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Smoking and quality of life in lung cancer patients: systematic review

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ABSTRACT

Objectives Lung cancer (LC) accounts for the largest number of cancer deaths worldwide, with smoking being the leading cause for its development. While quality of life (QoL) is a crucial factor in the treatment of patients with LC, the impact of smoking status on QoL remains unclear. This systematic review aims to provide a comprehensive overview of available evidence on the relationship between smoking status and QoL among patients with LC.

Methods A systematic search of Embase, Medline and Web of Science was conducted. Studies reporting the impact of smoking status on QoL among patients with LC were eligible for inclusion. Two reviewers independently assessed the eligibility of studies, extracted data and evaluated the risk of bias using the Critical Appraisal Skills Programme appraisal tool for cohort studies. A descriptive synthesis was performed due to the heterogeneity of the studies.

Results A total of 23 studies met the inclusion criteria (17 studies providing cross-sectional and 6 longitudinal data). The studies included a total of 10 251 participants. The results suggested a tendency towards lower QoL among smokers compared with non-smokers. The effect of smoking cessation on QoL was insufficiently investigated in the included studies and therefore remains inconclusive.

Conclusions The findings of this review suggest that current smokers may experience worse QoL than former and never smokers. The results of this systematic review should, however, be viewed in the context of the difficulty of data collection in this patient group given the low survival rates and low performance status, among other factors and in light of the large variety of different QoL measures used. Future research requires uniform QoL measures, a holistic representation of all patients with LC as well as a comprehensive consideration of all potential determinants of QoL. The potential benefits of smoking cessation on QoL among patients with LC require investigation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although evidence shows that smoking represents the most significant risk factor for lung cancer (LC) as well as a harmful determinant regarding the progression of the disease, no clear statement on its effect on the quality of life (QoL) in patients with LC has been reached so far.

WHAT THIS STUDY ADDS

⇒ Overall, based on the findings of this review, a tendency towards a lower quality of life among smokers compared with non-smokers appears likely. No conclusion can be derived regarding the impact of smoking cessation on quality of life based on the results of the included longitudinal studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Implementing smoking cessation as an integral component of LC treatment is of utmost importance considering the positive impact of smoking cessation on outcomes such as mortality, recurrence and the development of a second primary tumour, particularly in patients at an early stage of LC. Future studies employing a prospective study design seem necessary to determine the impact of smoking cessation on QoL, especially as smoking cessation may initially be perceived as a restriction by affected patients.

INTRODUCTION

Cancer constitutes one of the leading causes of death, especially for middle-income to high-income countries, resulting in a reduced life expectancy of the general population.¹ Among all types of cancers, lung cancer (LC) represented the second most common cancer diagnosis after female breast cancer for both sexes combined, accounting for 11.4% of all initial cancer diagnoses worldwide in 2020.¹ Simultaneously, LC killed 1 796 144 patients in 2020, corresponding to 18.0% of all cancer deaths and thus

making it the most common cause of cancer deaths.¹ Although the global tobacco smoking prevalence has been continuously decreasing,² solid evidence showed that smoking remains the leading avoidable cause of LC.³ Approximately 90% of patients with LC were smokers at some point in their lives and 10%–35% of patients continue to smoke during the course of diagnosis.^{4–7} One possible reason for persistent smoking after LC diagnosis, especially in patients with an advanced LC stage, may be doubt about the benefits of smoking cessation at such a stage of the disease.⁸ Further, a small study including 43 patients with LC showed that depression and lack of social support were the main reasons for smoking relapse among this sample.⁹ Moreover, a meta-analysis of 55 studies indicated that passive smoking increases the risk of LC in non-smokers by 27%, further highlighting the health risk posed by smoking.¹⁰ Thus, tobacco dependence is a significant environmental factor in the development of LC.

One possible cause for the high mortality rate associated with LC is the oftentimes late initial diagnosis at an advanced cancer stage, which applies to approximately 80% of patients with LC at presentation.¹¹ Late detection, partly due to prolonged periods with low symptom burden, hampers surgical removal of the tumour and increases the risk of metastasis formation.¹¹ Besides surgery, commonly used treatment options include medical therapy (chemotherapy, immune therapy, targeted kinase inhibitors), radiotherapy and various forms of combinations of these.¹² A large prospective cohort study conducted among a cohort of patients with cancer undergoing chemotherapy showed that 86% of patients with LC experienced at least one side effect and 68% suffered from six or more side effects.¹³ Reported side effects of medical cancer therapy include, for instance, diarrhoea, constipation, vomiting, dyspnoea, fatigue and pain.¹³ Adverse effects of radiotherapy involve, among others, fatigue, cardiovascular disease, pneumonitis and depression.¹⁴ Not surprisingly, the symptoms of the disease as well as the described side effects have a negative impact on the quality of life (QoL) of patients with LC. Several studies demonstrated that QoL is significantly lower among patients with LC compared with the general population.^{15–16} Additional factors that have previously been shown to be associated with poorer QoL in patients with LC include female gender, younger age, advanced disease stage,¹⁵ lack of exercise and sleep as well as low income.^{17–18}

Generally, QoL is considered a complex and inconsistently defined concept in the healthcare context, comprising physical, psychological, spiritual, environmental, social and functional domains.^{19–20} Simultaneously, QoL represents a pivotal endpoint in health research, providing insight into the relative benefits of available treatment options.¹⁹ Further, the assessment of patients' QoL provides information about the

individual well-being of patients with certain diseases and may pose an important predictor of treatment success, especially concerning survival.²¹ Therefore, QoL is a crucial factor in medical decision-making processes¹⁹ and represents one of the most important endpoints for new drug approvals by legal authorities, such as the Food and Drug Administration. Regarding the instruments used to assess QoL, a distinction must be made between generic and disease-specific as well as between self-reported and proxy-reported measurements.¹⁹ Generic measures may be used among patients of various diseases as well as the general population, whereas disease-specific measures place particular focus on the characteristics and domains relevant to the respective patient population.²² Cancer-specific instruments to assess QoL among patients with LC include the European Organization for the Research and Treatment of Cancer QLQ-C30 (EORTC QLC-C30),²³ The Functional Assessment of Cancer Therapy-Lung (FACT-L)²⁴ or Lung Cancer Symptom Scale (LCSS).²⁵

Regardless of the type and stage of LC, continued smoking has a negative impact on the disease trajectory. In a randomised controlled trial, for instance, preoperative smoking cessation reduced the post-operative complication rate from 41% to 21%.²⁶ In patients undergoing radiotherapy or chemotherapy or a combination of both, smoking cessation reduced medication doses and decreased the likelihood of adverse effects during treatment, such as infectious pneumonia.²⁷ According to one systematic review and meta-analysis, the mortality risk for patients with LC who continue to smoke after diagnosis is more than doubled.²⁸ Considering the reduced QoL of patients with LC compared with the general population and the negative impact of smoking on the development and progression of this type of cancer, a relationship between smoking status and smoking history of patients with LC and QoL appears likely in terms of poorer QoL in active as well as former smokers. To the best of our knowledge, only one systematic review, which was conducted by Rowland *et al* in 2012, investigated the association between QoL and smoking status among patients with LC.²⁹ Due to the relatively small number of existing studies at that time and the rapidly growing medical knowledge gained from research, an updated review of available evidence is required. Therefore, the objective of this systematic review was to expand the previous review of Rowland *et al*, analysing the scientific evidence to evaluate how smoking status impacts QoL in patients with LC and whether continued smoking compared with smoking cessation leads to differences in QoL in this patient group. Understanding the potential impact of smoking status on QoL in patients with LC is of particular interest, as it may affect practitioners' treatment decisions, especially given the proven negative effects of smoking on treatment effectiveness,³⁰ as well as aid

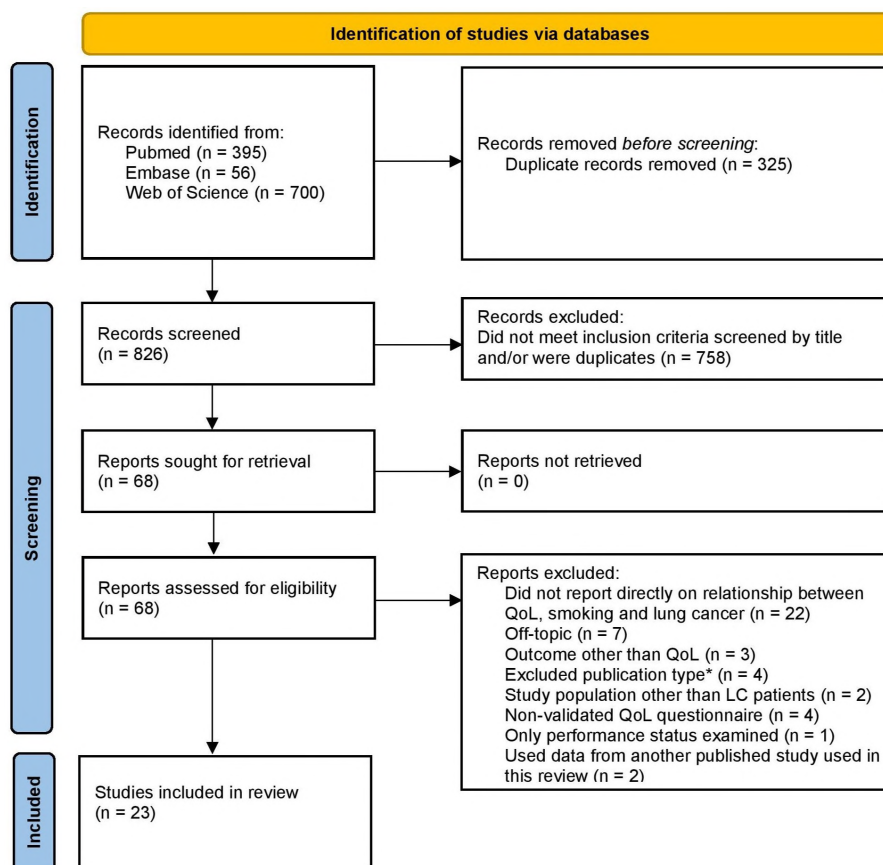


Figure 1 Flow chart of study selection process. *Excluded publication types are case reports, opinion pieces, letters to the editor, comments, conference abstract, poster abstracts, systematic reviews, meta-analyses. LC, lung cancer; QoL, quality of life.

in the effective implementation of smoking cessation programmes.

METHODS

This review was carried out according to recommendations of the Preferred Reporting Items for Systematic Reviews (PRISMA).³¹ To identify articles published up until 25 January 2023, analysing the influence of tobacco smoking on QoL in patients with LC, a search of the databases Embase, Medline and Web of Science was conducted. The following search terms were used and combined with Boolean operators: ‘lung cancer’, ‘pulmonary carcinoma’, ‘lung tumor’, ‘lung carcinoma’, ‘tobacco’, ‘smok* [ing] [ers] [er] [e]’, ‘quality of life’. All search results were transferred to the systematic review tool Rayyan³² and thereby assessed separately by two independent reviewers (MS and TH). Titles and abstracts of the articles were screened for relevance independently by both reviewers and eligible articles were retrieved for full texts. Disagreements were solved through discussion or in consultation with a third author (MG), when necessary. The study selection process displaying the numbers of screened titles, abstracts, full-texts and reasons for exclusion are presented in a PRISMA flow chart³³ (figure 1). The protocol of this systematic review was registered with the Centre for Reviews and Dissemination at the

University of York and revised once due to changes in the timeline as well as the participation of additional collaborators (ID: CRD42022341593, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=341593).

Studies were included if they reported primary research involving a study population of adult patients with a primary LC diagnosis, contained direct information about a possible association between smoking status and QoL and used validated QoL measures. We excluded articles which were case studies, opinion pieces, letters to the editor, comments, conference abstracts, poster abstracts, reviews, exclusively used performance status measures or non-validated QoL tools or were published in a language other than English or German.

Relevant data of the selected articles was further extracted, and the information obtained was transferred into tables. Extracted data from each study included: study population and sample size, study design, distribution of gender, type of LC (non-small cell lung cancer (NSCLC) or other) and smoking status (current, former or never smoker), QoL measurement tools, measures of smoking status, smoking definitions, statistical results (p values) and overall contents. In case of missing information, the respective variable was listed as not reported.

To evaluate the quality of the included studies, we used the National Health Service Public Health Resource Unit Critical Appraisal Skills Programme (CASP) appraisal tool for cohort studies.³⁴ The quality assessment checklist consists of 12 items that address the focus of the study's objectives, appropriateness of methods used, accuracy of measurement tools, validity and reliability of results as well as quality and credibility of proposed practice implications. Two reviewers independently performed the quality appraisal (MS and TH) and an overall quality score was derived by calculating the mean of both scores given by the reviewers. For each item of the CASP checklist, one point was assigned if the respective study met the necessary requirements. No point was awarded if the study failed to fulfil the relevant criteria or if no information regarding the contents of the item was provided. A maximum score of 12 could be obtained.

RESULTS

Study selection

The literature search identified a total of 1151 records, which included 325 duplicates that were removed before further assessment. After screening the titles for relevance, 758 articles were excluded, leaving 68 records that were assessed for eligibility by full texts. For a small number of articles, disagreements during the screening process occurred due to unclear information on the respective study design (eg, case studies), the publication type (eg, poster abstracts) or the measured outcome (eg, only performance status was assessed), which were resolved through screening of the full texts or in consultation with a third reviewer (MG). The full-text screening eliminated 45 citations, resulting in 23 articles remaining for final analysis (see figure 1).

Study characteristics

Online supplemental table 1 provides an overview of the included study characteristics as well as the respective study population. Nearly half of the studies were conducted in the USA,^{35–44} seven were carried out in Europe,^{45–51} five were from Asian countries^{52–56} and one was executed in Brazil.⁵⁷ The majority of studies included patients with LC in general, seven studies exclusively included patients with NSCLC,^{41–43 45 46 50 53} while two other studies exclusively included survivors of small cell lung cancer (SCLC)³⁸ and NSCLC,⁵⁵ respectively. Sample sizes ranged from 33⁵⁷ to 6420⁴⁰ participants. In 15 out of 22 studies,^{36–40 43–45 47–49 51–53 57} gender ratios were relatively balanced, ranging from 42%^{52 57} to 63%⁵¹ male subjects. One study intentionally included female subjects only,⁴¹ while six studies^{35 46 50 54–56} showed unbalanced gender ratios, with two studies reporting 25%³⁵ and 36%⁵⁶ male subjects, respectively. Four studies included an increased proportion of male subjects ranging from 70%⁴⁶ to 87%.⁵⁴ One study

did not report on gender ratios.⁴² The association between smoking and QoL was the primary outcome in four of the analysed studies^{38 39 46 47} and a secondary outcome in the remaining 19 studies. Approximately half of the studies were carried out with a cross-sectional study design,^{35–37 39 40 43 48 51–55} nine were longitudinal studies,^{38 41 42 44–47 56 57} of which three assessed the association between smoking status and QoL only at T1.^{41 45 56} Two studies were randomised controlled trials^{41 50} and one was a case-control study.⁴⁹ Regarding data assessment techniques, several tools were used to measure QoL. The majority of studies used a single measure and six studies included two QoL measures or a combination of the lung-cancer specific supplement LC-13 and the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).^{36 38 42 42 43 46 51} The number of studies using disease-specific questionnaires or symptom scales (EORTC QLQ-C30+LC-13, Functional Assessment of Cancer Therapy-Lung instrument (FACT-L), Lung Cancer Symptom Scale (LCSS), Quality of Life in Long-Term Cancer Survivors (QoL-Survivor)) was nearly equal to the number of studies applying generic measures (QoL Inventory, Medical Outcomes Study 36-/12-item Short Form (SF-12/SF-36), Abbreviated WHO Quality of Life Questionnaire (WHO-QoL-Bref)). The QoL assessment instruments used in the studies are detailed in online supplemental table 1.

Quality assessment

All selected studies were critically appraised using the CASP appraisal tool.³⁴ Scores ranged from 6.5^{41 41 51 53 54 57} to 10^{41 48} (see figure 2). Factors that frequently led to a reduced quality score were the use of subjective methods of measuring smoking status, lack of consideration of all potential confounding factors as well as neglecting longitudinal effects and the quality of repeated measures in terms of insufficient time periods between follow-ups and inadequate response rates. The mean quality score was 7.9. Studies rated very high in quality (scores of 9 or 10) were given particular consideration in this systematic review.

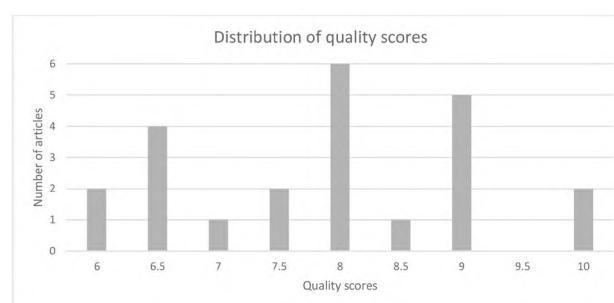


Figure 2 Number of included articles given respective quality score resulting from critical quality appraisal using Critical Appraisal Skills Programme tool for cohort studies.

Assessment of smoking status

Regarding the definitions and categorisations as well as methods used to determine smoking status, the included studies varied greatly. While the majority of studies either divided smoking status into the three categories of ‘current’, ‘former’ and ‘never’ smokers, or further subdivided the category of ‘former’ smokers based on the amount of time since smoking cessation, three studies distinguished only between ‘ever’ and ‘never’ smokers.^{35 45 52} Further, one study categorised smoking status into the two subgroups of ‘active’ and ‘non’-smokers⁵⁷ and one study did not present any categorisations of smoking behaviour.³⁶ Never smokers were further defined as participants who smoked less than 100 cigarettes in their lifetime in four studies.^{37–39 44} Five of the included studies defined never smokers as individuals who have not smoked at all in their lifetime^{35 42 45 46 52} and one study identified never smokers as participants having smoked less than five cigarettes in their lifetime.⁴⁷ Current smokers were defined as patients who smoked at the time of cancer diagnosis in three studies^{38 39 46} and in one study as those who smoked during the past 12 months.⁴⁵ The group of former smokers was subdivided into ‘late’, ‘recent’ and ‘early’ quitters in one study,³⁸ depending on the time between smoking cessation and first diagnosis of cancer. Sarna *et al*⁴² divided former smokers into patients who quit at least 1 year ago and those who quit smoking less than a year before assessment. While the majority of studies determined current smoking status by self-report, two studies^{41 43} used biochemical verification methods to counteract possible misreporting of smoking status.

Impact of smoking on QoL

Within the studies analysed, a total of 17 assessed the relationship between smoking status and QoL on a one-time basis,^{35–37 39–43 48–56} while 6 studies provided data on the association between smoking and QoL using

a longitudinal study design^{38 39 44–47 57} (online supplemental table 2). Figure 3 provides a compact overview of the findings on the impact of smoking status on QoL based on the results of the included studies.

Among the studies assessing the association between smoking status and QoL at one time point only, seven found no significant differences in QoL dependent on smoking status.^{35 37 41 43 50 52 54} However, two of these studies noted trends. Mohan *et al* observed that longer duration of smoking—measured in pack years—had a negative impact on QoL compared with patients who had smoked for shorter periods or had never smoked.⁵⁴ Rotonda *et al* found a trend towards shorter time until definitive deterioration of functional well-being in smokers and former smokers.⁵⁰ Further, a trend of lower QoL for increasing packs per day among a group of 74 persistent smokers was reported in one study.³⁹ Significant differences in QoL between the groups of smokers, former smokers and non-smokers were found in 10 studies.^{36 39 40 42 48 49 51 53 55 56} Of these, four studies reported higher overall QoL among never smokers compared with former and persistent smokers.^{39 40 48 55} Four other studies showed better scores in never smokers for specific subscales, involving two studies demonstrating better scores on the mental component summary of the SF-36 and SF-12, respectively,^{49 51} one study reporting significantly higher pain scores among current smokers and recent quitters⁴² and one study observing significantly lower scores for physical function, pain, insomnia, dyspnoea and arm pain among active smokers compared with non-smokers.⁵⁶ Browning *et al*³⁶ compared their results, obtained from a cohort of smokers only, to the cohort of smokers and non-smokers of Garces *et al*³⁹ and found lower QoL among the respondents in their sample when compared with the participants of the Garces *et al* study. However, one study came to a contrary conclusion and showed better scores on the

Significantly higher QoL in nonsmokers compared to smokers	Significantly higher QoL in smokers compared to nonsmokers	Trends in QoL dependent on smoking status	No significant differences in QoL dependent on smoking status
<ul style="list-style-type: none">• Negative impact of smoking on QoL reported in a total of 12 studies (9 providing data for one time point [36, 39, 40, 42, 48, 49, 51, 55, 56], 3 investigating longitudinal effects [38, 46, 47])• 4 of these 12 studies received high quality scores of 9 or 10 according to critical quality appraisal using CASP tool [38, 39, 47, 48]• 9 studies reported higher overall QoL or better scores for specific QoL subscales among nonsmokers compared to former and persistent smokers [36, 39, 40, 42, 48, 49, 51, 55, 56]• 3 studies showed better improvement in QoL and higher scores for QoL subscales at multiple time points in nonsmokers and former smokers compared to active smokers [38, 46, 47]	<ul style="list-style-type: none">• Positive impact of smoking on QoL reported in a total of 1 study providing data for one time point [53]• Study did not receive a high quality score of 9 or 10 according to critical quality appraisal using CASP tool• 1 study reported better scores for physical QoL among former and current smokers compared to never smokers [53]	<ul style="list-style-type: none">• Trends were observed in a total of 3 studies (2 providing data for one time point [50, 54], 1 investigating longitudinal effects [38])• 1 of these 3 studies received a high quality score of 9 according to critical quality appraisal using CASP tool [38]• Trends point towards a negative impact of smoking and high number of pack years on QoL [38, 50, 54]	<ul style="list-style-type: none">• 10 studies (7 providing data for one time point [35, 37, 41, 43, 50, 52, 54], 3 investigating longitudinal effects [44, 45, 57]) reported no significant differences in QoL dependent on smoking status• 2 of these 10 studies received high quality scores of 9 or 10 according to critical quality appraisal using CASP tool [41, 50]
In summary, results suggest a negative impact of smoking status on quality of life measures among patients with lung cancer. However, despite the importance of this topic, this knowledge has not found its way into clinical routine.			

Figure 3 Impact of smoking status on QoL reported in included studies. CASP, Critical Appraisal Skills Programme; QoL, quality of life.

physical component summary of the SF-36 among former and current smokers compared with never smokers.⁵³

Among the studies that investigated longitudinal effects of smoking status on QoL, three found no association at any time points.^{44 45 57} Chen *et al* compared subgroups within the group of smokers and showed that early quitters had the best overall QoL scores.³⁸ Further, a trend towards an improvement of QoL in recent quitters compared with late quitters and current smokers was observed.³⁸ The remaining two studies with a longitudinal design indicated there was a relationship between smoking status and QoL.^{46 47} Balduyck *et al* demonstrated that among never smokers, all QoL scores returned to baseline 1 month after surgery, whereas smokers did not return to baseline in physical, role and social functioning during the 12 months' follow-up.⁴⁶ Furthermore, Danson *et al* found better physical functioning in never smokers compared with former smokers at T1, whereas at T2, never smokers reported better cognitive functioning than former and current smokers.⁴⁷ Additionally, former smokers had significantly better social functioning scores than current smokers at T2.⁴⁷

DISCUSSION

The results of our systematic review show ambivalence regarding the relationship between smoking status and QoL. Whereas Rowland *et al*²⁹ indicated a negative impact of tobacco smoking on QoL in patients with LC, we were unable to reach a clear conclusion about the relationship based on the included studies in this work. However, it should be noted that four of the eight studies included in the systematic review from 2012 did not find a relationship between the two variables either. Nevertheless, based on the quality scores determined by Rowland *et al*, some studies were weighted more heavily, leading the authors to their conclusion. In the present review, 10 out of the included 23 studies found no significant association between smoking status and impaired QoL.^{35 37 41 43–45 50 52 54 57}

Among these, two studies received high-quality scores of 9 or 10, strengthening the significance of their results.^{41 50} The remaining 13 studies demonstrated a significant association between smoking status and QoL,^{36 38–40 42 46–49 51 53 55 56} although one study found that smokers and former smokers reported better QoL than never smokers.⁵³ However, Lee *et al* attribute their results of better QoL in former and current smokers to a presumably worse QoL among females in general and a disproportionately high ratio of male smokers compared with female smokers among their cohort.⁵³ This in return leaves 12 studies confirming worse QoL among smokers compared with never or former smokers. Out of the remaining 12 studies, four had higher-quality scores.^{38 39 47 48} Despite the inconclusive nature of our systematic review, the number of higher-quality studies that found a relationship between

smoking status and QoL in favour of non-smokers or ex-smokers suggests that smoking tends to have a negative impact on QoL. In comparison to studies on the relationship between QoL and smoking status among other study populations, a similar tendency can be observed. According to several studies, smoking was found to have a negative impact on QoL in patients with different types of cancer (eg, colon, breast, head and neck cancer).^{58–60} However, research on cohorts of patients with coronary heart disease or the general population found no or only small differences between (persistent) smokers and former or non-smokers in QoL,^{61 62} further emphasising the ambivalence between the two variables. Possible reasons for the lower QoL in smokers observed in some studies are, on the one hand, increased physical symptoms, such as dyspnoea or coughing.^{40 47 56} Further, smoking has been proven to be a significant risk factor for a variety of pulmonary conditions, such as pulmonary haemorrhage, spontaneous pneumothorax,⁶³ chronic obstructive pulmonary disease, asthma and tuberculosis,⁶⁴ which, in the event of simultaneous occurrence, may exacerbate the symptoms of LC and therefore contribute to lower QoL. On the other hand, mental QoL may be negatively impacted by social stigma due to LC frequently being viewed as a self-inflicted disease, as well as feelings of guilt and shame of patients with LC about their smoking habits, which may in turn lead to depression and anxiety.^{35 37 65 66}

In general, however, the studies in this review indicated that factors besides smoking status may have equal or even greater impact on QoL. Several of the presented studies that found no relationship between smoking status and QoL identified an association between other determinants and QoL. Chang *et al*, for instance, found gender to be a significant determinant of QoL, with male patients reporting better QoL than females.⁵² Further, Sarna *et al* demonstrated that dyspnoea, depressed mood and comorbidities were significantly associated with poorer QoL among a cohort of women.⁴¹ Additionally, Sarna *et al* revealed distressed mood, older age and white ethnicity to be predictors of worse QoL.⁴³ Similarly, the influence of numerous factors on QoL was shown in a systematic review of 52 studies among patients with prostate cancer, which identified older age, comorbidities, advanced disease stage, impaired mental health and low educational level as factors negatively affecting QoL.⁶⁷ Another significant factor that has an adverse effect on QoL is pain, as shown in a systematic review of 21 studies on determinants of QoL in patients with advanced cancer.⁶⁸ While the influence of smoking on the development and progression of LC must be highlighted in this context, the concurrent impact of other determinants on QoL may be equally important.

Although a conclusive statement on the relationship between smoking status and QoL in patients with LC is not possible based on the results presented in this

review, previous studies found numerous other positive effects of smoking cessation among this patient group. One meta-analysis of observational studies on the influence of smoking cessation after diagnosis of early stage LC showed that smoking cessation positively impacted prognostic outcomes, such as development of a second primary tumour, recurrence and mortality.²⁸ Similarly, a recently published meta-analysis found significantly improved overall survival in patients with LC who quit smoking around the time of diagnosis.⁶⁹ Further, there is substantial evidence for improved efficacy and reduced side effects of treatment with immunotherapy, irradiation and chemotherapy in patients with LC who are non-smokers compared with smokers.⁷⁰ While the beneficial effects of smoking cessation at an earlier, non-metastatic stage of LC have been demonstrated repeatedly, no comprehensive evidence is available for patients at an advanced cancer stage.

Limitations

Moreover, several obstacles and challenges need to be considered when investigating the association between QoL and smoking status among patients with LC. For example, data collection among the particularly vulnerable population of patients with LC may hold several difficulties, such as inability to obtain information due to patients' declining performance status, language barriers or poor compliance.⁷¹ As previously acknowledged by Rowland *et al*, longitudinal study designs may face additional difficulties due to poor survival rates of patients.²⁹ However, the number of studies employing a longitudinal assessment of the relationship between smoking status and QoL has increased when compared with the longitudinal data available in 2012.²⁹ Further, most samples in the studies included in our analysis largely consisted of former smokers, while the proportion of never smokers and, in particular, of persistent smokers, was relatively small, limiting the comparability of the groups. In addition to group comparability, the comparability of the results presented here is further compromised by the large variety of QoL measures as well as the varying definitions of smoking status applied in the included studies. Another limitation of the included studies is the under-representation of patients with SCLC. Eight of the included studies exclusively investigated samples of patients with NSCLC,^{41–43 45 46 50 53 55} which impede the results from being equally applicable to all patients with LC. Moreover, smoking status was assessed by self-reporting in all but two studies,^{41 43} which used biochemical validation to confirm smoking status. This allows the possibility of biased results due to inaccurate patient statements, which may include under-reporting of smoking habits as a result of social desirability. Further, there is a possibility that other eligible studies remained undetected by our search and were thus not included. Additionally, we cannot exclude publication bias, potentially resulting in studies that showed

no association between smoking status and QoL not being published and therefore not being included in our results.

CONCLUSIONS

Overall, based on the findings of the current review, a conclusive statement regarding the relationship between tobacco smoking and QoL in patients with LC cannot be reached. However, based on the quality scores of the included studies, a tendency towards a lower QoL among smokers compared with non-smokers appears likely. Future research requires uniform QoL measures, a holistic representation of all patients with LC as well as a comprehensive consideration of all potential determinants of QoL. Further studies employing a prospective study design seem necessary to determine the impact of smoking cessation on QoL, especially as smoking cessation may initially be perceived as a restriction by patients who are active smokers. Ideally, future studies should follow patients over a study period of at least 3 years, confirm smoking status by biochemical verification and consider all potentially relevant variables, such as gender, age, comorbidities, disease stage and treatment. Nevertheless, in view of the existing evidence on the negative impact of smoking on the course of disease among patients with LC, implementing smoking cessation as an integral component of LC treatment is of utmost importance. The relevance of smoking cessation is further emphasised by the positive impact of smoking cessation on outcomes such as mortality, recurrence and the development of a second primary tumour, particularly in patients at an early stage of LC.

Contributors Conceptualisation: TH and MG; methodology: TH and MG; data collection: TH and MS; analysis and interpretation of results: TH, MS, MG; writing – original draft preparation: TH; writing – review and editing: MS, AH, TR, SR, MT, MG; supervision: AH and MG. TH is responsible for the overall content as guarantor. All authors have read and agreed to the published version of the manuscript.

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Competing interests The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. AH is coeditor of the German (DGPPN) Schizophrenia treatment guidelines and first author of the WFSBP Schizophrenia treatment guidelines. AH has received paid speakerships from Janssen, Otsuka, Rovi, Recordati, Advanz and AbbVie. He was member of Rovi, Recordati, Otsuka, Lundbeck and Janssen advisory boards. MG is chair person of the German Federal Association of Sexualized Substance Use (BISS) and received honorariums for talks from several HIV and drug counselling centers. Furthermore he received honorariums from Gilead sciences and travel expenses for a conference journey and is medical consultant of the district of

Swabia for addiction issues. TR received travel expenses and congress fees from the Sanofi company. SR received travel support and congress fees from MedXpert. Within the past 5 years, MT has received speakers or advisory honoraria and travel support from Novartis, Amgen, Roche, Celgene, Janssen, Klinikum Stuttgart, ConEvent, MedUpdate, Sirtex, COCS, FOMF, Klinikum Esslingen, VHS Stadtbergen.

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