ORIGINAL ARTICLE

Prognostic value of pretreatment smoking status for small cell lung cancer: A meta-analysis

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Abstract

Background: Although tobacco exposure remains the most important risk factor of tumorigenesis of small cell lung cancer (SCLC), its prognostic value has failed to reach a consensus until now. Accordingly, we conducted a meta-analysis to investigate the prognostic value of pretreatment smoking status (smokers vs. never-smokers) in SCLC.
Methods: The four databases PubMed, Medline, Embase, and Cochrane library were searched to identify the relevant literature from the inception dates to 24 June 2020. The primary outcome was overall survival (OS), and the secondary endpoint was progression-free survival (PFS). The hazard ratios (HRs) with 95% confidence intervals (CIs) were extracted to assess the relationship between pretreatment smoking status and patient survival. Sensitivity analysis was performed to assess the stability of the pooled results. Begg's funnel plot and Egger's test were applied to detect the publication bias. All statistical analyses were performed using RevMan V.5.3 and STATA version 15.0 software.
Results: A total of 27 studies involving 12 047 patients with SCLC (9137 smokers and 2910 never-smokers) were included in this meta-analysis. The results showed that smoking history was closely related to poorer survival outcome (OS: HR = 1.17, 95% CI: 1.12–1.23, $P < 0.00001$; $I^2 = 0\%$; PFS: HR = 1.20, 95% CI: 1.06–1.35, $P = 0.004$; $I^2 = 0\%$).
Conclusions: Smoking history should be considered as an independent poor prognostic factor for patients with SCLC. More large-scale prospective studies are warranted to testify the prognostic value of pretreatment smoking status.

Introduction

According to GLOBOCAN 2018, lung cancer ranks as the leading cause of death worldwide.[1] Small cell lung cancer (SCLC) is one of the most aggressive and lethal type which accounts for approximately 15% of patients diagnosed with lung cancer.[2] In the era of precision medicine, the ability to precisely evaluate prognosis is of significant assistance in order to improve survival outcome of patients with SCLC. For decades, numerous retrospective studies and some meta-analyses have been conducted to investigate poor prognostic factors of SCLC, factors like distant metastases (extensive stage)[3] and tumor biomarkers (eg, neuron-specific enolase [NSE])[4] have all been proposed as poor prognostic indicators in SCLC patients.

The tumorigenesis of lung cancer, especially SCLC, is strongly linked to tobacco exposure. Based on large-population-based epidemiological data, 97.5% of 4782 patients with SCLC were found to be current or ever smokers.[5] Furthermore, smoking history is a popular item to be extracted in studies for prognostic analysis of SCLC, but results are contradictory and no consensus has been reached until now. Herein, we conducted a systemic review and meta-analysis to evaluate the prognostic value of pretreatment smoking status for patients with SCLC.

Methods

Search strategy

The four databases PubMed, Medline, Embase, and Cochrane library were searched to identify the relevant

literature from the inception dates to 24 June 2020 based on the combination of two search words: "small cell lung cancer NOT non-small cell lung cancer" and "prognosis OR prognostic factors". The range was then greatly narrowed by screening studies under the inclusion criteria of containing smoking status and its association with overall survival (OS) and/or progression-free survival (PFS). Furthermore, the reference lists of every relevant article were checked with an expectation that additional articles would be highlighted for inclusion. The protocol of this meta-analysis was open on PROSPERO, the International Prospective Register of Systematic Reviews (CRD42020194028).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) studies that enrolled patients who were histologically or cytologically confirmed to have SCLC (both limited-stage or extensive-stage were allowed); (ii) contained pretreatment smoking status of all patients; (iii) contained evaluation of the association between with smoking status and OS and/or PFS, the hazard ratio (HR) and 95% confidence interval (95% CI) or P-value were available; and (iv) the language of the document was English.

The exclusion criteria were as follows: (i) reviews, meta-analyses, case reports, and conference reports; (ii) duplications; (iii) studies without analysis of prognostic value of pretreatment smoking status SCLC; and (iv) studies where necessary effect data was unable to be obtained from the text.

Data extraction and quality assessment

Data including first author, publication year, number of patients, numbers of smokers and non-smokers, country, ethnicity, median age and range, percentage of limited-disease and extensive-disease SCLC, percentage of male and female patients, treatments (chemotherapy, radiotherapy, surgery), types of survival analysis (univariate or multivariant) and outcome (in particular, HRs and their 95% CIs for OS and PFS,
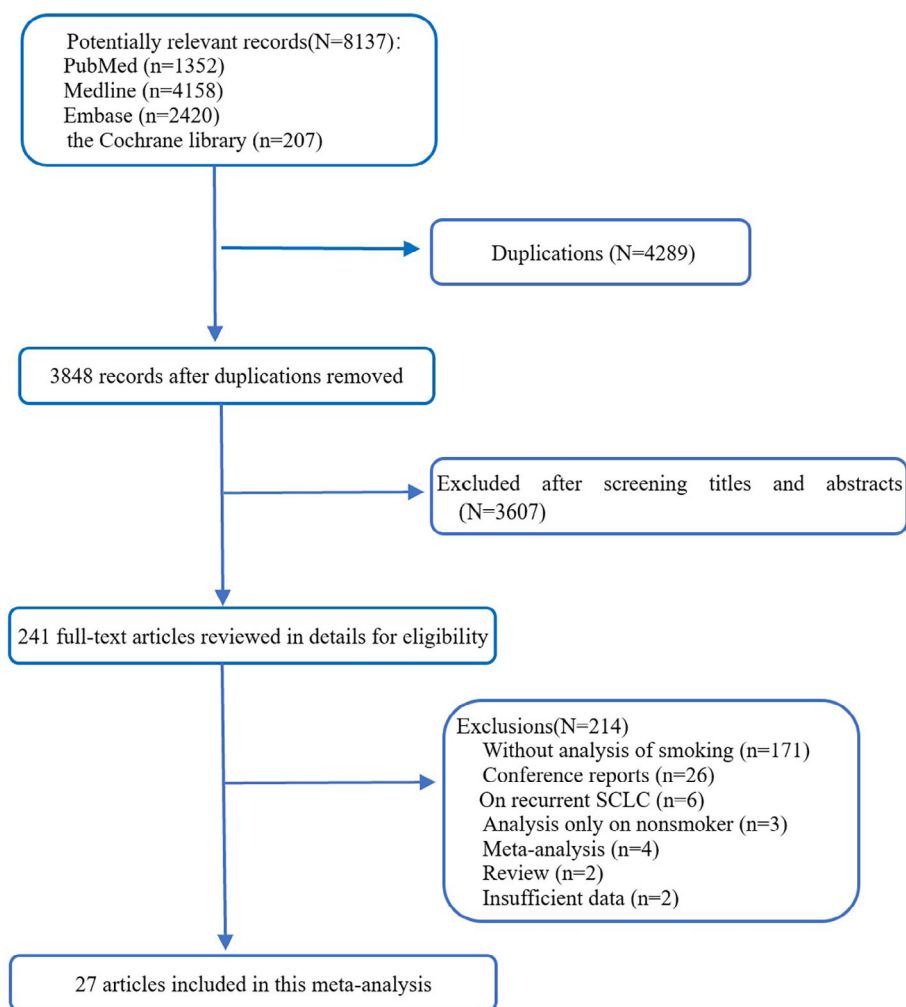

Figure 1 Flow diagram of included studies.

Table 1 Characteristics of all included studies in the meta-analysis

First author	Year	Study design	Country	E	N	Smokers (%)	LD-SCLC (%)	Male (%)	Age (mean, range)	Treatment	Outcome	Analysis type	NOS
Zhou et al.[6]	2020	R	China	A	219	81.74%	0%	87.90%	60.5	C, R	O	U	7
Yilmaz et al.[7]	2020	R	Japan	A	216	56.94%	27.30%	85.20%	NA	C, R	O	U	7
Xu et al.[8]	2020	R	China	A	136	61.03%	47.80%	76.50%	61.6	C, R	O	U	6
Wu et al.[9]	2020	R	China	A	146	73.97%	40.40%	78.10%	57 (19–74)	C, R	O	U	7
Wang et al.[10]	2020	R	China	A	653	62.48%	58.50%	64.60%	NA	C, R	O	M	8
Wang et al.[11]	2019	R	China	A	228	79.39%	50%	69.70%	58 (39–71)	C, R	O	U	7
Li et al.[12]	2019	R	China	A	122	54.92%	100%	68.90%	58	C, R	O, P	U	7
Liu et al.[13]	2018	R	China	A	303	77.23%	37.30%	90.10%	63	C, R	O, P	M	9
Jin et al.[14]	2018	R	China	A	1156	57.96%	61.90%	64.40%	57 (23–85)	C, R	O	M	8
Guo et al.[15]	2018	R	China	A	128	61.72%	52%	55.50%	62 (30–83)	C, R	O	U	7
Fan et al.[16]	2018	R	China	A	120	72.50%	39.20%	71.70%	63.2	C, R	O	U	7
Hong et al.[17]	2018	R	China	A	936	66.03%	59.10%	69.30%	NA	C, R	O, P	M	8
Pan et al.[18]	2017	R	China	A	275	70.18%	54%	87%	62 (33–86)	C, R	O	M	8
Jiang et al.[19]	2017	R	China	A	107	87.85%	39.30%	78.50%	63	C, R	O	U	7
Deng et al.[20]	2017	R	China	A	320	67.19%	38.10%	74.70%	58 (24–81)	C, R	O, P	U	7
Chen et al.[21]	2016	R	China	A	393	71.76%	39.90%	81.90%	57	C, R	O, P	U	7
Cai et al.[22]	2016	R	China	A	144	68.06%	40.50%	88.50%	60 (25–80)	C, R	O	M	8
Xie et al.[23]	2015	R	China	A	383	73.11%	100%	47.50%	66.7	C, R	O	M	7
Sun et al.[24]	2015	R	China	A	391	87.21%	46.30%	85.40%	65	C, R	O	M	8
Liu et al.[25]	2015	R	China	A	247	67.21%	52.20%	81.40%	70.7 (65–83)	C, R	O	U	7
Hong et al.[26]	2015	R	China	A	919	61.70%	60.10%	69.10%	NA	C, R	O	M	7
Hong et al.[27]	2015	R	China	A	724	82.87%	55.40%	86.60%	59 (19–86)	C, R	O	M	7
Liu et al.[28]	2013	R	China	A	485	67.84%	44.50%	74.00%	NA	C, R	O	U	7
Wu et al.[29]	2012	R	China	A	200	77.50%	0%	62.40%	NA	C, R	O	U	6
Chen et al.[30]	2010	R	China	A	264	97.35%	100%	N	65	C, R	O	M	8
Arinc et al.[31]	2010	R	Turkey	A	200	92.00%	55.80%	91.40%	57 (35–78)	C, R	O	U	7
Ou et al.[5]	2009	R	multiple countries	C, A	2632	96.47%	0%	53.40%	68	C, R, S	O	M	8

A, Asian; C, Caucasian; E, ethnicity; M, multivariate analysis; NA, not available; NOS, Newcastle-Ottawa Scale; O, overall survival; P, progression-free survival.; R, retrospective study; U, univariate analysis. [Correction added on 13 October 2020, after first online publication: in Arinc et al. 2010, Ethnicity has been updated from 'C' to 'A'. In Ou et al. 2009, Country and Ethnicity have been updated from 'China' to 'multiple countries' and 'C' to 'C, A'.]

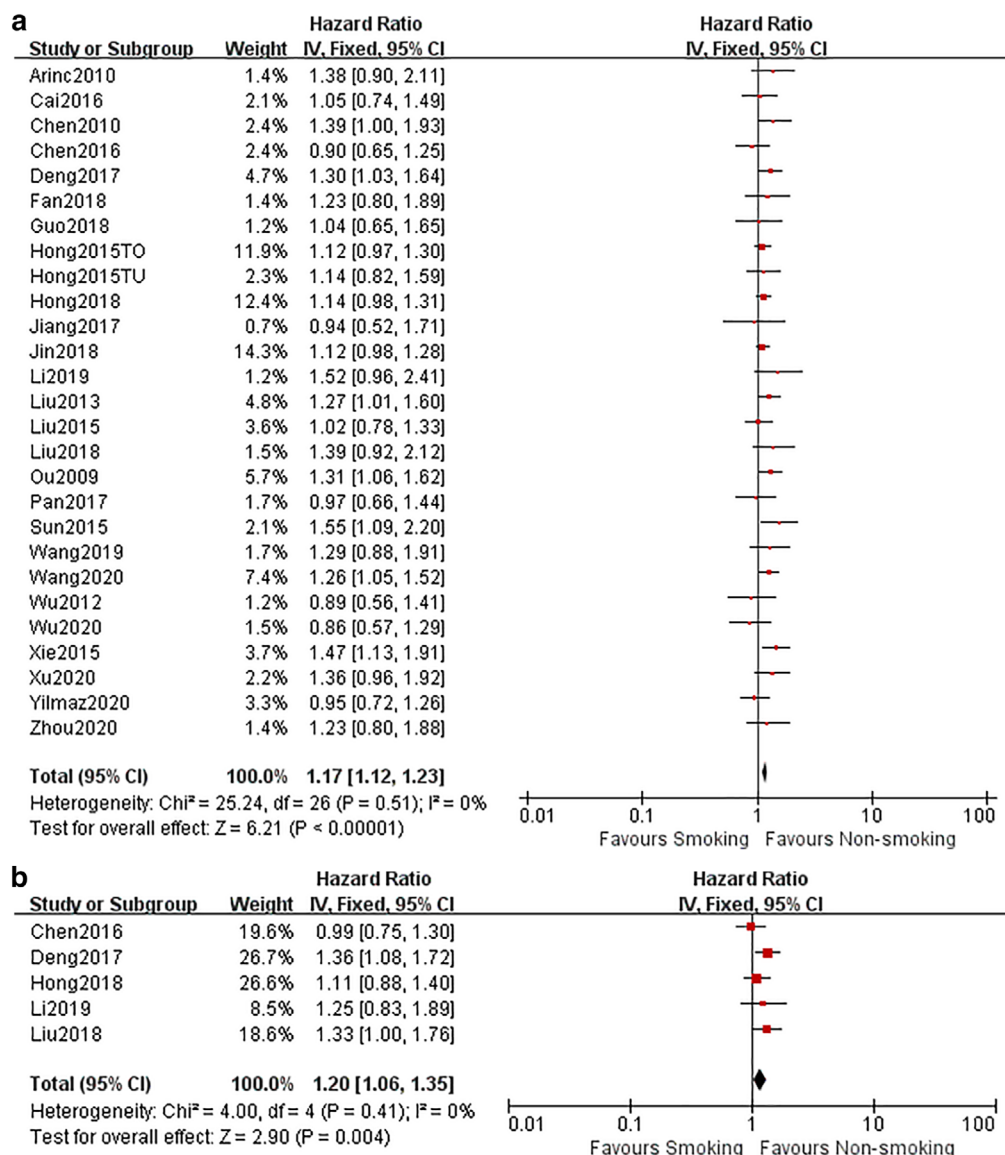**Figure 2** (**a**) Forest plots of HRs for the association of pretreatment smoking status with overall survival (OS) of patients with SCLC. (**b**) Forest plots of HRs for the association of pretreatment smoking status with progression-free survival (PFS) outcome of patients with SCLC. [Correction added on 2 October, after first online publication: figure 2a has been amended.]

P-value). The primary outcome was OS, and the secondary endpoint was PFS. In general, patients with a documented smoking history (current or former smokers) were classified as smokers, and those without any documented smoking history were classified as never-smokers.

Quality assessment was performed by the Newcastle-Ottawa Scale (NOS), consisting of three domains: selection (0–4 points), comparability (0–2 points), and outcome assessment (0–3 points). Two independent reviewers evaluated the risk of bias of each study, and disagreement was resolved by discussion or consultation with an independent

third reviewer. A study was considered to be of high quality if its NOS score was six or higher.

Statistical analysis

The primary outcome was overall survival (OS), and the secondary endpoint was progression-free survival (PFS). The effect sizes namely HR and 95% CI or *P*-value of the dichotomous variable ("smokers" or "never-smokers" of pretreatment smoking status) were extracted from each study and pooled to assess the prognostic value of pretreatment smoking status for

SCLC. Cochran's Q test and Higgins' I^2 statistic were performed to evaluate the heterogeneity of the included studies based on I^2 and P-values. If I^2 was ≤50% and P-value was >0.10, the heterogeneity in different included studies was acceptable and we chose a fixed-effects model to combine all studies, otherwise a random-effects model was used. We also conducted sensitivity analysis to assess the influence of each study on the overall analysis and final result. Publication bias was assessed by Begg's funnel plot and Egger's linear regression. When the combined HR was >1, the range of 95% CI did not cross 1, and for two-tailed P-values <0.05, the result was considered statistically significant and served as an adverse prognostic factor. All statistical analyses were performed using the Review Manager software (RevMan V.5.3, Cochrane Collaboration, London, UK) and Stata/SE version 15.0 for Windows (Stata Corporation, College Station, TX, USA).

Results

Study research

A total of 8137 records were retrieved from four databases (1352 from PubMed, 4158 from Medline, 2420 from Embase, and 2017 from the Cochrane library). After removing duplicated publications and screening titles or abstracts, 241 full text relevant articles were reviewed for eligibility, and 27 studies met the inclusion criteria and were finally included in our analysis. The process of identification for eligible articles is shown in Fig 1.

Study characteristics

In total, 12 047 patients with SCLC (9137 smokers and 2910 never-smokers) in 27 studies were included in this meta-analysis. All studies were retrospective and had been published between 2009 and 2020 with a NOS score of six or higher. Most of the enrolled studies (26/27) were from an Asian population, and among them 24 studies were from China. [Correction added on 13 October 2020, after first online publication: the preceding sentence has been amended.] Pretreatment smoking status were analyzed by both univariate and multivariate analysis in 12 studies, and the multivariate results extracted, while in the remaining 15 studies only univariate outcomes were available, the results of which were extracted. Effect sizes of correlation between pretreatment smoking status and OS were reported in all 27 studies, and those between smoking status and PFS were available in five studies. Other characteristics of the incorporated literatures are presented in details in Table 1.

Correlation between pretreatment smoking status and survival of SCLC

All 27 studies provided data on effect size of pretreatment smoking status for OS of patients with SCLC. As presented in Fig 2a, smoking history predicted a poor OS outcome of SCLC with a HR of 1.17 (95% CI: 1.12–1.23, $P < 0.00001$; $I^2 = 0\%$).

Furthermore, pooled data of five studies were available to analyze the impact of smoking history to PFS of SCLC, which again identified the passive prognostic value of pretreatment smoking status (HR = 1.20, 95% CI: 1.06–1.35, $P = 0.004$; $I^2 = 0\%$) (Fig 2b).
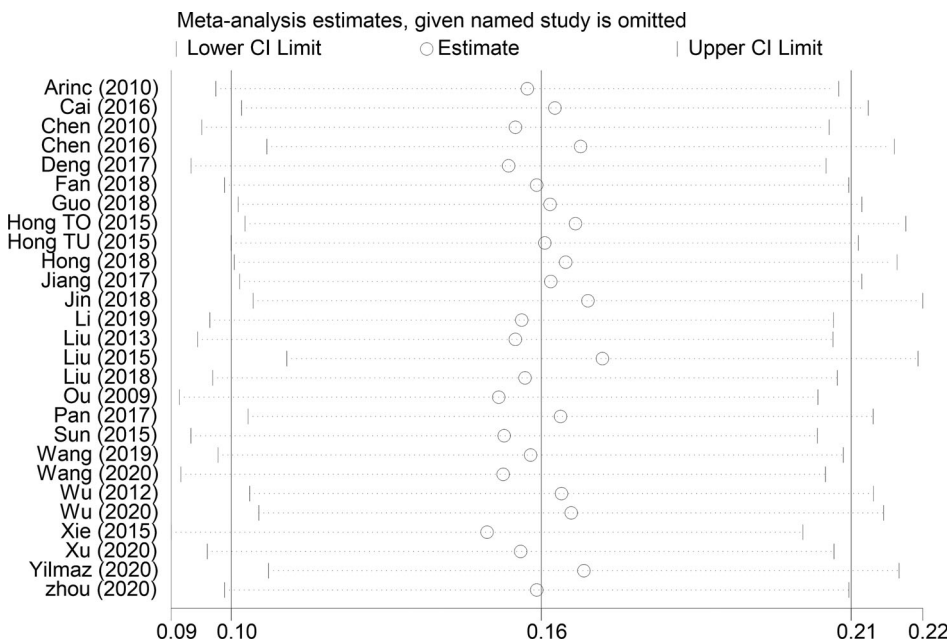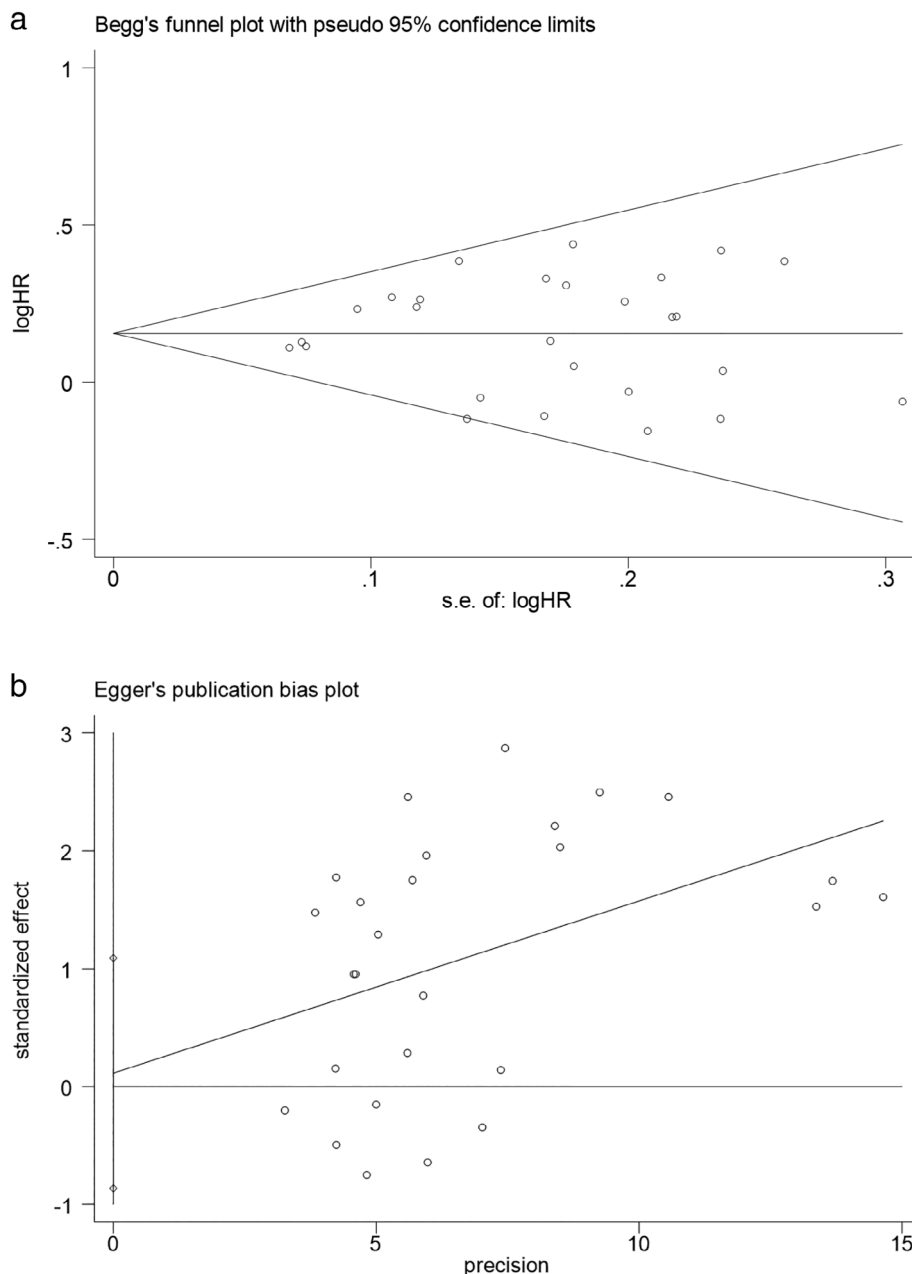

Meta-analysis estimates, given named study is omitted

Figure 3 Sensitivity analysis of the included studies.

Figure 4 (**a**) Publication bias of included studies: Begg's funnel plot of OS. (**b**) Publication bias of included studies: Egger's test of overall survival (OS).

Sensitivity analysis

We conducted a sensitivity analysis to assess the influence of each study on the overall analysis and final results, which showed that any of the studies could be removed without exerting a significant impact on the combined HRs (Fig 3). These findings indicate the favorable stability of our pooled results.

Publication bias

Publication bias were evaluated in the Begg's funnel plot and Egger's linear regression test, both of which similarly identified no significant publication bias existed in this meta-analysis: the Begg's funnel plot was symmetrical with a *P*-value of 0.868 for OS and 0.806 for PFS, respectively (Fig 4a); and in the Egger's test, *P*-value was 0.812 for OS and 0.966 for PFS, respectively (Fig 4b).

Discussion

Our meta-analysis investigated the clinicopathological characteristics and prognostic value of pretreatment smoking status in SCLC patients. In the 27 included

studies, 75.8% of 12 047 patients with SCLC were current or former smokers, and 24.2% were never-smokers. The results suggested that smoking history was inversely proportional to patient survival (OS: HR = 1.17, 95% CI: 1.12–1.23, $P < 0.00001$; $I^2 = 0\%$; PFS: HR = 1.20, 95% CI: 1.06–1.35, $P = 0.004$; $I^2 = 0\%$).

Although smoking history remains the most important risk factor of tumorigenesis of SCLC, 24.2% of 12 047 patients with SCLC were non-smokers in our meta-analysis, the frequency of which seems higher than those reported in previous studies. One recognized etiological factor of SCLC in non-smokers is radon exposure.[32] The gene landscapes of smoker and never-smoker patients with SCLC differs, and never-smoker patients were revealed to possess a higher frequency of EGFR, MET, and SMAD4 mutations,[33] but whether the differential mutation profile is a consequence of a diverse pathological mechanism for disease onset and whether potentially actionable oncogenic drivers exist are still unknown. In terms of clinical characteristics, several studies proposed that never-smoker SCLC was related to a female-gender predisposition.[33, 34] In the study by Cardo et al. the authors also found that SCLC patients with a smoking history presented with a higher incidence of brain metastasis, which might partly explain the poorer survival of smoker SCLC patients.[33] Overall, the mechanism behind the prognostic difference between smokers and never-smokers in SCLC still needs further investigation.

Our meta-analysis results were limited in that most of our included retrospective studies failed to match the basic characteristics between cohorts of smokers and never-smokers. Some studies presented multivariate analysis results of smoking status which enabled us to reduce the impact of other unmatched factors on evaluation of prognostic value of smoking status, while in other studies only univariate analysis results were available. However, the reliability of our results has been strongly supported by favorable data under analysis of both sensitivity and publication bias. The reason for negative results reported in some studies may be due to the limited number of non-smokers along with interference of other factors.

In conclusion, smoking history should be considered as an independent poor prognostic factor for patients with SCLC. More large-scale prospective studies are warranted to testify the prognostic value of pretreatment smoking status in patients with SCLC.

Acknowledgment

Disclosure

The authors declare that there are no conflicts of interest.

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