A systematic review of symptomatic diagnosis of lung cancer

Joanna Shim*a,*, Lucy Brindle*a, Michael Simon*a and Steve Georgeb

aFaculty of Health Sciences and bFaculty of Medicine, Southampton General Hospital, University of Southampton, Southampton, UK.

*Correspondence to Joanna Shim, Faculty of Health Sciences, University of Southampton, Building 45, Highfield Campus, University of Southampton, Southampton SO17 1BJ, UK; E-mail: js1g08@soton.ac.uk

Received August 16 2013; revised October 18 2013; Accepted October 26 2013.

Abstract

Background. Lung cancer (LC) is often diagnosed late when curative intervention is no longer viable. However, current referral guidelines (e.g. UK National Institute for Health and Care Excellence guidelines) for suspected LC are based on a weak evidence base.

Aim. The purpose of this systematic review is to identify symptoms that are independently associated with LC and to identify the key methodological issues relating to symptomatic diagnosis research in LC.

Methods. Medline, Ovid and Cumulative Index to Nursing and Allied Health Literature were searched for the period between 1946 and 2012 using the MeSH terms ‘lung cancer’ and ’symptom*’. Quality of each paper was assessed using Scottish Intercollegiate Guidelines Network and Consolidated Criteria for Reporting Qualitative Research Checklists and checked by a second and third reviewer.

Results. Evidence regarding the diagnostic values of most symptoms was inconclusive; haemoptysis was the only symptom consistently indicated as a predictor of LC. Generally, evidence was weakened by methodological issues such as the lack of standardized data collection (recording bias) and the lack of comparability of findings across the different studies that extend beyond the spectrum of disease. Qualitative studies indicated that patients with LC experienced symptoms months before diagnosis but did not interpret them as serious enough to seek health care. Therefore, early LC symptoms might be under-represented in primary care clinical notes.

Conclusion. Current evidence is insufficient to suggest a symptom profile for LC across the disease stages, nor can it be concluded that classical LC symptoms are predictors of LC apart from, perhaps, haemoptysis. Prospective studies are now needed that systematically record symptoms and explore their predictive values for LC diagnosis.

Key words: Diagnostic accuracy, epidemiology, lung cancer, lung neoplasm, predictive value, symptoms.

Introduction

Lung cancer (LC) continues to be the leading cause of cancer mortality worldwide, accounting for approximately 1.4 million deaths each year (1). Over the last four decades, survival rates have only improved slightly with most LC being diagnosed at late stages when curative intervention is no longer viable in both developing and developed regions of the world (1,2). Evidence from large population-based studies has since associated relatively lower survival in some regions with delays in diagnosis (3,4).

In the UK, efforts to improve the survival rate of LC included National Institute for Health and Care Excellence (NICE) guidelines, which recommended urgent chest X-ray referral for patients experiencing any persistent symptoms that might indicate LC (5). However, most of these symptoms are non-specific and
could also suggest other differential diagnosis of lung and respiratory diseases, such as chronic obstructive pulmonary disease (COPD). The most common methods found in symptom-based research in LC are retrospective cohort studies and case-control studies that use clinical records and databases; these studies are generally limited by methodological issues regarding symptom data collection. For example, these studies are subject to the possibility of recording bias by clinicians that might have implications for the predictive values obtained. The absence of prospective studies of the predictive value of symptoms mainly reflects the large study sizes and costs involved in longitudinal studies that commence prior to referral for investigation.

Two systematic reviews have addressed the diagnostic value of symptoms in LC: Hamilton and Sharp (6) and Shapley et al. (7). Hamilton and Sharp (6) reviewed features of symptomatic LC across studies and estimated the likelihood ratios (LRs) of some of the symptoms in LC diagnosis. The estimated LRs reported were based on referred populations in secondary care settings with hardly any research to be found in primary care populations. The study of Shapley et al. (7) identified symptoms, signs and non-diagnostic test results that were highly predictive of specific cancers [where positive predictive values (PPVs) ≥5% were reported]. The review analysed all higher quality evidence of symptoms that predicted LC in an unsolicited primary care population and reported two studies for LC (8,9). Only haemoptysis was identified as having high PPVs (≥5%) in LC diagnosis. Owing to the lack of high-quality research in primary care populations in the most recent systematic review identified, this systematic review will investigate the diagnostic value of symptoms for LC, regardless of national health care system or spectrum of disease, and identify any new primary care evidence since 2010. The review will also include qualitative studies to explore the symptom experience of people diagnosed with LC and identify factors associated with patient reporting of symptoms that might have implications for the design of future diagnostic studies. This qualitative component could also reveal any non-classical symptoms or characteristics of symptoms experienced before LC diagnosis not investigated in diagnostic studies.

Similar search methods were applied for all the electronic databases listed below:

In addition, the contents pages of four journals (two for quantitative and two for qualitative studies) between 1 January 2009 and 31 December 2011 were hand searched: Thorax and the British Journal of General Practice for quantitative studies and the Psychooncology and the European Journal of Cancer Care for qualitative studies. Based on the search strategy, journals with the highest number of relevant papers for quantitative and qualitative studies were selected. This generated a total of 3017 papers (1830 quantitative and 1187 qualitative). All records were retrieved and screened for relevance.

**Inclusion and exclusion criteria**

The following criteria were used to determine the eligibility of studies for this review:

- Quantitative study design—Studies that reported diagnostic values (PPVs, hazard ratios (HRs), odds ratios (ORs) and/or LRs) for the symptom, sign or test, or provide the necessary information needed to calculate these values (2 x 2 contingency tables could be reconstructed).
- Qualitative study design—Studies that explored the trajectory of symptoms from when symptoms were first experienced before diagnosis, or studies that described the onset of symptoms or first symptoms at presentation to clinician (primary care) were of interest for the purposes of the review.
- Participants—Only adult populations recruited from hospitals, outpatient clinic, specialist clinic, specific community or the general population.
- Outcomes—The group with the positive outcome (LC) must have had a confirmed clinical diagnosis of LC that met diagnostic standards set by the health service provider.
- Others—Studies written in a language other than English, German, Spanish, Malay and Chinese were excluded. Studies on multi-site cancers were included provided that LC was distinguished from other cancers in reporting of results.

**Methods**

**Search strategy**

Electronic databases were searched from their commencement to July 2012 using search terms ‘lung cancer*’, and ‘symptom*’ for title abstracts. The key terms were exploded to include alternative MeSH descriptors such as ‘Lung Neoplasms’, ‘Signs and Symptoms’, and ‘Differential Diagnosis’. Search hits were filtered using qualifying restrictions: diagnosis, epidemiology and aetiology for ‘Lung Cancer’, ‘Symptoms’ and ‘Differential, Diagnosis’. Details of the complete search strategies of all the databases performed are included in Appendix I (see supplementary data).
symptoms in advanced LC, studies measuring the effect of toxicity and quality of life studies on symptom burden where baseline reported only post-treatment symptoms that will not provide diagnostic values. Single case studies, case reports, editorials, symposiums, reviews (literature) and practical guidelines were excluded.

• Participants—Studies that reported symptoms of metastatic cancer, where LC is the secondary cancer, were excluded.

**Study selection and quality assessment**

The initial screening of the titles and abstracts was carried out independently by the first reviewer (JS). A second and third reviewer (LB and MS) each checked a random sample of 75 (2.5%) of the abstracts. All papers shortlisted were retrieved in full. A second reviewer (LB) checked 100%, and a third reviewer (MS) 25%, of the full papers that were shortlisted to ensure that they met the eligibility criteria. Methodological quality was assessed using the Scottish Intercollegiate Guidelines Network Checklist for cohort studies and case–control studies, and the Consolidated Criteria for Reporting Qualitative Research checklist was used to assess qualitative studies. Disagreements or uncertainties about satisfaction of quality criteria were discussed with the second and third reviewers (LB and MS) and consensus achieved.

**Data extraction and analysis**

The reviewers requested raw data of potentially relevant data from main authors to ensure a comprehensive inclusion of existing literature. Data on the type of study, characteristics of the study population, duration of follow-up and the effect sizes were extracted systematically and tabulated for each study that met inclusion criteria. If diagnostic values were not reported, the positive and negative likelihood ratios and sensitivity and specificity were calculated using the 2 × 2 contingency tables (10). PPVs were also calculated where possible.

Owing to the large variance in populations and research methodologies between the studies in this review, a meta-analysis to pool the predictive values of the symptoms reported in all the studies was considered to be inappropriate. As a result, the study used narrative summaries (narrative review approach) and meta-synthesis of data to analyse the quantitative and qualitative evidence, respectively.

**Results**

A total of 6037 papers were retrieved using the search strategy (11). Result of the search strategy and selection process is shown in the flow diagram in Figure 1. Duplicates were removed using EndNote reference manager. The final update was performed in July 2012. In total, 9054 articles (including the 3017 hand-searched journals) were assessed for relevance. Out of which, 11 studies (5 quantitative and 6 qualitative) were eligible for inclusion in the final review.

**Results of quantitative studies**

Table 1 and Appendix (II) (see supplementary data) summarizes the main characteristics of the quantitative studies.

**Symptomatic prevalence**

In general, cough, dyspnoea and haemoptysis were the most commonly ‘measured’ symptoms, based on patient-reported symptoms and those recorded by a general practitioner (GP)/primary care clinician (shown in Table 2). In the four studies that reported symptom frequencies, systemic symptoms such as appetite loss, weight loss, fatigue and fever/flu were less frequently reported (8,12,13). On the whole, the duration of symptoms onset to diagnosis reported in the studies ranged from 6 months to no more than 2 years before diagnosis.

**Symptomatic diagnosis**

Table 2 and Appendix (III) (see supplementary data) show symptoms that were recorded in the study and which of these predicted LC (P ≤ 0.05). In two of the studies, P-values or confidence intervals (CIs) were not provided (12,14).

Table 3 present the PPVs and ORs of the individual symptoms reported in the case–control studies and cohort studies, respectively. Most symptoms reported in the study of Hamilton et al. (8) had reasonably high ORs (OR 4.40 to 16.24). However, even with the high ORs, the likelihood of a patient presenting with that symptom having LC (as indicated by the PPV) was low (<1.0 for most symptoms).

PPVs of 2.0 and higher (2.4 ≤ PPV ≤ 7.5) were consistently found for the symptom haemoptysis across the studies. Jones et al. (9) evaluated the diagnostic value of haemoptysis in LC, reported an increase in PPV from 5.8, at 6 months after symptom onset, to 7.5—3 years after the first symptom occurrence was recorded in the male group. Similar increase was observed in the female cohort: 3.3–4.3. A gender difference in PPV was also identified (9). However, no statistically significant differences in gender-specific PPVs were identified in Hippesley-Cox and Coupland’s study (2011) (13); the remaining three studies did not carry our separate analysis for men and women (8,12,14).

Hippesley-Cox and Coupland (13) calculated the HRs of individual symptoms in the derivative cohort to develop a model strategy that predicts LC risk in a population (13). Only variables of HR <0.80 or HR >1.20 were included into the final model. The study also observed that haemoptysis had a higher HR in comparison to the other symptoms for the final model for LC for both genders (Male HR: 21.5 and Female HR: 23.9) followed by weight loss, appetite loss and cough (symptom variables included...
Family Practice, 2014, Vol. 31, No. 2

Cinahl®ebsco: 715
Embase®EMBASE: 2052
Medline®OVID: 846
Multiple search (Ovid): 2424

Total no. of papers originally downloaded into EndNote: 6037

Citations (titles and abstracts) remaining in EndNote: 2996

- Full papers retrieved for detailed evaluation (n=49)
- Further papers identified from results of hand searching 4 chosen journals (n=12)

Duplicates removed from EndNote: 3041

Papers excluded after reading abstracts: 2918

Papers excluded after reading full text ** (n=49)
- Insufficient details to calculate predictive values of symptoms (n=5)
- Editorial (n=1)
- LC as secondary metastasis (n=3)
- No lung cancer cases reported (n=4)
- All LC cases (n=3)
- All subjects had the reported symptom e.g. haemoptysis (n=12)
- All subjects reported no symptoms (by study’s definition) (n=7)
- Symptoms were not specific but grouped as symptoms or not (n=4)
- Unable to determine whether symptoms were collected before or after diagnosis (n=5)
- Tumour of the pleura (mesothelioma not included as respiratory cancer ICD-10) (n=1)
- Paper in non-English language and not accessible (n=4)

** Includes 5 non-English language papers

Papers that met inclusion criteria: 11*
*Includes 1 non-English language paper

Total number of papers included in the qualitative analysis: 6
Total number of papers included in the quantitative analysis: 5*

Figure 1. Flow diagram of results of search strategy adopted from the QUOROM statement flow diagram (11)
A systematic review of symptomatic diagnosis of lung cancer

in the final model). In their final model, the top 0.5% of their risk score produced a PPV of 9.5 (8.8–10.3).

The remaining two studies did not identify any statistically significant associations of symptoms with LC (12, 14).

Key methodological strengths and limitations of the studies

The included studies displayed several methodological weaknesses that included: the lack of standardized data collection, the potential for recall bias and recording bias, retrospective design, selection bias, confounding and limited generalizability.

Data collection issues

A variety of data collection methods were applied across the studies. Four of the studies extracted their symptom data retrospectively using medical and GP records or medical databases (8, 9, 12, 13); Kubik et al. (14) used a standardized questionnaire, the Medical Research Council (MRC) respiratory questionnaire (see Appendix (IV) in supplementary data), to prospectively record symptoms. A strength of most studies was that they included symptoms reported and recorded at the time of presentation to the clinician, as far as indicated, which reduced the likelihood of recall bias or retrospective reinterpretation of symptoms following diagnosis.

However, reports of symptoms based on these records can be restricted as they only reflect the occurrence of symptoms at the time of reporting and often tend to be diagnosis focused (15) rather than symptom focused, potentially only including symptoms thought to be relevant to a differential diagnosis, resulting in partial recording of symptoms. Therefore, medical notes or records can be subject to recording bias, as clinicians may have recorded symptoms more thoroughly if LC was suspected (8). The use of prospectively completed checklists or questionnaires might avoid recording bias if administered systematically to patients. However, this

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Country (city)</th>
<th>Study design</th>
<th>Data source of LC</th>
<th>Sample characteristic</th>
<th>Period symptom data were collected before diagnosis</th>
<th>Method of recording symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton et al. (2005)</td>
<td>UK</td>
<td>Case–control study</td>
<td>GP records</td>
<td>Population of Exeter aged above 40 years with cases cohort diagnosed with primary LC</td>
<td>≤2 years</td>
<td>Coded using the ICPC-2 coding system</td>
</tr>
<tr>
<td>Hoppe (1977)</td>
<td>Germany</td>
<td>Cohort study</td>
<td>Medical records</td>
<td>People attending a chest clinic in the state of Northrhine–Westphalia on suspicion of LC</td>
<td>&lt;6 months</td>
<td>–</td>
</tr>
<tr>
<td>Hippesley-Cox and Coupland (2011)</td>
<td>UK</td>
<td>Cohort study</td>
<td>GP record (using ICD-9 or ICD-10 codes), patient’s electronic record (EMIS), QRResearch database (including 564 practices in England and Wales)</td>
<td>Population of primary care patients registered to a GP practice in England and Wales; 30–84 years</td>
<td>2 years</td>
<td>Established predictors were recorded from patient’s electronic records using a symptom checklist</td>
</tr>
<tr>
<td>Jones et al. (2007)</td>
<td>UK</td>
<td>Cohort study</td>
<td>GP records, patient’s record</td>
<td>Primary care population registered to a GP practice aged ≤100 and had reported the occurrence of haemoptysis before</td>
<td>≤3 years</td>
<td>Occurrences of alarm symptom recorded from patient’s record</td>
</tr>
<tr>
<td>Kubik et al. (2001)</td>
<td>Czech Republic</td>
<td>Case–control study</td>
<td>Participant reported</td>
<td>Cases were female Czech patients with confirmed LC receiving treatment at the hospital in Prague. Controls were women spouses, relatives or friends of other patients of the same hospital (aged 25–84 years)</td>
<td>&lt;2 years</td>
<td>MRC Questionnaire on respiratory symptoms (interviewer administered).</td>
</tr>
</tbody>
</table>

ICPC, International Classification of Primary Care; ICD, International Classification of Diseases; EMIS, Egton Medical Information Systems.
stands the risk of only recording common chest symptoms (see Appendix (IV) in supplementary data for MRC questionnaire) and excluding systemic symptoms (14).

Retrospective versus prospective study design
In most of the studies (8,9,12,13), the symptoms were recorded/measured before diagnosis but were obtained from previously recorded data (medical records) not systematically recorded for research purposes. The limitations of retrospective study design for these studies largely relates to recording bias.

Incomplete reporting of symptoms and recording bias
In general, recording bias could over inflate the LRs of symptoms, if GPs/clinicians are more likely to record symptoms if LC is suspected. Similarly, the ratios could also be under-estimated if patients with LC under-reported their symptoms which would then go unrecorded (13). Four of the five quantitative studies evaluated within this review used clinical records to ascertain symptoms. Therefore, the ORs and LRs obtained might lead to the under- or over-estimation of the true predictive values of symptoms.

Selection bias
Studies using clinical records that capture data on every patient in a region are less likely to be subject to selection bias than studies that rely on the recruitment or inclusion of individual patients (8,9,13). However, the eligibility criteria for LC diagnoses in some of the clinical records-based studies included in this review could have some selection effect. For example, Kubík et al. (14), using a prospective study design (recruitment rate 87%) with the potential for self-selection bias, only included histologically confirmed LC cases. Therefore, it is possible that those with advanced LC were more likely to be excluded (advanced LC patients will less likely be subjected to further invasive investigation to confirm diagnosis).

Risk factors
Two of the studies did not adjust for the most likely risk factors (COPD and smoking status) (9,12). Smoking status and COPD have independent associations with LC and might cause symptoms; from 40% to 90% of LC is preceded by COPD (16). Therefore, COPD and smoking might account for the observed effect of a symptom on the disease outcome (LC) in these studies.

Limited generalizability
All studies recruited adults of both genders above the age of 18 (see Table 1) except Kubík et al. (14); this study only represented women ≥18, in the Czech Republic presenting at a secondary care centre at the time of recruitment. This inevitably reduces the generalizability of their findings to the general population.
Table 3. Diagnostic values (ORs, PPVs and HRs) for symptoms reported in case-control studies and cohort studies

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Case-control studies</th>
<th>Cohort studies</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Cough</td>
<td>0.40 (0.3–0.5)</td>
<td>4.40</td>
<td>0.96 (0.32–2.82)</td>
<td>5.8 (5.0–6.7)</td>
<td>3.3 (2.3–4.3)</td>
<td>7.5 (6.6–8.5)</td>
<td>4.3 (3.4–5.3)</td>
<td>6.4 (5.9–7.0)</td>
</tr>
<tr>
<td>Chronic cough with phlegm</td>
<td>0.44 (0.28–0.6)</td>
<td>1.92</td>
<td>0.96 (0.32–2.82)</td>
<td>5.8 (5.0–6.7)</td>
<td>3.3 (2.3–4.3)</td>
<td>7.5 (6.6–8.5)</td>
<td>4.3 (3.4–5.3)</td>
<td>6.4 (5.9–7.0)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>0.66 (0.5–0.8)</td>
<td>6.99</td>
<td>1.51 (0.85–2.67)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>2.40 (1.4–4.1)</td>
<td>16.24</td>
<td>0.96 (0.32–2.82)</td>
<td>5.8 (5.0–6.7)</td>
<td>3.3 (2.3–4.3)</td>
<td>7.5 (6.6–8.5)</td>
<td>4.3 (3.4–5.3)</td>
<td>6.4 (5.9–7.0)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0.82 (0.6–1.1)</td>
<td>4.92</td>
<td>0.79 (0.34–1.82)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1.1 (0.8–1.6)</td>
<td>8.14</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6.09 (5.33–6.95)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>0.87 (0.6–1.3)</td>
<td>5.69</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>4.71 (3.69–6.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.43 (0.3–0.6)</td>
<td>3.07</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Abnormal spirometry</td>
<td>1.6 (0.9–2.9)</td>
<td>9.39</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Worsening cough</td>
<td>–</td>
<td>–</td>
<td>5.45 (3.81–7.79)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Flu/Fever</td>
<td>–</td>
<td>–</td>
<td>0.58 (0.21–1.6)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>General unwell</td>
<td>–</td>
<td>–</td>
<td>0.76 (0.31–1.85)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

OR, odds ratio.
*Positive predictive values (PPVs) in %.
†For a separate validation cohort of the same study.
Most of the studies were of unselected primary care populations \(8,9,12,13\). Therefore, the results might be transferable to consulting patients in comparable primary care populations. However, the spectrum of disease will differ between referred secondary care and primary care populations and ratios (LRs, ORs, HRs) and PPVs obtained in secondary care populations \{e.g. Kubik et al. \(14\)} or already referred primary care populations \{e.g. Hoppe \(12\}} are unlikely to be generalizable to patients presenting with symptoms in primary care; Hoppe \(12\} retrospectively extracted data from medical records in primary care but specifically selected only those who were referred to chest clinics on the basis of possible LC. These latter two studies involving populations referred to secondary care only identified one symptom with an independent association with LC (cough with phlegm) \(14\).

### Results of qualitative studies

Table 4 summarizes the qualitative studies according to the characteristics of the sample population, data collection method and data analysis performed. The purpose of the review of the qualitative studies was to explore patient’s interpretation of symptoms before diagnosis, and whether patients recalled any change in symptom with disease duration to provide a more complete overview of symptoms experienced before LC diagnosis. All studies were retrospective but interviews were conducted close to the time of diagnosis and therefore likely to represent the patient’s symptom experience before diagnosis \(17–22\).

#### Time intervals between symptom onset and diagnosis

Using an interval event chart to demonstrate the time intervals between key events in the pathways to diagnosis, operable and inoperable LC patients recalled health changes that occurred 12 months (median) before the time of diagnosis \(18\). However, the study was underpowered and found no significant differences between the two groups \(P > 0.05\) across the time intervals between key events and time of diagnosis. Patients’ recollections of key events were verified using GP and medical notes, and high levels of agreements were obtained \(18\).

#### Pre-diagnostic bodily experiences (symptoms and health changes)

Participants reported experiencing a broad spectrum of bodily experiences prior to diagnosis \(18,20–22\). Both systemic (lethargy, weakness, fatigue, weight loss and appetite change) and chest and respiratory symptoms were reported. Often, systemic symptoms have been related to advanced stages of the disease in previous literature but several studies have reported systemic symptoms in patients with operable LC or patients in the earlier stage of the disease \(18,20,22\). Participants were unable to discern between ‘normal’ and ‘symptomatic’, particularly systemic symptoms resulting in the normalization of symptoms \(18,20\}; where symptoms were attributed to occurrences in daily living or ‘everyday’ bodily changes rather than a health problem \(18,20,22\). In light of this ‘normalization’ of symptoms, symptoms then had to become severe before they were presented to the GP/clinician \(19\).

Generally, most of the literature agreed that the existence of co-morbidity (especially those respiratory related) often complicated the process of becoming aware of a new and different disorder (masks new symptom) \(19,21,22\). There was a tendency to attribute symptoms to other acute or chronic conditions \(21\).

### Discussion

This review has updated evidence obtained from previous reviews and, unlike previous reviews, was not limited to primary care studies. As there is a lack of evidence about early symptom epidemiology in LC, the inclusion of studies in secondary care and non-UK health systems could potentially enable the identification of diagnostics values of symptoms across a broader spectrum of the disease. However, diagnostic values of symptoms obtained in non-UK or non-primary care health services research are not generalizable to symptoms presented in UK primary care \(23\).

Based on the PPVs \(P > 0.05\), there is little evidence to suggest that symptoms other than haemoptysis consistently predicted LC. This is in keeping with previous studies and reviews \(6\). However, individual studies within this review have identified other symptoms that were independently associated with an LC diagnosis such as appetite loss, weight loss, fatigue and fever/flu presentations; some of which, for example, appetite loss despite increasing LC risk from 4- to 5-fold \(13\}, are currently not included in the UK NICE guidelines as grounds for referral and may be worthy of further investigation. That being said, stronger claims beyond this cannot be made due to the methodological difficulty of non-comparability of findings across the different studies that extend beyond the spectrum of disease. For example, methods of recording symptoms were highly divergent between studies.

Four of the five quantitative studies reviewed used routine data sets; i.e. symptoms recorded in GP notes or electronic medical databases, with the potential for recording bias and incomplete presentation of symptoms \(8,9,12,13\}. The one study that did prospectively and systematically record symptoms used a predefined symptom checklist, raising the possibility that symptoms with diagnostic value for LC were omitted \(14\}. Studies have not yet to date, systematically recorded systemic symptoms as well as non-systemic respiratory symptoms prospectively for research purposes. The possibility of recording biases by GPs/clinicians, and the incomplete recording of symptoms in published
Table 4. Summary of qualitative studies

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Aim</th>
<th>Study design</th>
<th>Method of data collection</th>
<th>Period of data collection</th>
<th>No. recruited/eligible (%)</th>
<th>Sample characteristics</th>
<th>Method of data analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Driscoll et al. (1999)</td>
<td>Recorded detailed notes of how patients described their breathlessness and its impact have been analysed and presented in order to offer descriptive material regarding the experience of breathlessness in LC. These data were from a previous study looking to develop and evaluate a breathlessness intervention</td>
<td>Retrospective</td>
<td>Assessment notes recorded by nurse research-practitioner regarding the reported experience of the patient, or how both nurse and patient agree to describe the symptom and the patient’s coping strategies (a collaboration)</td>
<td>Notes were recorded at each subsequent visit to the nursing clinic</td>
<td>52</td>
<td>Thirty men (58%), and 22 women (42%) with a LC diagnosis who had completed chemotherapy or radiotherapy and experienced breathlessness aged ranging from 33 to 76 years (mean age: 60 years). Patients must have been healthy enough to be able to provide adequate material for data analysis</td>
<td>Content analysis— with frequency counts; descriptive analysis</td>
</tr>
<tr>
<td>Corner et al. (2005)</td>
<td>To develop a detailed picture of the pathway to diagnosis by mapping the pre-diagnosis symptom history and the events leading up to diagnosis of a group of patients diagnosed with LC</td>
<td>Retrospective</td>
<td>Directed interviews—semi-structured (entitled ‘what happened to me?’) and structured approach</td>
<td>Twenty patients—interviewed between 3 days and 4 weeks post-diagnosis, and two patients were interviewed 2–3 months after diagnosis</td>
<td>22/30 (73)</td>
<td>Twelve males and 10 females; aged 42–82 years recently diagnosed with LC to map. A third (n = 7) of the patients had operable LC and the remaining (n = 15) had inoperable LC</td>
<td>Thematic analysis</td>
</tr>
<tr>
<td>Corner et al. (2006)</td>
<td>To further analyse the data of previous study (Corner et al 2005) to re-address unexpected findings/themes that emerged so as to better understand how individuals through the way they responded to their health changes, might have influenced the timing of their LC diagnosis</td>
<td>Retrospective</td>
<td>Results were from the same study conducted (Corner et al. 2005) therefore the study design and sample characteristic are the same (refer to the study above).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study (year)</td>
<td>Aim</td>
<td>Study design</td>
<td>Method of data collection</td>
<td>Period of data collection</td>
<td>No. recruited/eligible (%)</td>
<td>Sample characteristics</td>
<td>Method of data analysis</td>
</tr>
<tr>
<td>-------------</td>
<td>-----</td>
<td>--------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
<td>----------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Levealahti et al. (2007)</td>
<td>To explore how people with inoperable LC frame and conceptualize the onset of their sickness; testing a theoretical construct of viewing illness as a biographical continuity over existing theory of disruption</td>
<td>Retrospective narratives</td>
<td>Semi-structured explorative interviews with open questions</td>
<td>Within 1 year post diagnosis</td>
<td>37</td>
<td>Thirty-seven patients (21 women and 6 men) aged 48–86 years who ‘survived’ the first year post LC diagnosis. Twenty-four had their LC staged (19 were diagnosed at stage IIIb–IV, and 5 people at ‘earlier’ stages) but all inoperable LC. Participants survived between 2 months to over 3 years after the interview.</td>
<td>Narrative analysis—deductive approach</td>
</tr>
<tr>
<td>Tod et al. (2007)</td>
<td>To identify factors influencing delay in reporting symptoms of LC</td>
<td>Retrospective</td>
<td>Semi-structured interviews. Questions were informed by the study of Corner et al. (2003).</td>
<td>Within 1 year after LC diagnosis of 6–18 months</td>
<td>20</td>
<td>Purposive sample of people diagnosed with LC in the previous 6 months or longer. 18 participants were diagnosed 6 months ago and 2 were 18-month survivors. 8 females and 12 males with age ranging from 47 to 81 years.</td>
<td>Framework analysis (Ritchie &amp; Spencer 1994)</td>
</tr>
<tr>
<td>Molassiotis et al. (2010)</td>
<td>To map the pathway from initial persistent change in health to diagnosis of cancer and explore the patient and system factors mediating this process</td>
<td>Retrospective accounts</td>
<td>In-depth interviews opened with broad question, asking patients’ to recall when they first became aware of a change in their health</td>
<td>In 2–3 weeks after initial cancer diagnosis and prior to or at initiation of treatment</td>
<td>75 cancer diagnosis; 14 (18.7%) LC diagnosis</td>
<td>In general, the sample characteristic represent patients from seven diagnostic groups, including LC (n = 14). Patients aged from 18 to 93 years (mean 58.5 years). Consecutive sample consisted of attendees of outpatient cancer clinics at a large centre hospital.</td>
<td>Content analysis—with frequency counts; descriptive analysis</td>
</tr>
</tbody>
</table>
prospective studies, limits the value of current evidence regarding the diagnostic value of symptoms for LC. Undoubtedly, a symptom profile specific to early stage of the disease would be useful as reduction in mortality is related to early stage LC diagnosis. However, beyond reporting the frequency of symptoms, very few studies explored and even fewer reported the severity or change in frequency of the symptoms that might occur over time. Hamilton et al. (8) reported episodes of cough with each subsequent clinic consultation suggesting persistence of the symptom but did not report severity or duration of symptoms as they were not recorded in most notes (personal communication). The level of reporting of the disease staging and histology also varied across the studies. Some studies provided more detail of the types of LC histology than others but none of the studies included in this review reported the stages of the disease (e.g. I-II, Ia-Ib or TNM). One study reported the percentage of LC cases with operable LC (12) but none of the quantitative studies distinguished between symptoms of operable and inoperable LC.

The qualitative studies report LC patients’ recollections of their symptom experience before LC diagnosis, with the potential for reinterpretation of symptoms in light of a diagnosis. These studies indicated that patients experienced bodily changes including systemic and non-systemic symptoms months before diagnosis. Although they reported the occurrence and interpretation of symptoms, the studies did not report the characteristics of symptoms experienced before LC diagnosis in any detail. These retrospective reports indicated that some symptoms were not interpreted as being serious or alarming enough to prompt help seeking and, therefore, were not presented to primary care clinicians until late. Furthermore, less severe and normalized symptoms might never be presented to primary care clinicians by consulting patients (24). This could possibly have implications for the symptoms recorded in the GP clinical notes. Therefore, primary care records-based studies might not provide predictive values of early symptoms not fully elicited by clinicians, or not thought serious enough by the GP/clinician to record. The literature also suggests that symptoms that might precede LC further complicated the process of recognizing new symptoms for both patients and clinicians, when there is a pre-existing co-morbidity such as COPD.

This is the first review to have included qualitative studies of the available evidence in symptomatic detection of LC. Although qualitative studies do not inform the diagnostic value of symptoms in LC, they provide information about participants’ interpretations of symptoms occurring before diagnosis that might inform the design of future prospective studies and methods of symptom data collection. For example, systematic methods of eliciting and recording symptoms are required in primary care studies. Furthermore, having recognized that patients could easily under-appraise the significance of symptoms, it is important that community-based prospective studies are designed to accurately record symptoms that patients do not interpret as serious or present to GPs/clinicians.

**Recommendation for future research**

At present, there is not enough evidence to suggest a signs-and-symptom profile for LC from the pool of study samples. Prospective studies that record symptoms systematically, and identify symptoms experienced at early stages of LC, are required in order to strengthen the evidence base for symptomatic diagnosis in LC. Future research might also explore the predictive values of changes in symptoms in those with pre-existing chronic respiratory disease, which is highly prevalent in LC patients.

**Supplementary material**

Supplementary material is available at Family Practice online.

**Declaration**

Funding: Faculty of Health Sciences, University of Southampton (PhD studentship to JS).

Ethical approval: The study does not require ethical approval.

Conflict of interest: All authors have no conflicts of interest to declare. We certify that there is no conflict of interest with any financial organization, individual authors’ commitments, editors or reviewers regarding the material discussed in the manuscript.

**References**


