Lung cancer in symptomatic patients presenting in primary care: a systematic review of risk prediction tools

INTRODUCTION
Lung cancer is the leading cause of cancer deaths, with an estimated 1.8 million new diagnoses worldwide and 1.6 million deaths each year (2012). In 2012, there were 449 000 new cases of lung cancer and 388 000 lung cancer deaths in the World Health Organization (WHO) Europe region. Lung cancer survival is different across countries, even when they have equally well-resourced healthcare systems. The UK and Denmark have the worst survival. Only 9.0% of people with a diagnosis of lung cancer in England survived for ≥5 years in 2005–2009, although this improved to 12.9% in 2010–2012. In Denmark, survival is marginally better. However, 5-year relative survival in Sweden and Canada exceeds 15%. Both England and Denmark have a primary care-based healthcare system where gatekeeper role may contribute to diagnostic delay. There is also evidence that some of this survival difference is explained by early deaths. This has led to a focus on early diagnosis to improve outcomes.

Lung cancer outcomes are so poor mainly because around 70% of patients first present to specialist care with advanced disease, at which point current treatment has little effect on survival. This applies across all age groups and in all countries. Curative treatments for lung cancer are only available for those with cancers diagnosed in the early stages. In England, the ‘Be Clear on Cancer’ campaign increased awareness of lung cancer symptoms and encouraged early presentation. The issue for primary care is how to approach the problem of recognising those most at risk. Merely doing more chest X-rays may not be the whole answer. One study showed that practices with higher use of chest X-rays identified more patients who died within 90 days. What is needed is a way to recognise at-risk patients earlier, and investigate appropriately. The latest National Institute for Health and Care Excellence (NICE) guidance attempts to do this by recommending chest X-ray for people aged >40 years with two warning symptoms, or a history of smoking and one warning symptom. Although this approach may help, it has been suggested that multivariate risk prediction tools may be more accurate and cost-effective.

The aim of this study was to conduct a systematic review of risk prediction tools for use in patients presenting in primary care with symptoms that may indicate lung cancer.
Lung cancer is the leading cause of cancer deaths, with most patients having advanced disease at diagnosis. It would be better to recognise at-risk patients earlier and investigate appropriately. In a systematic review of all existing risk prediction tools for patients presenting in primary care with symptoms of possible lung cancer, the authors found five promising tools. However, none of them has been fully validated or compared to each other.

Presently, there is insufficient evidence for the recommendation of any one of the available risk prediction tools.

**Box 1. Study methods**

**Criteria for considering studies for this review**
The target studies for inclusion were any studies (retrospective, prospective) reporting on risk prediction tools or clinical decision tools for use in patients presenting to primary care with symptoms that may indicate lung cancer. The authors defined such tools as analyses that examined the risk of lung cancer associated with one or more factors, such as smoking, family history, age, or comorbidity, in combination with one or more symptoms in patients presenting in primary care for whom follow-up data were available. Studies reporting on the risk of lung cancer associated with single symptoms were not included, and neither were studies on asymptomatic or non-presenting patients (for example, screening).

**Search methods for identification of studies**
The authors searched Medline, Premedline, Embase, the Cochrane Library, Web of Science (SCI & SSCI), and ISI Proceedings from 1980 to 7 March 2016 using the search strategy outlined in the Appendix. One of the authors performed the search and screened the initial search results, excluding all obviously irrelevant studies. A second author then screened the titles and abstracts of the remaining records, excluding irrelevant studies and examining the full text of all potentially relevant studies. The final lists of included and excluded studies were agreed in consensus between three of the authors.

**Data collection and analysis**
Data extraction and quality assessment of the included studies was performed by two authors. For each included study, the following characteristics were extracted:
- study design
- inclusion/exclusion criteria
- setting
- patient characteristics (number, age, sex, country, any other relevant characteristics reported, such as relevant history or comorbidities)
- definition of symptom(s)
- method of verification of diagnosis (outcome)
- predictor variables
- missing data handling
- presentation and availability of the tool
- details about validation and evaluation of the tool; and
- any other relevant details reported in the studies.

**RESULTS**
The search of all the databases identified 10 866 (before de-duplication) possibly relevant articles, with two further identified through contact with reviewers, of which 10 821 articles were excluded based on title/abstract, and 46 were obtained for full-text review. Seven studies reported in nine articles were included in this review,12–20 while 38 were excluded for the following reasons:

- review (n = 6);
- patients, setting, or outcomes did not meet the inclusion criteria (n =25);
- guideline (n = 2);
- letter (n =1);
- no original data (n =1); and
- because not enough information could be extracted to include the study/ascertain relevance (n = 3).

The studies were all conducted in the UK, using either the databases from all 21 general practices in Devon,13-15 the QResearch® database,16-18 The Health Improvement Network (THIN) database,12 or the General Practice Research Database,17,20 and were either case-control studies,12-15,21 or prospective16-18 or retrospective cohort studies.19 The sample sizes are shown in Table 1 with the number of cases ranging from 23920 to 12 074,12 and controls from 123513-18 to 2 402 342.14 Two of the studies only included patients aged ≥40 years,12-15 with another two studies including patients aged 25-89 years,17,18 while one study included each of the following ages: 30–84 years,16 15–100 years,19 and ≥50 years.20 Further study details are shown in Table 1, and Table 2 details the risk prediction tools reported by the studies. Further information on the studies is also available from the authors on request.

Although Hamilton et al included all patients with a lung cancer diagnosis in Exeter in the study period (except for 13 (5%) whose records could not be traced), the sample may not be wholly representative of the whole of the UK lung cancer patient population in terms of tumour pathological subtype, because the small-cell lung cancer rate in the study was double that in the UK as a whole (21% versus 10%).14,15 Histological confirmation was available for 237 of the 247 cases. Small-cell lung cancer is a more aggressive tumour and more likely to be associated with systemic manifestations and extensive disease at presentation. Moreover, the sample size (247 events) is likely to be inadequate, considering the high number of variables examined in univariate (n = 225) and multivariate (n = 97) analyses. In addition, data were not available for all of the patients: platelet count was available in 32% of controls and 52% of cases. This gave thrombocytosis rates of 4.8% and 26% for controls and cases, respectively. Ades et al performed further analyses on the tool data and found that ‘any two symptoms within 3 months’ was the most discriminating criterion (between cases and controls), with a sensitivity of 80.6%, and a false positive
Table 1. Characteristics of the included studies

<table>
<thead>
<tr>
<th>Predictor variables examined</th>
<th>Hamilton et al., 2009&lt;sup&gt;23–16&lt;/sup&gt;</th>
<th>Hippisley-Cox and Coupland, 2011&lt;sup&gt;14&lt;/sup&gt;</th>
<th>Hippisley-Cox and Coupland, 2013&lt;sup&gt;17,18&lt;/sup&gt;</th>
<th>Iyen-Omofoman et al., 2013&lt;sup&gt;12&lt;/sup&gt;</th>
<th>Jones et al., 2007&lt;sup&gt;19&lt;/sup&gt;</th>
<th>Jordan et al., 2013&lt;sup&gt;10&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictor variables in final tool</td>
<td>Haemoptysis, cough, fatigue, dyspnoea, chest pain, weight loss and appetite loss, thrombocytosis, and abnormal spirometry</td>
<td>Haemoptysis, appetite loss, weight loss, cough, anaemia, BMI, smoking status, chronic obstructive airways disease, Townsend deprivation score, previous diagnosis of cancer apart from lung cancer, previous diagnosis of cancer within the first year of follow up</td>
<td>A large number of symptoms of lung cancer and risk factors, including smoking, alcohol intake, age, BMI, haemoptysis, appetite loss, weight loss, cough, dyspnoea, tiredness, anaemia, abdominal pain, dysphagia, indigestion, neck lump, night sweats, venous thromboembolism, COPD</td>
<td>Age, sex, SES, smoking status, cough, haemoptysis, dyspnoea, chest/shoulder pain, weight loss, haemoptysis, URTI, LRTI, non-specific chest infections, constipation, depressive disorders, COPD, outcome of blood tests, and number of GP consultations. All recorded 4–12 and 13–24 months before lung cancer diagnosis</td>
<td>Age, sex, and haemoptysis</td>
<td>Age, sex, BMI, smoking status, drinking status, deprivation, and comorbidity, and musculoskeletal pain in the back, neck, shoulder, and hip</td>
</tr>
<tr>
<td>Missing data handling</td>
<td>Unclear, but no imputation appears to have been performed</td>
<td>Multiple imputation to replace missing values for smoking status and BMI</td>
<td>Multiple imputation to replace missing values for smoking status, alcohol status, and BMI</td>
<td>No imputation has been performed. Low levels of missing data</td>
<td>No imputation appears to have been performed. All patients appear to be accounted for</td>
<td>Unclear, but no imputation appear to have been performed</td>
</tr>
<tr>
<td>Tool development</td>
<td>Multivariate analysis with univariate pruning. Used PPVs as the risk measure</td>
<td>Cox regression analysis with univariate pruning, age used as the underlying time variable</td>
<td>Multinomial logistic regression with univariate pruning. Used RRs as the risk measure</td>
<td>Multivariate logistic regression with univariate pruning; used ORs as the risk measure</td>
<td>Calculation of PPVs for haemoptysis split by age group and sex</td>
<td>Cox proportional hazards regression analysis</td>
</tr>
<tr>
<td>Tool presentation</td>
<td>Tabular presentation of two tools (all patients, smokers) of the risks associated with single symptoms, repeat presentation of single symptoms, and symptom pairs. The PPVs ranged from 0.4% (cough, fatigue, both in all patients) to 17% (repeat presentation of haemoptysis in all patients)</td>
<td>Tabular presentation of two tools (males, females) with adjusted HRs for each predictor variable. The tools are also available on a website as a risk calculator</td>
<td>Tabular presentation of two tools (males, females) with adjusted HRs for each predictor variable. The tools are also available on a website as a risk calculator</td>
<td>As an equation with all the necessary β-coefficients for patients aged ≥40 years</td>
<td>Tabular format of adjusted HRs of musculoskeletal pain at the four locations. HRs were adjusted for age, sex, BMI, smoking status drinking status, deprivation, and comorbidity. Only back pain within the first year of follow up was associated with an increased risk of lung cancer (HR 1.67).</td>
<td>Tabular format of adjusted HRs of musculoskeletal pain at the four locations. HRs were adjusted for age, sex, BMI, smoking status drinking status, deprivation, and comorbidity. Only back pain within the first year of follow up was associated with an increased risk of lung cancer (HR 1.67).</td>
</tr>
</tbody>
</table>

... continued
<table>
<thead>
<tr>
<th>Tool availability</th>
<th>Underlying computer code, HRs adjusted for other variables associated with the tool</th>
<th>Underlying computer code, or all the numbers underlying the tool do not appear to be readily available</th>
<th>Fully available from the intercept</th>
<th>Internal</th>
<th>None</th>
<th>No</th>
<th>No</th>
<th>None</th>
<th>No</th>
<th>None</th>
<th>No</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact study</td>
<td></td>
<td></td>
<td>Before-and-after study</td>
<td>Internal</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>No</td>
<td>None</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

BMI = body mass index. COPD = chronic obstructive pulmonary disease. HR = hazard ratio. LRTI = lower respiratory tract infection. OR = odds ratio. PPV = positive predictive value. RR = risk ratio. SES = socio-economic status. URTI = upper respiratory tract infection.

Includes the number of cases (see a). Supplementary data available from the authors on request.

Not reported separately for development and validation cohorts, so this is the total for both cohorts.

Hamilton et al further reported that the GPs’ referral thresholds and decision making were affected to varying extent, with GPs reporting that they used the tool to support a referral decision already made, to urge a decision to refer that may otherwise not have been made, and to confirm a decision not to refer. Generally, using the tool seemed to lead to some change in practice and to be perceived positively, although not to override clinical judgement or supersede other guidance. Although these results are encouraging, they need to be replicated in an appropriate randomised controlled trial design, because the current study design precludes the assignment of causality, with time (or season) being a serious confounding variable in the qualitative comparisons of additional cancers diagnosed and their stages, because positive predictive values vary with season.

Green et al reported further qualitative results from a subgroup of the Hamilton study, showing that the majority of GPs reported finding the tool useful in consultations, heightening their awareness of potential cancer symptoms, reminding them of potential cancer risks, and affecting their referral thresholds, although not all of the participating GPs found the tool a valuable addition to their practice. Similar results were reported by Dikomitis et al: a qualitative study that examined 23 GPs’ experiences of using an electronic version of the tool (one for smokers and one for non-smokers) in addition to their practices’ clinical software package. The GPs in the study by Dikomitis et al reported that the tool raised their awareness of the potential for cancer as the cause of the symptoms, and that their referral rates were affected to varying degrees, but the authors of the study undertook no quantitative measurements of actual impact; for example, referral rates, new cancers diagnosed, or stage of new cancers diagnosed.

The sample used in the Hippisley-Cox and Coupland studies, drawn from the QResearch database, appears to be representative of the UK primary care population, and the sample sizes also appear to be adequate for the evaluation of the original variables in the tools. In separate, non-overlapping samples from the QResearch database, randomly chosen for the validation cohort, the authors undertook internal validation of the tools and found excellent discrimination between new cases of lung cancer and non-cases (area under the curves [AUCs] = 0.91 to 0.92), with one of the studies reporting a highest sensitivity of 77.3% found in the top 10% risk score group (relative to the top 5%, 1%, and 0.5%, with sensitivities of 62.7%, 36.2%, and 27.4%, respectively). The other two studies reported sensitivities, specificities, positive predictive values, and negative predictive values in the top 10% risk groups of 72.1%, 90.1%, 1.2%, and 99.9%, respectively, in females, and of 71.5%, 90.2%, 1.9%, and 99.9%, respectively, in males. Calibration was assessed by comparing observed versus mean predicted risk within each tenth of predicted risk over 2 years, while taking account of competing risks in the calculation of observed risks. This assessment showed excellent calibration overall for two of the tools, which was also the case for the other two tools at the lower risk levels, but as the risk increased these tools began to increasingly overestimate the expected risk, especially in males.

Including all incident cases of lung cancer in the study period in patients aged ≥40 years along with 10 randomly selected matched controls ensures that the sample used by Øyen-Omoforan et al is representative of the general UK primary care population, and that the sample size is adequate (12 074 events with 18 predictor variables analysed at two time intervals). However, it should be noted, as Tammemägi also points out, that the intercept of the tool presented, due to the case-control design, reflects the proportion of cases sampled and not the general population proportion of disease. However, the population studied represented more than 15% of the total English population so it is unlikely that this is a significant source of error. A unique aspect of this study was that the model was developed using data from between 12 and 4 months prior to diagnosis. This was done to avoid ascertainment bias. The authors noted that at 4 months the chest X-ray rate rose in lung cancer cases compared with controls, indicating that this is when GPs suspect cancer, and is the time when
Table 2. The adjusted hazard ratios, odds ratios, risk ratios, and positive predictive values of the final tools of the included studies

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Hippisley-Cox and Coupland&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Hippisley-Cox and Coupland&lt;sup&gt;a&lt;/sup&gt;</th>
<th>lyen-Omofoman et al&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Jones et al&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Jordan et al&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td>One tool for smokers and non-smokers each</td>
<td>Increasing from 1/1 for non-smokers up to 10.6/6.35 for current smokers</td>
<td>Increasing from 1/1 for non-smokers up to 12/6.61 for heavy smokers</td>
<td>Increasing from 1 for non-smokers up to 15.91 for current heavy smokers</td>
<td>Not in tools</td>
</tr>
<tr>
<td>Townsend deprivation score</td>
<td>Not in tools</td>
<td>1.17/1.17 per unit increase</td>
<td>1.04/1.03</td>
<td>Not in tools</td>
<td>HRs were adjusted for smoking</td>
</tr>
<tr>
<td>Age</td>
<td>Not in tools</td>
<td>Included in tools as underlying time function</td>
<td>All the RRs are adjusted for age (and BMI)</td>
<td>Increasing from 1 at age 40–45, up to 65.55 at age &gt;80 years</td>
<td>Different PPVs for each decade starting from &lt;45 to &gt;85 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Not in tools</td>
<td>One tool for each sex</td>
<td>One tool for each sex</td>
<td>One tool for each sex relative to females</td>
<td>One tool for each sex</td>
</tr>
<tr>
<td>Cough</td>
<td>0.9/0.4</td>
<td>1.90/1.47</td>
<td>1.90/1.67</td>
<td>1.63</td>
<td>Not in tools</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>4.5/4.4</td>
<td>23.9/21.5</td>
<td>18.7/16.8</td>
<td>8.7</td>
<td>4.3/7.9</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2.1/1.1</td>
<td>4.5/2/6.09</td>
<td>3.12/3.95</td>
<td>2.66</td>
<td>Not in tools</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.8/0.4</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tool</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>1.8/0.9</td>
<td>4.1/4.71</td>
<td>2.05/2.11</td>
<td>Not in tool</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>1.2/0.7</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>1.41</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Abnormal spirometry</td>
<td>4.0/1.6</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tool</td>
<td>Not in tool</td>
</tr>
<tr>
<td>LRTI</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>1.56</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Chest infection</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>1.55</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Chest/shoulder pain</td>
<td>1.3/0.8</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>1.39</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Back pain</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tool</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Voice hoarseness</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>1.79</td>
<td>Not in tool</td>
</tr>
<tr>
<td>URTI</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>1.15</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tool</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tool</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Indigestion</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tool</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Neck lump</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>1.35/0.02</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tool</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Night sweats</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tool</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>2.4/2.22</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>4.2/1.6</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>1.61</td>
<td>Not in tool</td>
</tr>
<tr>
<td>COPD</td>
<td>Not in tools</td>
<td>1.82/1.51</td>
<td>2.21/1.74</td>
<td>Not in tool</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Prior cancer diagnosis, except lung cancer</td>
<td>Not in tools</td>
<td>1.33/Not in tool</td>
<td>Not in tool</td>
<td>Not in tool</td>
<td>Not in tool</td>
</tr>
<tr>
<td>Number of GP consultations</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Not in tools</td>
<td>Increasing from 1.00 at 0–10 consultations to 1.23 and 1.36 for 11–20 and ≥21 consultations, respectively</td>
<td>Not in tool</td>
</tr>
</tbody>
</table>

BMI = body mass index. COPD = chronic obstructive pulmonary disease. HR = hazard ratio. LRTI = lower respiratory tract infection. OR = odds ratio. PPV = positive predictive value. RR = risk ratio. URTI = upper respiratory tract infection. a The Hamilton et al. tools also consist of positive predictive values for symptom combinations. Please see the original study for these. b These are the overall PPVs at 3 years after first presentation. The tools also consist of PPVs for 6 months after first presentation and PPVs for each of the following age groups at 3 years after first presentation: <45 years, 45–54 years, 55–64 years, 65–74 years, 75–84 years, and ≥85 years. Please see the original study for these. c This value is at 1-year follow-up.
there may be ascertainment bias in that symptoms are preferentially recorded in cases.

Iyen-Omofoman et al also assessed the tool’s performance in a validation cohort, also from the THIN database, consisting of 1826 293 patients with a total of 1728 incident cases of lung cancer during the 1-year follow up, and reported a maximum tool sensitivity of 93.98% at a cut-off value of –3, with an accompanying specificity of 59.67%. Discrimination of the tool, as assessed by receiver operating characteristic (ROC) curve and AUC analysis, was shown to be excellent, with AUC 0.88, but no calibration of the tool was reported.12

Although the sample in Jones et al can be considered to be representative of the UK primary care population, and the sample size is adequate relative to the number of predictors examined, the tool does not take account of a number of other confounding variables, most notably smoking.19 Any tool not taking into account the effect of smoking on lung cancer risk is of limited utility for the practising GP considering the risk of lung cancer in a symptomatic patient.

The sample used by Jordan et al can be considered to be representative of the general population presenting to general practice in the UK. However, the study is underpowered, especially for neck, shoulder, and hip pain.20 Moreover, the utility of the tool for the practising GP is limited due to the non-reporting of the actual effects of the adjusting variables, which is also impossible to assess by independent investigators.

Finally, it should be noted that all database studies using routinely collected consultation data underreport symptoms: some symptoms are unvoiced, some are unrecorded, and some are recorded in irretrievable form. The latter may give rise to biased estimates, as GPs appear to record data preferentially in retrievable form when the patient has cancer.25 It is important that ascertainment bias is avoided when such tools are used because this does not reflect the way in which they were developed. The Iyen-Omofoman study design minimises this effect.

DISCUSSION

Summary

The authors identified five risk prediction tools developed for primary care in patients presenting with symptoms that may indicate lung cancer. The studies were all based on UK primary care data, but differed in complexity of development, in the number and type of variables examined and included, and in their outcome time frame, which varied from lung cancer diagnosis within 1 year to diagnosis within 6–10 years, although the majority of the studies aimed to predict lung cancer within 1–2 years. The tools were all subject to a number of limitations that compromise their results to varying degrees, such as representativeness of sample,13–15 power,13–15,20 availability of data underlying the tools,12,14–18,20 and the inclusion of important confounders, such as smoking.19 Moreover, only few of the studies clearly reported how they handled missing data,16–18 although this quality criterion was arguably not applicable to one of the other studies given the nature of their only three predictors.19

To date, none of the tools have been externally validated, which is a critical criterion that must be met on the way towards their widespread implementation in general practice, and only four of them have been internally validated.12,14–16,18 This internal validation showed excellent discrimination between new lung cancer cases and non-cases by the tools, but also that some of the Hippisley-Cox and Coupland tools tended to overestimate risk of lung cancer at the higher risk levels.14 Iyen-Omofoman et al did not report calibration results for their tool, so it is unclear how well lung cancer risk predicted by the tool corresponds to the observed risk in their internal validation cohort.

Similarly, the clinical and cost-effectiveness of the different tools in general practice have yet to be evaluated in appropriately designed randomised controlled trials, as none of them have so far been thus examined. However, one study22 was found that suggests that the Hamilton tool14,15 is promising in terms of increasing the number of new lung cancers diagnosed at an early, potentially curative stage, although, as already mentioned, these results await replication in a more robust study design.

Strengths and limitations

This systematic review was conducted in accordance with the best practice methods as outlined by the Cochrane Collaboration. Moreover, the authors aimed to be very inclusive and therefore included both simple and complex tools, although they did not search for grey or unpublished literature. The study may therefore be at risk of publication bias. However, the authors believe this risk to be negligible as any large, properly conducted relevant study is likely to have been published because of

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Competing interests
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the number of variables and type of analysis typically seen in such studies.

Implications for research and practice
Although there are limitations in the tools reviewed, in particular the lack of external validation and evaluation in clinical practice, there is a pressing need to improve early diagnosis of lung cancer to improve mortality. Four of the multivariate tools are, not unexpectedly, somewhat similar in terms of the risk factors and their relative contribution to the overall risk (Table 2). Thus, although tools can be refined, there is sufficient merit to proceed with evaluation owing to their promising discrimination. Future evaluation of the latest NICE guidelines on recognition and referral of lung cancer in primary care, which used data from the included tools, may provide some such information for some of the tools. Moreover, the Hamilton tool is currently being evaluated in an implementation project supported by Macmillan. The QCancer® tools are available and being used in some practices. There is, however, no prospect with this approach to determine which tool is best at bringing forward the diagnosis. A tool such as that described by Iyen-Omofoman, based on factors recorded up to 4 months prior to diagnosis may be more accurate in this regard, because the data on which it is based are unlikely to be influenced by ascertainment bias. However, this tool is not currently being used or evaluated to see if it has any effect on the point at which a diagnosis is made. What is needed to guide clinical practice is a comparative study so that the best tools can be incorporated into clinical decision tools used in primary care. At present, the evidence is therefore not at a stage where any one of the available lung cancer risk prediction tools can be clearly recommended above and beyond the others.
REFERENCES


Appendix. Medline search strategy

This search strategy is adapted to each database.
1. exp Primary Health Care/.
2. exp Physician's Practice Patterns/.
3. exp Family Practice/.
4. exp Physicians, Primary Care/.
5. exp General Practice/.
6. exp Physicians, Family/.
7. exp General Practitioners/.
8. exp Ambulatory Care Facilities/.
9. exp Community Health Centers/.
10. exp Outpatient Clinics, Hospital/.
11. GUM clinic*.tw.
12. exp Ambulatory Care/.
13. casualty*.tw.
14. exp "Referral and Consultation/".
15. [primary or community?] adj5 care.l.t.
16. family pract* or family doctor* or family physician* or gp* or general practi*.l.t.
17. or/1–16
18. [suspect* or cancer* or carcinogenesis or tumour* or tumor* or lymphoma* or blastoma* or microcytic* chrondosarcoma* or sarcoma* or teratoma* or adenocarcinoma* or angiosarcoma* or bronchus* or lung* or pancreas* or colon* or rectum* or stomach* or prostate* or bladder* or ovary* or testis* or ovary* or breast* or thyroid* or breast* or uterus* or ovary* or cervix* or vulva* or penis* or lower limb* or arm* or neck] exp Cancer/.
19. or/20–33
20. (risk* adj cancer*).tw.
21. (interval adj5 (cancer* or neoplas* or carcinogen* or tumour* or tumor*)).tw.
22. (delay* diagnos* adj5 (cancer* or neoplas* or carcinogen* or tumour* or tumor*).tw.
23. (missed diagnos* adj5 (cancer* or neoplas* or carcinogen* or tumour* or tumor*)).tw.
24. (early diagnos* adj5 (cancer* or neoplas* or carcinogen* or tumour* or tumor*)).tw.
25. (initial investigat* adj5 (cancer* or neoplas* or carcinogen* or tumour* or tumor*)).tw.
26. (initial assess* adj5 (cancer* or neoplas* or carcinogen* or tumour* or tumor*)).tw.
27. or/17–26
28. family pract* or family doctor* or family physician* or gp* or general practi*.l.t.
29. or/11–16
30. exp Lung Neoplasms/
31. or/27–30
32. or/17–33
33. (NSCL or SCLC).tw.
34. (interval adj5 (cancer* or neoplas* or carcinogen* or tumour* or tumor*)).tw.
35. (delay* diagnos* adj5 (cancer* or neoplas* or carcinogen* or tumour* or tumor*)).tw.
36. (missed diagnos* adj5 (cancer* or neoplas* or carcinogen* or tumour* or tumor*)).tw.
37. (early diagnos* adj5 (cancer* or neoplas* or carcinogen* or tumour* or tumor*)).tw.
38. (initial investigat* adj5 (cancer* or neoplas* or carcinogen* or tumour* or tumor*)).tw.
39. (initial assess* adj5 (cancer* or neoplas* or carcinogen* or tumour* or tumor*)).tw.
40. exp Pulmonary Disease/
41. exp Respiratory System/
42. exp Respiratory Sounds/
43. (breathless* or short*.l.t. or stridor or crack* or rale*).tw.
44. exp Hemoptysis/
45. (hemoptysis* or haemoptysis*).tw.
46. exp Shoulder Pain/
47. (shoulder* adj2 pain*).tw.
48. exp Pancoast Syndrome/
49. exp Pancoast.tw.
50. (fingers* adj clubbing or drumstick finger* or hypertrophic osteopathy).tw.
51. exp Pleural Effusion/
52. (pleural adj effusion*).tw.
53. (persistent or recurrent) adj chest infection*.tw.
54. exp Dizziness/
55. (dizziness or dizzyness or light headed* or lighthead* or thostasis).tw.
56. exp Abdominal Pain/
57. (abdominal or abdomen) adj pain*.tw.
58. exp Hematuria/
59. (hematuria* or haematuria*).tw.
60. (blood adj urine*).tw.
61. exp Confusion/
62. (confus* or disorder*).tw.
63. exp Urinary Tract Infections/
64. (urin* adj infection*).tw.
65. exp Fatigue/
66. (fatig* or tired* or exhaust* or letharg* or langua* or lassitude or listless*).tw.
67. exp Lower Urinary Tract Symptoms/
68. (frequent* or urgency* or cystiti*).tw.
69. (pain adj liver*).tw.
70. (pelvic adj mass*).tw.
71. (loin adj pain*).tw.
72. (frequen* or urgency* or cystiti*).tw.
73. (radiculitis or (radicular adj pain*).tw.
74. (confus* or disorient*).tw.
75. (personal adj (change* or disturbance*).tw.
76. (headache* or imbalance* or seizure*).tw.
77. exp Jaundice/
78. (enlarged adj liver*).tw.
79. (walking adj impair*).tw.
80. (bone* or skeletal) adj (pain* or fracture*).tw.
81. (upper limb* or arm*1) adj swelling.tw.
82. (lower limb* or arm*1 or neck) adj distended vein*.tw.
83. (flower limb* or leg*1) adj paraplegia.tw.
84. (upper limb* or arm*1 or neck) adj swelling.tw.
85. (bone* or skeletal) adj (pain* or fracture*).tw.
86. (primary or community?) adj5 care.l.t.
87. abdomin* mass*.tw.
88. (blood adj clot*).tw.
89. cramp*.tw.
90. spasm*.tw.
91. growth*.tw.
92. night sweat*.tw.
93. exp Sweating/
94. fever*.tw.
95. exp Fever/
96. (dull adj pain*).tw.
97. abdomin* mass*.tw.
98. abdomin* distention*.tw.
99. exp Vomiting/
100. (vomit* or nause*).tw.
101. exp Urinary Incontinence/ or Fecal Incontinence/
102. exp Incontinence*.	w.
103. exp Constipation/.
104. constipat* tw.
105. (fistula adj pain*).tw.
106. (eruct* adj pain*).tw.
107. (grom* adj pain*).tw.
108. exp Varicocoele/
109. varicocoele*.tw.
110. exp Liver Function Tests/.
111. (jaundice adj3 loss*).tw.
112. exp Lymphadenopathies/.tw.
113. (chest adj2 pain*).tw.
114. (rib* adj pain*).tw.
115. (thorac* adj pain*).tw.
116. exp Trigeminal Neuralgia/
117. exp Dizziness/
118. (pleurisy or pleuritis).tw.
119. (rheumatic or painful).tw.
120. (face or facial or neck) adj (pain* or swelling or dilation or flushing).tw.
121. (cervical or supraclavicular) adj adrenopathy.tw.
122. (upper limb* or arm*1) adj swelling.tw.
123. (upper limb* or arm*1 or neck) adj distended vein*.tw.
124. (flower limb* or leg*1) adj paraplegia.tw.
125. (muscle* or muscular) adj (paraplegias or weakness*).tw.
126. (spine or spinal) adj [paraplegias or weakness or tenderness or pain*].tw.
127. (bone* or skeletal) adj (pain* or fracture*).tw.
128. exp Tachypnea/
129. exp Tachypnea/
130. exp Bronchial Asthma/
131. exp Jaundice/.
132. exp Jaundice/.
133. (headache* or imbalance* or seizure*).tw.
134. (visual adj disturbance*).tw.
135. exp Sensation Disorders/
136. exp Hypersomnolence/
137. exp Hypersomnolence/
138. exp Hypersomnolence/
139. exp Hypersomnolence/
140. exp Hypersomnolence/
141. exp Hypersomnolence/
142. exp Hypersomnolence/
143. exp Hypersomnolence/
144. exp Hypersomnolence/
145. exp Hypersomnolence/
146. exp Hypersomnolence/
147. exp Hypersomnolence/
148. exp Hypersomnolence/
149. exp Hypersomnolence/
150. exp Hypersomnolence/