee 2019 was the opposite.[15-17] (2) In the 4 studies comparing the efficacy of EGFR-TKIs with chemotherapy, there was no significant difference in improving OS between smokers and non-smokers NSCLC patients treated with EGFR-TKIs compared with chemotherapy. However, after treatment with EGFR-TKIs, PFS in the non-smoker group was significantly better than the chemotherapy group. Two studies suggested that PFS in the smoking group was better than that in the chemotherapy group; 1 study suggested that there was no significant difference between EGFR-TKIs and chemotherapy in improving PFS in

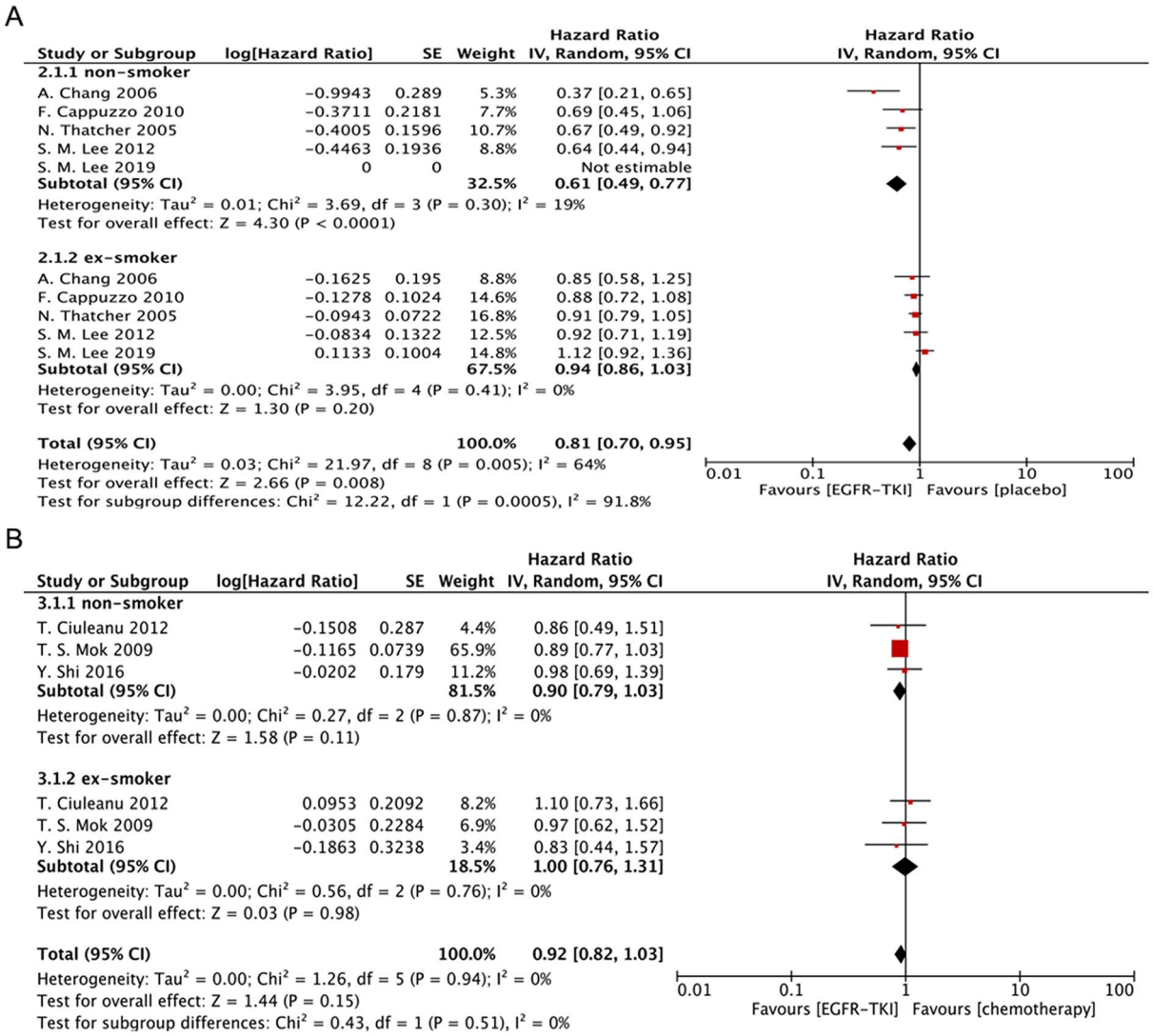

Figure 3. Effect of EGFR-TKIs on improving OS in patients with advanced NSCLC. (A) Comparison of EGFR-TKIs with placebo; (B) comparison between EGFR-TKIs and chemotherapy group.
CI indicates confidence interval; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; OS, total survival; SE, standard error; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

the smoker group after treatment.[3,5,10] (3) In 2 studies comparing the efficacy of EGFR-TKIs combined with VEGF and EGFR-TKIs monotherapy, the effect on OS after treatment was not provided in the study. Previous studies have suggested that EGFR-TKIs combined with VEGF have a tendency to improve PFS in patients with NSCLC who smoke compared with EGFR-TKI monotherapy. In the non-smoker group, Saito et al[11] suggested that EGFR-TKIs combined with VEGF significantly improved PFS in patients with NSCLC, whereas Soo et al[12] suggested that EGFR-TKIs monotherapy significantly improved PFS in patients with NSCLC.

There are still inconsistencies in the efficacy of EGFR-TKIs in smoker and non-smoker NSCLC. In this study, among the literature with inconsistent conclusions, the sample size of Lee et al is 527 cases, the sample size of Shi et al is 155 cases, the sample size of Saito et al is 224 cases, and the sample size of Soo et al is 155 cases. All of these may have inconsistent conclusions due to small sample sizes. In the future, the conclusions of this meta-analysis should be verified in larger RCTs.

We explored the mechanisms that may lead to this conclusion and concluded that (1) smoking is considered to be a major risk factor for lung cancer, especially for adenocarcinoma patients younger than 64 years.[19] Gene sequencing of patients with different smoking status indicated that with increased tobacco exposure, EGFR, reactive oxygen species (ROS), and anaplastic lymphoma kinase (ALK) mutations were significantly decreased, whereas KRAS mutations significantly increased. It is worth noting that the KRAS mutation level is relatively stable among patients with smoking levels ranging from 1 to 15 packets per year to 60+ years old.

Smoking promotes the progression of cancer cells and reduces the sensitivity of NSCLC cells to EGFR-TKIs through the liver kinase B1/AMP-activated protein kinase (LKB1/AMPK) pathway, promoting Src (Y527F/K295R), epithelial-mesenchymal transition (EMT), and ROS, as well as abnormal EGF receptor activation.[20-24] Previous research works also suggest that nicotine in tobacco can mediate resistance to EGFR-TKIs in NSCLC patients with EGFR mutations.[25] Therefore, we believe that smoking may affect the efficacy of EGFR-TKI by altering the expression of driving genes in NSCLC patients and mediating EGFR-TKIs resistance. (2) Tobacco exposure is more likely to induce TP53 mutations in lung cancer patients, and NSCLC patients with EGFR and TP53 mutations tend to have a poor response to EGFR-TKIs.[26,27] However, some studies have suggested that TP53 mutations may promote the upregulation of vascular endothelial growth factor receptor (VEGFR) expression, thereby enhancing the efficacy of VEGF and VEGFR inhibitors.[28-30] At the same time, many studies suggest that different subtypes of TP53 mutations may have inconsistent effects on the efficacy of EGFR-TKIs. In the future, it is necessary to verify the efficacy of EGFR-TKI combined with VEGF in the treatment of different types of TP53 mutations in patients.

The most common serious adverse events in both Asians and Caucasians after EGFR-TKIs treatment were rash and diarrhea, which is consistent with the previous reports.[31] Impaired liver function with increased aspartate aminotransferase (AST) and alanine transaminase (ALT) was also found particular in Asians, whereas anorexia was only found in Caucasians, suggested that adverse events of TKIs were different between the 2 populations. The EGFR variants in different populations may explain the difference.[31]

This study aimed to explore the efficacy of EGFR-TKIs in patients with different smoking habits and provide evidences of effective treatments for NSCLC patients who smoke. However, this study inevitably still has some limitations: (1) Even though the distribution of EGFR is different in Caucasians compared with Asians, studies focus on both Caucasians and Asians were still included. There will be not enough data if we separate these 2 populations, the conclusion should be updated in the future when we have enough research works. (2) The smoking patients included in this study are current smokers or former smokers, the data of these 2 populations have largely heterogeneous, and there may be differences in treatment effectiveness. In addition, we should also pain attention to patients with passive smoking. However, it is impossible to clearly distinguish these patients from this study, and future studies should be conducted on these 2 groups of patients. (3) Tumor treatment drugs are changing rapidly, but most of the clinical trials currently included are mainly focused on the efficacy comparison of first-generation and second-generation EGFR-TKIs. There are fewer RCTs of third-generation EGFR-TKIs, and the number of included studies is also small, which may affect the accuracy and reliability of conclusions. We will continue to pay attention to this topic and update the literature and conclusions in a timely manner. (4) This study only summarizes the results of multiple RCTs and does not clarify the causal relationship between smoking history and the efficacy of EGFR-TKIs nor does it determines the combination of EGFR-TKIs. The mechanism by which VEGF treatment can improve the efficacy of smoking NSCLC patients requires further clinical and basic trials to explore the correlation between smoking and EGFR-TKIs treatment.

Conclusions

This study systematically reviewed relevant literature through meta-analysis and found that smoking significantly reduces the PFS and OS in comparison to non-smoking patients in the treatment of NSCLC with EGFR-TKIs. In addition, EGFR-TKIs combined with anti-VEGF therapy can reduce the risk of disease progression in smokers. This study can provide a basis for selecting appropriate treatment strategies for such patients in clinical practice, and further confirmation in RCTs is needed in the future.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for publication

Not applicable.

Author Contributions

ZM, ZZ, YL, and SW made a substantial contribution to the design of the work. MY, HH, XH, and WG contributed to the acquisition of data. ZM and MY contributed to the analysis of data. ZM and MY drafted the article. ZZ, YL, and SW revised it critically for important intellectual content. All the authors approved the version to be published.

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approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Research data sharing

Data sharing not applicable to this article as no data sets were generated or analyzed during this study.

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SUPPLEMENTAL MATERIAL

Supplemental material for this article is available online.

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