Mia Schmidt-Hansen, Sabine Berendse, Willie Hamilton and David R Baldwin

Lung cancer in symptomatic patients presenting in primary care:

a systematic review of risk prediction tools

Abstract

Background
Lung cancer is the leading cause of cancer deaths. Around 70% of patients first presenting to specialist care have advanced disease, at which point current treatments have little effect on survival. The issue for primary care is how to recognise patients earlier and investigate appropriately. This requires an assessment of the risk of lung cancer.

Aim
The aim of this study was to systematically review the existing risk prediction tools for patients presenting in primary care with symptoms that may indicate lung cancer

Design and setting
Systematic review of primary care data.

Method
Medline, PreMedline, Embase, the Cochrane Library, Web of Science, and ISI Proceedings (1980 to March 2016) were searched. The final list of included studies was agreed between two of the authors, who also appraised and summarised them.

Results
Seven studies with between 1482 and 2 406 127 patients were included. The tools were all based on UK primary care data, but differed in complexity of development, number/type of variables examined/included, and outcome time frame. There were four multivariable tools with internal validation area under the curves between 0.88 and 0.92. The tools all had a number of limitations, and none have been externally validated, or had their clinical and cost impact examined.

Conclusion
There is insufficient evidence for the recommendation of any one of the available risk prediction tools. However, some multivariable tools showed promising discrimination. What is needed to guide clinical practice is both external validation of the existing tools and a comparative study, so that the best tools can be incorporated into clinical decision tools used in primary care.

Keywords
clinical decision tool; diagnosis; lung neoplasms; primary health care; risk prediction; symptoms.

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).[1] 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.[2] In Denmark, survival is marginally better. However, 5-year relative survival in Sweden and Canada exceeds 15%.[3,4] Both England and Denmark have a primary care-based healthcare system whose gatekeeper role may contribute to diagnostic delay.[5] 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.[6–8]

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 mortality. 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.[9] 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.[10] 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.[11] Although this approach may help, it has been suggested that multivariate risk prediction tools may be more accurate and cost-effective.[12]

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. Throughout this article, the authors refer to models when considering the multivariate equations and their performance characteristics, and tools when considering the format aimed at clinical usage.

METHOD

The study was conducted in accordance with the methods outlined by the Cochrane Collaboration (Box 1).

M Schmidt-Hansen, PhD, systematic reviewer; **S Berendse**, MA, information specialist, National Guideline Alliance, The Royal College of Obstetricians and Gynaecologists, London. **W Hamilton**, MD, professor of primary care diagnostics, University of Exeter, Exeter. **DR Baldwin**, MD, professor, consultant physician Respiratory Medicine Unit, David Evans Centre, Nottingham University Hospitals, Nottingham.

Address for correspondence
Mia Schmidt-Hansen, National Guideline Alliance, The Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG, UK.

E-mail: SchmidtHansenM1@cf.ac.uk

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How this fits in

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.

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,[19,20] and were either case-control studies,[12–15,20] or prospective[16–18] or retrospective cohort studies.[19] The sample sizes are shown in Table 1 with the number of cases ranging from 239[20] to 12 074,[12] and controls from 1235[13,15] to 2 402 342.[16] 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

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.

Table 1. Characteristics of the included studies

	Hamilton *et al*, 2005[13–15]	Hippisley-Cox and Coupland, 2011[16]	Hippisley-Cox and Coupland, 2013[17,18] *Tool for women/men*	Iyen-Omofoman *et al*, 2013[12]	Jones *et al*, 2007[19]	Jordan *et al*, 2013[20]
Outcome	Lung cancer risk within 2 years	Lung cancer risk within 2 years	Lung cancer risk within 2 years	Lung cancer risk within 4–12 months	Lung cancer risk within 3 years	Lung cancer risk within 0–1, 2–5, and 6–10 years
Cases	247	3785	2043[a]/3351[a]	12 074	301	239
Controls	1235	2 402 342	1 240 864[b]/1 263 071[b]	120 731	4511	17 451
Predictor variables examined	All symptoms, physical signs, and investigation results from the primary care records recorded in the 2 years prior to the cases' lung cancer diagnosis. Entered into the analyses if they occurred in ≥2.5% of cases or controls	Haemoptysis, appetite loss, weight loss, cough, dyspnoea, tiredness, hoarseness, BMI, smoking status, chronic obstructive airways disease, Townsend deprivation score, family history of lung cancer, previous diagnosis of cancer apart from lung cancer, asthma, pneumonia, asbestos exposure, and anaemia	A large number of symptoms of any 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[c]	Age, sex, SES, smoking status, cough, haemoptysis, dyspnoea, chest/shoulder pain, weight loss, hoarseness, 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 diagnosis	Age, sex, and haemoptysis	Age, sex, BMI, smoking status, drinking status, deprivation, and comorbidity, and musculoskeletal pain in the back, neck, shoulder, and hip
Predictor variables in final tool	Haemoptysis, cough, fatigue, dyspnoea, chest pain, weight loss and appetite loss, thrombocytosis, and abnormal spirometry	Haemoptysis, appetite loss, weight loss, cough, anaemia, BMI, smoking status, chronic, obstructive airways disease, Townsend deprivation score, and previous diagnosis of cancer apart from lung cancer (the latter was only included in the tool for females)	In both tools: haemoptysis, appetite loss, weight loss, cough, anaemia, dysphagia, indigestion, neck lump, venous thromboembolism, COPD, smoking status, Townsend deprivation score. In tool for males only: abdominal pain, night sweats	Age, sex, SES, smoking status, cough, weight loss, haemoptysis, chest/shoulder pain, dyspnoea, hoarseness, URTI, LRTI, non-specific chest infections, COPD, and number of GP consultations. Recorded 4–12 months before lung cancer diagnosis	Age, sex, and haemoptysis	Age, sex, BMI, smoking status, drinking status, deprivation, and comorbidity, and musculoskeletal pain in the back, neck, shoulder, and hip
Missing data handling	Unclear, but no imputation appears to have been performed	Multiple imputation to replace missing values for smoking status and BMI	Multiple imputation to replace missing values for smoking status, alcohol status, and BMI	No imputation has been performed. Low levels of missing data	No imputation appears to have been performed. All patients appear to be accounted for	Unclear, but no imputation appear to have been performed
Tool development	Multivariate analysis with univariate pruning. Used PPVs as the risk measure	Cox regression analysis with univariate pruning, age used as the underlying time variable	Multinomial logistic regression. Used RRs as the risk measure	Multivariate logistic regression with univariate pruning; used ORs as the risk measure	Calculation of PPVs for haemoptysis split by age group and sex	Cox proportional hazards regression analysis
Tool presentation	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)	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	Tabular presentation of two tools (males, females) with adjusted RRs for each predictor variable. The tools are also available on a website as a risk calculator	As an equation with all the necessary β-coefficients for patients aged ≥40 years	Tabular format with the PPVs for haemoptysis split by age group and sex. These risk measures varied from 0.21% (in males aged <45 years) to 20.43% (in males aged ≥85 years)	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).

... continued

Table 1 continued. Characteristics of the included studies

Tool availability	Fully available	Underlying computer code, or all the numbers underlying the tool do not appear to be readily available	Underlying computer code, or all the numbers underlying the tool do not appear to be readily available	Fully available, apart from the intercept	Fully available	HRs adjusted for other variables associated with risk of lung cancer, but their individual effects not reported
Validation	None	Internal	Internal	Internal	None	None
Impact study	Before-and-after study	No	No	No	No	No

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. [a]Not reported separately for development and validation cohorts, so this is the total for both cohorts. [b]Includes the number of cases (see [a]). [c]Supplementary data available from the authors on request.

rate of 23.2%. However, beyond these analyses the tool has not been internally or externally validated.[13]

Despite the lack of validation, the impact of the tool has been examined in a before-and-after study investigating the utility and acceptability of the tool (which along with another tool for colorectal cancer was displayed on mousemats and desktop flipcharts) in 614 GPs.[21] The study found that new lung cancer diagnoses increased from 127 (in the 6 months preceding the use of the tool) to 174 during the study, and that stage I–II cancers increased from 26 to 31 during the same time period. 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.[21] 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 quantitative 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,[21] 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.[22] 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.[23] 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,[16–18] 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),[16–18] 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).[16] 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,[18] and of 71.5%, 90.2%, 1.9%, and 99.9%, respectively, in males.[17] Calibration was assessed by comparing observed versus mean predicted risk within each tenth of predicted risk over 2 years,[16–18] while taking account of competing risks in the calculation of observed risks.[16] This assessment showed excellent calibration overall for two of the tools,[17,18] 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.[16]

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 Iyen-Omofoman *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).[12] 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'.[24] 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

	Hamilton *et al*[13–15]	Hippisley-Cox and Coupland[16]	Hippisley-Cox and Coupland[17,18]	Iyen-Omofoman *et al*[12]	Jones *et al*[19]	Jordan *et al*[20]
Covariate	**PPVs Smokers/ non-smokers[a]**	**Adjusted HRs Females/ males**	**Adjusted RRs Females/males**	**Adjusted ORs Females and males**	**PPVs Females/males**	**Adjusted HRs Females and males**
Smoking status	One tool for smokers and non-smokers each	Increasing from 1/1 for non-smokers up to 10.6/6.35 for current smokers	Increasing from 1/1 for non-smokers up to 12/6.61 for heavy smokers	Increasing from 1 for non-smokers up to 15.91 for current heavy smokers	Not in tools	HRs were adjusted for smoking
Townsend deprivation score	Not in tools	1.17/1.17 per unit increase	1.04/1.03	Increasing from 1.00 at scores 1 and 2, up to 1.07, 1.12, and 1.1 at scores 3, 4 and 5, respectively.	Not in tools	HRs were adjusted for deprivation
Age	Not in tools	Included in tools as underlying time function	All the RRs are adjusted for age (and BMI)	Increasing from 1 at age 40–45, up to 65.55 at age >80 years	Different PPVs for each decade starting from <45 to ≥85 years	HRs were adjusted for age
Sex	Not in tools	One tool for each sex	One tool for each sex	1.62 for males relative to females	One tool for each sex	HRs were adjusted for sex
Cough	0.9/0.4	1.90/1.47	1.90/1.67	1.63	Not in tools	Not in tool
Haemoptysis	4.5/2.4	23.9/21.5	18.7/16.8	8.7	4.3/7.5[b]	Not in tool
Weight loss	2.1/1.1	4.52/6.09	3.12/3.95	2.66	Not in tools	Not in tool
Fatigue	0.8/0.4	Not in tools	Not in tools	Not in tool	Not in tools	Not in tool
Appetite loss	1.8/0.9	4.14/4.71	2.05/2.11	Not in tool	Not in tools	Not in tool
Dyspnoea	1.2/0.7	Not in tools	Not in tools	1.41	Not in tools	Not in tool
Abnormal spirometry	4.0/1.6	Not in tools	Not in tools	Not in tool	Not in tools	Not in tool
LRTI	Not in tools	Not in tools	Not in tools	1.56	Not in tools	Not in tool
Chest infection	Not in tools	Not in tools	Not in tools	1.55	Not in tools	Not in tool
Chest/shoulder pain	1.3/0.8	Not in tools	Not in tools	1.39	Not in tools	Not in tool
Back pain	Not in tools	Not in tools	Not in tools	Not in tool	Not in tools	1.67[c]
Voice hoarseness	Not in tools	Not in tools	Not in tools	1.79	Not in tools	Not in tool
URTI	Not in tools	Not in tools	Not in tools	1.15	Not in tools	Not in tool
Anaemia	Not in tools	1.75/1.89	2.37/2.28	Not in tool	Not in tools	Not in tool
Dysphagia	Not in tools	Not in tools	1.96/2.83	Not in tool	Not in tools	Not in tool
Indigestion	Not in tools	Not in tools	1.44/1.31	Not in tool	Not in tools	Not in tool
Neck lump	Not in tools	Not in tools	3.35/3.02	Not in tool	Not in tools	Not in tool
Abdominal pain	Not in tools	Not in tools	Not in tool/1.49	Not in tool	Not in tools	Not in tool
Night sweats	Not in tools	Not in tools	Not in tool/2.20	Not in tool	Not in tools	Not in tool
Venous thromboembolism	Not in tools	Not in tools	2.44/2.22	Not in tool	Not in tools	Not in tool
Thrombocytosis	4.2/1.6	Not in tools	Not in tools	Not in tools	Not in tools	Not in tool
COPD	Not in tools	1.82/1.51	2.21/1.74	1.61	Not in tools	Not in tool
Prior cancer diagnosis, except lung cancer	Not in tools	1.33/not in tool	Not in tools	Not in tool	Not in tools	Not in tool
Number of GP consultations	Not in tools	Not in tools	Not in tools	Increasing from 1.00 at 0–10 consultations to 1.23 and 1.36 for 11–20 and ≥21 consultations, respectively	Not in tools	Not in tool

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 1 826 293 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,[12,16–18,20] 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.[12,16–18] 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.[16] 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 study[21] was found that suggests that the Hamilton tool[14,15] 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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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).[12,16–18] 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,[11] 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[16–18] 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.

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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 communit*) adj5 care).ti,ab.
16. (family practi* or family doctor* or family physician* or gp*1 or general practi*).ti,ab.
17. or/1–16
18. (suspect* adj5 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
19. (early adj5 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
20. (risk* adj cancer*).tw.
21. (initial assess* adj5 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
22. (initial investigat* adj5 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
23. (early diagnos* adj5 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
24. (missed diagnos* adj5 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
25. (delay* diagnos* adj5 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
26. (symptomat* adj5 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
27. or/18–26
28. 17 or 27
29. exp Lung Neoplasms/
30 (lung adj (neoplas* or cancer* or carcinoma* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcinogenesis or tumour* or tumor* or metast*)).tw.
31. (NSCL or SCLC).tw.
32. or/29–31
33. 28 and 32
34. exp "Signs and Symptoms"/
35. Cough/
36. cough*.tw.
37. Dyspnea/
38. (dyspn?ea* or (short* adj3 breath)).tw.
39. breathless*.tw.
40. Hoarseness/
41. hoarse*.tw.
42. Respiratory Sounds/
43. (wheez* or ronch* or stridor or crackl* or rale*).tw.
44. Hemoptysis/
45. (hemopty* or haemopty*).tw.
46. Shoulder Pain/
47. (shoulder* adj2 pain*).tw.
48. Pancoast Syndrome/
49. pancoast.tw.
50. ((finger* adj clubbing) or drumstick finger* or hypertrophic osteopathy).tw.
51. Pleural Effusion/
52. (pleural adj effusion*).tw.
53. ((persistent or recurrent) adj chest infection*).tw.
54. Dizziness/
55. (dizziness or dizzyness or light headed* or lightheaded* 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 disorient*).tw.
63. exp Urinary Tract Infections/
64. (urin* adj infection*).tw.
65. exp Fatigue/
66. (fatig* or tired* or exhaust* or letharg* or langui* or lassitude or listless*).tw.
67. exp Lower Urinary Tract Symptoms/
68. (frequen* or urgen* or cystiti*).tw.
69. (loin adj pain*).tw.
70. (pelvic adj mass*).tw.
71. (pelvic adj pain*).tw.
72. exp Weight Loss/
73. (weight adj los*).tw.
74. exp Anemia/
75. (iron deficien* or anaemi* or anemi*).tw.
76. exp Hypercalcemia/
77. (hypercalcaemia* or hypercalcemia*).tw.
78. (inflammat* adj marker*).tw.
79. exp Thrombocytosis/
80. (high platelet* adj (count* or level*)).tw.
81. thrombo*.tw.
82. Thromboembolism/
83. Venous Thrombosis/
84. (blood adj clot*).tw.
85. exp Dysuria/
86. (dysuria* or burning* or stinging* or painful urin*).tw.
87. lump*.tw.
88. spasm*.tw.
89. cramp*.tw.
90. growth*.tw.
91. exp Sweating/
92. night sweat*.tw.
93. exp Fever/
94. fever*.tw.
95. (high adj temperature*).tw.
96. (dull adj pain*).tw.
97. abdomin* mass*.tw.
98. abdomin* distention*.tw.
99. exp Vomiting/
100. (vomit* or nause*).tw.
101. Urinary Incontinence/ or Fecal Incontinence/
102. incontinen*.tw.
103. exp Constipation/
104. constipat*.tw.
105. (flank adj pain*).tw.
106. (scrot* adj pain*).tw.
107. (groin* adj2 pain*).tw.
108. exp Varicocele/
109. varicocoele*.tw.
110. exp Liver Function Tests/
111. (appetite adj3 loss*).tw.
112. lymphadenopath*.tw.
113. (chest adj2 pain*).tw.
114. (rib* adj pain*).tw.
115. (thora* adj pain*).tw.
116. (radiculitis or (radicular adj pain*)).tw.
117. Pleurisy/
118. (pleurisy or pleuritis).tw.
119. ((face or facial or neck) adj (pain* or swelling or dilation or flushing)).tw.
120. Facial Pain/ or Neck Pain/
121. ((cervical or supraclavicular) adj adenopathy).tw.
122. ((upper limb* or arm*1) adj swelling).tw.
123. ((upper limb* or arm*1 or neck) adj distended vein*).tw.
124. ((lower limb* or leg*1) adj (parathesias or weakness)).tw.
125. ((muscle* or muscular) adj (parathesias or weakness)).tw.
126. ((spine or spinal) adj (parathesias or weakness or tenderness or pain*)).tw.
127. ((bone* or skeletal) adj (pain* or fracture*)).tw.
128. (walking adj impair*).tw.
129. exp Hepatomegaly/
130. (enlarged adj liver*).tw.
131. exp Jaundice/
132. jaundice*.tw.
133. (headache* or imbalance* or seizure*).tw.
134. Seizures/
135. (personality adj (change* or disturbance*)).tw.
136. exp Sensation Disorders/
137. (visual adj disturbance*).tw.
138. (sensory adj impair*).tw.
139. Hypersomnolence, Idiopathic/
140. (hyper-somnolence* or hypersomnolence).tw.
141. exp Deglutition Disorders/
142. dysphagia.tw.
143. (swallow* adj problem*).tw.
144. (swallow* adj difficult*).tw.
145. Hyponatremia/
146. hyponatr?emia*.tw.
147. (abnormal adj (chest x-ray* or spirometr*)).tw.
148. or/34–147
149. 33 and 148
150. limit 149 to yr="1980 -Current"