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Evidence-Based Series 24-2 Version 2

Referral of Suspected Lung Cancer by Family Physicians and Other Primary Care Providers

Members of the Referral of Suspected Lung Cancer Expert Panel

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

January 6, 2019

An assessment conducted in March 2024 deferred the review of Evidence-Based Series (EBS) 24-2 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 24-2 Version 2 is comprised of 4 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/216

Section 1:	**Guideline Recommendations (ENDORSED)**
Section 2:	**Evidentiary Base**
Section 3:	**EBS Development Methods and External Review Process**
Section 4:	**Document Assessment and Review**

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original version 2011	2007 to 2011	Full Report	Web publication	NA
Current Version 2 January 2019	2011 to May 2018	New data found in Section 4: Document Assessment and Review	Updated web publication	2011 recommendations are **ENDORSED**

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Evidence-Based Series 24-2 Version 2: Section 1

Referral of Suspected Lung Cancer by Family Physicians and Other Primary Care Providers: Guideline Recommendations

The 2011 recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.
Please see Section 4: Document Assessment and Review for a summary of updated evidence published between 2011 and 2018, and for details on how this Guideline was ENDORSED.
Modifications made in 2019 to the content of this recommendations section are shown in highlighted text.

QUESTIONS

Overall Question

In patients presenting to primary care services with signs and/or symptoms of lung cancer, what should the referral process include?

The following questions are the factors considered in answering the overall question:

1. What signs, symptoms and other clinical features are predictive of lung cancer?
2. What is the diagnostic accuracy of investigations for lung cancer?
3. What major, known risk factors are predictive of lung cancer?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers? Does a delay in the time to consultation affect patient outcome?

TARGET POPULATION

Patients presenting in primary care settings comprise the target population. This guideline does not provide recommendations for patients in a screening program.

INTENDED USERS

This guideline is targeted to family physicians (FPs), general practitioners, emergency room physicians, other primary care providers (PCPs) (nurse practitioners, registered nurses, and physician assistants), respirologists, thoracic surgeons, and radiologists. For the purposes of this document, we have referred to FPs, general practitioners, emergency room physicians, and other PCPs as 'FPs and other PCPs. The guidelines are also intended for policymakers to help ensure that resources are in place so that target wait times are achieved. They are also intended to help guide referrals to Diagnostic Assessment Programs (DAPS) in Ontario. DAPs provide a single point of referral, coordination of care using a clinical navigator, fast tracking of diagnostic tests and a multidisciplinary team approach. They are an Ontario-wide strategic

priority designed to improve patient access and outcomes, and are outlined in the Ontario Cancer Plan since 2005-2011 and 2011-2014 (1).
Added in February 2021: Formal Cancer Care Ontario DAPs no longer exist in Ontario, but many hospitals provide ongoing multidisciplinary team approaches to diagnosing colorectal cancer.

RECOMMENDATIONS

The following recommendations were adapted from the New Zealand Guidelines Group (NZGG) guideline Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities and the National Institute for Health and Clinical Excellence (NICE 2005), Referral guidelines for suspected cancer (2,3).

The recommendations below reflect the 2019 endorsement by the PEBC Lung Cancer Referral Expert Panel, the integration of the NZGG 2009 and NICE 2005 recommendations, and the updated systematic review of the research evidence of those guidelines and consensus by the PEBC Lung Cancer Referral Working Group (see Section 2: Appendix 1) (2,3). Modifications made in 2019 to the content of this recommendations section are shown in highlighted text.

Special consideration for these recommendations:

Factors that Increase the Risk of Lung Cancer
The following factors have been shown to increase the risk of lung cancer and will be referred to in the recommendations below: • Tobacco exposure by means of: current or previous smoking of tobacco using cigarettes, vaping, cigars, dry pipe or water pipe (bong); second hand exposure to tobacco smoke • Previous exposure to asbestos or other known carcinogens (e.g., radon, chromium, nickel) • Occupational exposure to dust or microscopic particles (e.g., wood dust, silica, diesel engine emissions, or chlorinated solvents) • Personal or family history of cancer (especially lung, head and neck cancer) • Lung Diseases (chronic obstructive pulmonary disease, asthma, pulmonary fibrosis) • Infections (tuberculosis, HPV 16/18 of the respiratory tract, previous pneumonia, HIV) • Occupations (miners, painters, iron and steel workers, bricklayers, welders) • Environmental (in-home burning of coal and/or biomass, unventilated cooking over high heat, air pollution, low socioeconomic status, high caffeine intake) • Other underlying health issues (lupus, rheumatoid arthritis, systemic sclerosis [scleroderma], diabetes, periodontal disease, increased abdominal obesity, dyslipidemia)

Indications for Referral to the Emergency Department
A person should be referred to the Emergency Department for the following: • Stridor • Massive hemoptysis • New neurological signs suggestive of brain metastases or cord compression
Indications for Urgent Chest CT and/or Urgent Referral to DAP or Thoracic Surgeon
A person should be referred if presenting with any of the following: • Persistent non-massive hemoptysis (Multiple episodes of coughing blood or blood-streaked sputum)

- Superior vena cava syndrome/obstruction

The ordering physician (i.e., FP or other PCPs, specialist, radiologist, or clinicians in the DAP) will depend on locally available resources and processes for expedited CT scans.

Indications for Chest X-ray

A person should have a chest X-ray within two working days if they present with any of the following:

- Hemoptysis
- New finger clubbing
- Suspicious lymphadenopathy
- Dysphagia
- Features suggestive of lung cancer that has metastasized elsewhere or other cancers that have metastasized to the lung
- Features suggestive of paraneoplastic syndromes

OR any of the following **unexplained** signs or symptoms:

- Cough
- Weight loss/loss of appetite
- Shortness of breath
- Chest, rib, or shoulder pain
- Abnormal chest signs
- Hoarseness
- Horner's syndrome
- Thrombocytosis, anemia, and leukocytosis

Patients with underlying chronic respiratory problems should have a chest X-ray if they have **unexplained** changes in existing symptoms.

The requisition for a chest X-ray should include the presenting history, including signs and symptoms suspicious of lung cancer and whether risk factors exist.

Chest X-rays should be completed, reviewed, and reported by the radiologist, and the report received by the FP or other PCPs within one week of being ordered. If the chest X-ray is suspicious for lung cancer, this must be clearly noted on the X-ray report. Radiologists should consider using two or more mechanisms to directly inform the FP or other PCPs of the suspicion of lung cancer. (e.g., fax, flagging, telephone call, email)

Indications for Chest CT scan

A person should have a chest CT scan within two weeks if they have any of the following:

- An abnormal chest X-ray that reports suspicion of lung cancer
- A normal chest X-ray, but there is a high suspicion of lung cancer, based on clinical judgement

The ordering physician (i.e., FP or other PCPs, specialist, radiologist, or clinicians in the DAP) will depend on locally available resources and processes for expedited CT scans.

Sputum Cytology

Sputum cytology is not recommended for the investigation of suspected lung cancer.

Follow-up to diagnostic investigations

A person who has consolidation or unexplained pleural effusion on an initial chest X-ray should be treated and have a chest X-ray repeated within four weeks to confirm complete resolution.

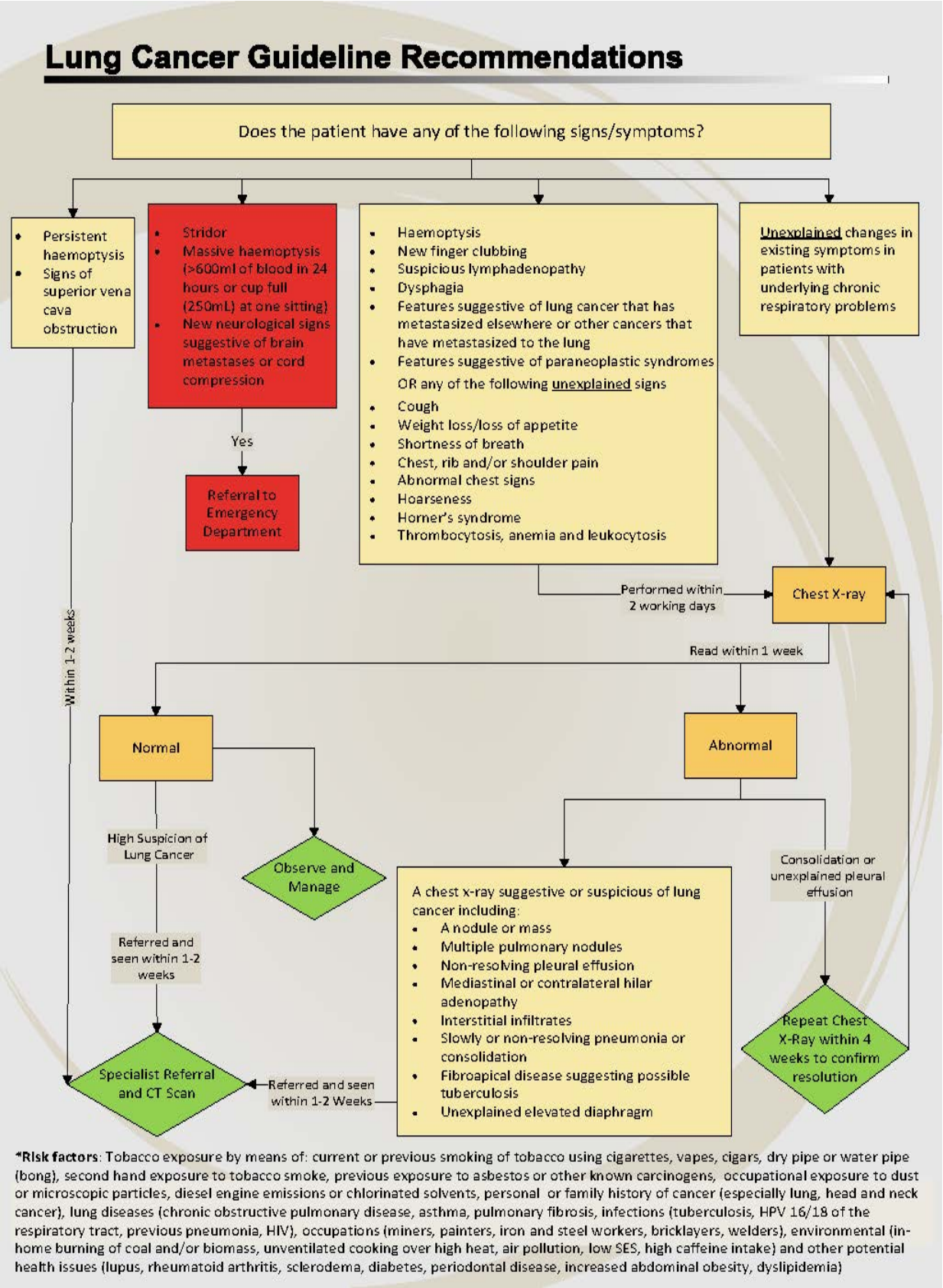
Indications for Referral to a Specialist (Respirologist or Thoracic Surgeon) or DAP

Patients should be referred and expect a consultation to a specialist or where locally available to a DAP within one to two weeks if they have any of the following:
• Persistent hemoptysis
• A chest X-ray suggestive or suspicious of lung cancer including:
  ○ A nodule or mass
  ○ Multiple pulmonary nodules
  ○ Non-resolving pleural effusion
  ○ Mediastinal or contralateral hilar adenopathy
  ○ Interstitial infiltrates
  ○ Slowly or non-resolving pneumonia or consolidation
  ○ Fibroapical disease suggesting possible tuberculosis
  ○ Unexplained elevated diaphragm
• A normal chest X-ray, but there is a high suspicion of lung cancer, based on clinical judgement

If promptly accessible, a chest CT scan can be simultaneously ordered with the referral while waiting for the DAP or the specialist's consultation. This will depend on locally available resources. If the CT scan is entirely negative, then further referral to a DAP or specialist may no longer be required.
To expedite the diagnosis and avoid duplication of investigations, at a minimum, the following information should be provided to the specialist: • History of the patient, including all risk factors and signs or symptoms suspicious of lung cancer • All efforts should be made to provide all pre-existing imaging results, including chest X-rays and CT scans (films and digital images should be available at the time of consultation) • All relevant other medical conditions and medications taken by patient • All recent blood work
Recommendations to Reduce Diagnostic Delay
There should be appropriate educational tools developed and disseminated that highlight the signs and symptoms of lung cancer for FPs and other PCPs and for patients.
FPs and other PCPs should have a high index of suspicion with a low threshold for investigation of suspected lung cancer in ordering chest x-rays and referral to lung cancer specialists or the DAP. Decision support tools should be readily available to assist FPs and other PCPs.
FPs and other PCPs should include as much information as possible in their referral letters and should ask patients to help retrieve electronic copies of their imaging tests to bring to specialist appointments.
Counselling of patients should occur to address common fears and concerns.
Public health and other health agencies should work with local community leaders to address challenges, such as lower levels of education or demographic discrepancies in communities with high rates of lung cancer or known delays in lung cancer diagnosis.

There is a lack of awareness of changing epidemiology; with increasing numbers of young people and lifelong non-smokers being diagnosed with lung cancer. Therefore, a young age (<40 years) or being a lifelong non-smoker should not preclude investigation or referral if there is high suspicion of lung cancer, based on clinical judgement.

ALGORITHM



***Risk factors**: Tobacco exposure by means of: current or previous smoking of tobacco using cigarettes, vapes, cigars, dry pipe or water pipe (bong), second hand exposure to tobacco smoke, previous exposure to asbestos or other known carcinogens, occupational exposure to dust or microscopic particles, diesel engine emissions or chlorinated solvents, personal or family history of cancer (especially lung, head and neck cancer), lung diseases (chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, infections (tuberculosis, HPV 16/18 of the respiratory tract, previous pneumonia, HIV), occupations (miners, painters, iron and steel workers, bricklayers, welders), environmental (in-home burning of coal and/or biomass, unventilated cooking over high heat, air pollution, low SES, high caffeine intake) and other potential health issues (lupus, rheumatoid arthritis, sclerodema, diabetes, periodontal disease, increased abdominal obesity, dyslipidemia)

KEY EVIDENCE

- Many of these recommendations were adapted or endorsed from the NZGG 2009 or NICE 2005 recommendations (2,3). Signs and symptoms listed in the NZGG 2009 or NICE 2005 recommendations were derived from their systematic reviews, which mainly included case-series studies (2,3). The development of the recommendations in this guideline can be found in Section 3 of this report.

- There was no evidence found on wait times and their effects on patient outcomes. One study found that wait times to referral for specialist consultation for patients with signs or symptoms suspicious for lung cancer can be reduced from 20 days to six days with the implementation of a DAP (4). For this guideline, the wait times for diagnostic investigations and referral developed by the Lung Cancer Referral Working Group were chosen because they considered them to be achievable targets in the Ontario health care system, especially with the introduction of DAPs across the province.

- The list of risk factors was broadened to include all risk factors summarized by NZGG 2009 based on the review by NICE 2005 (2,3).

Indications for Referral to Emergency Department

- This recommendation was adapted from the NICE 2005 guidelines for immediate referral. New neurological signs suggestive of brain metastases or cord compression were included based on common practice in Ontario and massive hemoptysis was included based on the Time-to-Treat Program (4).

Indications for Chest X-ray

- This recommendation was adapted from the NZGG 2009 guidelines for urgent referral for a chest X-ray (3). Based on expert opinion, it was felt that, for new finger clubbing, features suggestive of lung cancer that has metastasized elsewhere or other cancers that have metastasized to the lung, and suspicious lymphadenopathy, the three-week time frame was not required for referral for a chest X-ray. The Working Group chose to include dysphagia as an indicator for a chest X-ray, because it was reported in the NICE 2005 review as a symptom of lung cancer and was found to be a major clinical symptom among lung cancer patients in a tertiary care setting (2,5). Furthermore, paraneoplastic syndromes were included as indications for chest X-ray based on the review by Spiro et al (2007) that reported that paraneoplastic syndromes may occur in 10% of patients with lung cancer (6).

- For patients with underlying chronic respiratory problems, the Working Group chose to adapt the recommendation from NICE 2005 (2).

Indications for CT Scan

- There was little evidence to inform these recommendations; therefore, the Working Group decided to develop their own recommendations based on experiences within their own practices.

Sputum Cytology

- The updated literature search found high specificity but variable sensitivity of sputum cytology in detecting lung cancer (7-11). Therefore, this recommendation was endorsed from the NZGG 2009 referral guidelines (3).

Follow-up to Diagnostic Investigations

- The recommendation for follow-up to consolidation on a chest X-ray was adapted from the NZGG 2009 referral guideline, which was based on the experience of their guideline development team (3). The Working Group chose to modify the NZGG's 2009 recommendation by including all patients rather than specifying only patients with risk factors for lung cancer. In addition to consolidation, the Working Group also included unexplained pleural effusion based on their experience in their practices.

Indications for Referral to a Specialist (Respirologist or Thoracic Surgeon) or the DAP

- These recommendations were adapted from the NZGG 2009 and NICE 2005 referral guidelines, which were based on expert opinion (2,3). Additional abnormal chest X-ray results were included from the Time-to-Treat Program (4). Unexplained elevated diaphragm was included based on the suggestion of an expert panel member.

Recommendations to Reduce Diagnostic Delay

- There is evidence to suggest that the following may delay the diagnosis of lung cancer (2,3,5,12,13):

  - Patient-Related Delay:

- patient's lack of appreciation regarding the association of symptoms with lung cancer
- fear of cancer diagnosis

  - Family Physician related delay:

- not recognizing signs and symptoms suggestive of lung cancer
- co-morbidity of conditions increased delay
- multiple consecutive investigations in primary care
- over-reliance on chest X-ray results to diagnose lung cancer
- imaging follow-up failure
- initial referral to a non-respiratory physician

Algorithm

- The process used to develop this algorithm can be found in Section 3.

FUTURE RESEARCH

Further studies could be designed to investigate the diagnostic performance of signs, symptoms, or tests for lung cancer in the primary care setting. In addition, studies are needed to determine which educational initiatives would be best at decreasing practitioner- or patient-related delay.

GLOSSARY

Diagnostic Assessment Programs

Diagnostic Assessment Programs, provide a single point of referral, coordination of care using a clerical navigator, fast tracking of diagnostic tests and a multidisciplinary team approach, thereby improving the quality of care and the patient experience. They are an Ontario-wide strategic priority designed to improve patient access and outcomes and outlined in the Ontario Cancer Plan since 2005-2011 and 2011-2014 (1).

Abnormal Chest Signs

e.g., crackles or wheezes

Abnormal Chest X-ray that Reports Suspicion of Lung Cancer
e.g., nodule(s), infiltrates, non-resolving consolidation or effusion despite treatment

Features Suggestive of Metastatic Disease
Clinical and Organizational Factors in the Initial Evaluation of Patients with Lung Cancer Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 2013 Ost et al. (available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4694609/pdf/chest_143_5_suppl_e121S.pdf) (6)

Massive Hemoptysis
>600 mL of blood in 24 hours or one cup full of blood (250 mL) at one sitting

Features Suggestive of Paraneoplastic Syndromes
Clinical and Organizational Factors in the Initial Evaluation of Patients with Lung Cancer Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 2013 Ost et al. (available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4694609/pdf/chest_143_5_suppl_e121S.pdf) (6)

Signs of Superior Vena Cava Obstruction
Swelling of the face and or neck with fixed elevation of jugular venous pressure

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REFERENCES

1. Cancercare.on.ca [Internet]. Toronto (ON): Cancer Care Ontario (CCO); 2011 [cited 2010 Aug 3].
2. National Collaborating Centre for Primary Care. Referral guidelines for suspected cancer. London: National Institute for Health and Clinical Excellence (NICE); 2005 Jun. Clinical Guideline No.: 27.
3. New Zealand Guidelines Group. Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities. Wellington (NZ): New Zealand Guidelines Group (NZGG); 2009.
4. Lo DS, Zeldin RA, Skrastins R, Fraser IM, Newman H, Monavvari A, et al. Time to treat: a system redesign focusing on decreasing the time from suspicion of lung cancer to diagnosis. J Thorac Oncol. 2007 Nov;2(11):1001-6.
5. Chandra S, Mohan A, Guleria R, Singh V, Yadav P. Delays during the diagnostic evaluation and treatment of lung cancer. Asian Pac J Cancer Prev. 2009 Jul-Sep;10(3):453-6.
6. Spiro SG, Gould MK, Colice GL, American College of Chest Physicians. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest. 2007 Sep;132(3 Suppl):149S-60S.
7. Australian Cancer Network Staff, Cancer Council Australia, Australian Cancer Network, National Health and Medical Research Council (Australia). Clinical practice guidelines for the prevention, diagnosis and management of lung cancer. Sydney (Australia): National Health and Medical Research Council (NHMRC); 2004.
8. Scottish Intercollegiate Guidelines Network. Management of patients with lung cancer: a national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2005.
9. Choi Y-D, Han C-W, Kim J-H, Oh I-J, Lee J-S, Nam J-H, et al. Effectiveness of sputum cytology using ThinPrep method for evaluation of lung cancer. Diagn Cytopathol. 2008 Mar;36(3):167-71.
10. Kemp RA, Reinders DM, Turic B. Detection of lung cancer by automated sputum cytometry. J Thorac Oncol. 2007 Nov;2(11):993-1000.
11. Rivera MP, Mehta AC, American College of Chest Physicians. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007 Sep;132(3 Suppl):131S-48S.
12. Olsson JK, Schultz EM, Gould MK. Timeliness of care in patients with lung cancer: A systematic review. Thorax. 2009;64(9):749-56.
13. Singh H, Sethi S, Raber M, Petersen LA. Errors in cancer diagnosis: current understanding and future directions. J Clin Oncol. 2007;25(31):5009-18.

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Evidence-Based Series 24-2: Section 2

Referral of Suspected Lung Cancer by Family Physicians and Other Primary Care Providers: Evidentiary Base

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A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: August 29, 2011

QUESTIONS

Overall Question

In patients presenting to primary care services with signs and/or symptoms of lung cancer, what should the referral process include?

The following questions are the factors considered in answering the overall question:

1. What signs, symptoms and other clinical features are predictive of lung cancer?
2. What is the diagnostic accuracy of investigations for lung cancer?
3. What major, known risk factors are predictive of lung cancer?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers? Does a delay in the time to consultation affect patient outcome?

INTRODUCTION

Lung cancer is the most common cause of cancer death in Ontario for both men (26%) and women (22%) (1). Tobacco use is the primary cause of lung cancer, accounting for an estimated 86% of cases (1).The chance of surviving lung cancer in Ontario is low, with a five-year survival rate of 15% for both men and women combined (1). Lung cancers are frequently diagnosed at a late stage, and the prognosis is very poor (1). While some presenting symptoms might be vague and imprecise, delays in diagnosis might be avoided when patients with a history suggesting an increased risk of lung cancer and suspicious signs and symptoms receive a timely chest X-ray and, where warranted, are referred to a specialist or a Diagnostic Assessment Program (DAP) for further investigation. To date, there are no Ontario guidelines for FPs and other PCPs to assist them in identifying and initiating the management of these patients.

Because of a need for guidance regarding referral for suspected lung cancer, the CCO's Provincial Primary Care and Cancer Network (PPCCN) in collaboration with the Program in Evidence-based Care (PEBC) has developed this guideline for patients who present with signs and symptoms that might be indicative of lung cancer. The New Zealand Guidelines Group (NZGG) 2009 guideline, Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities and the National Institute for Health and Clinical Excellence (NICE) 2005 guideline, Referral guidelines for suspected cancer in adults and children were chosen as a baseline documents for the development of this systematic review (2,3). The aim of this guideline is to assist primary care physicians to recognize features that should raise their suspicion of lung cancer and ultimately lead to more timely and appropriate referrals of these patients.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's PEBC use the methods of the Practice Guidelines Development Cycle (4). A priori the Lung Cancer Referral Working Group chose the NZGG 2009 and NICE 2005 documents as a foundation because they were considered to be of high quality, comprehensive, recent in publication, and relevant to this topic (2,3). The Working Group updated the literature searches of the NZGG 2009 or NICE 2005 systematic reviews to determine if any new evidence would change the NZGG 2009 or NICE 2005 recommendations (2,3).

Evidence was selected and reviewed by nine members of the PEBC Lung Cancer Referral Expert Panel and one methodologist (Appendix 1). If the new evidence did not substantially change the recommendations of NZGG 2009 or NICE 2005, then the Working Group would adapt the NZGG 2009 and NICE 2005 recommendations as well as any recommendations from evidence-based guidelines found during the updated literature search or the environmental scan (2,3).

This updated evidentiary base and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

In order to determine if there were other higher quality guidelines compared to NICE 2005 or NZGG 2009, or guidelines with more recent systematic reviews, or what other agencies were recommending, a targeted environmental scan of international guideline developers and key organizations was conducted (March 5-8, 2010) for documents about primary care referral for suspected lung cancer (2,3). A listing of the organizations that were examined is given in Appendix 2.

Following this search of other guidelines, the Lung Cancer Referral Working Group considered the NICE 2005 and NZGG 2009 guidelines to be of the highest quality and updated their literature search strategies (2,3). The search strategies from NZGG 2009 and NICE 2005 were kindly provided to us for this systematic review (2,3). NZGG 2009 performed systematic reviews for questions concerning the diagnostic accuracy of signs, symptoms, and diagnostic tests and for the clinical questions investigating factors associated with delay in referral (3). For these clinical questions, an updated search since the NZGG 2009 publication of MEDLINE (Ovid, August 2007 – February Week 3 2010) and EMBASE (Ovid, 2007 - 2010 week 07) was performed using the NZGG 2009 literature search strategy (3). For the clinical question investigating risk factors for lung cancer, NZGG 2009 did not perform a systematic review (3). Therefore, an updated search, since the NICE 2005 publication, of MEDLINE (Ovid, June 2004-February Week 3 2010) and EMBASE (Ovid, 2004 - 2010 week 08) using the NICE 2005 search

strategies for systematic reviews for lung cancer was performed (2,3). A second literature search update of all strategies for literature available to June 27, 2011 was performed. The search strategies can be found in Appendix 3.

Study Selection Criteria

Guidelines were included if they addressed at least one of our research questions, were not cited in the NZGG 2009 or NICE 2005 guidelines, and included recommendations not found or different from those in either the NICE 2005 or NZGG 2009 guidelines (2,3).

For the clinical question about the predictive characteristics of signs or symptoms, all prospective or retrospective case series or cohort or case control studies of symptom recognition/identification for lung cancer were included. Studies conducted in the secondary care setting that provided predictive information about signs/symptoms for suspected lung cancer were included when limited evidence was available from the primary care setting. Screening studies were excluded because they include asymptomatic patients. This report focuses on patients presenting to primary care with signs or symptoms of lung cancer.

All diagnostic studies in which symptomatic primary care patients underwent one or more investigations including complete blood count, chest X-ray, spirometry, sputum cytology and CT scan were sought. If limited evidence was available from the primary care setting, studies conducted in secondary care settings were included if they provided diagnostic information for suspected lung cancer for the specified investigations. Screening studies were excluded.

For the clinical questions concerning risk factors and delay in referral, a search for practice guidelines, systematic reviews (with meta-analyses), and systematic reviews (without meta-analyses) was performed. If these articles did not definitively answer the particular clinical question, then searches for randomized phase III trials and randomized phase II trials followed by prospective or retrospective case series or cohort or case-control studies were performed. If information from systematic reviews definitively answered the question(s), then articles from the time of publication of the systematic review and onwards were retrieved.

Publications in a language other than English were not eligible because of lack of funding for translation. Non-systematic reviews, abstracts, case studies, letters, editorials, and commentaries were excluded.

Synthesizing the Evidence

There was considerable heterogeneity between studies; therefore, data were not pooled.

Quality Appraisal of Evidence-Based Guidelines

The Appraisal of Guidelines Research and Evaluation (AGREE II) tool was used by three independent methodologists to evaluate the quality of included evidence-based guidelines, or the AGREE II scores were taken from the Standards and Guidelines Evidence Inventory of Cancer Guidelines developed by the Canadian Partnership Against Cancer if available (5,6). Only clinical practice guidelines in which the objective of the guideline was specifically described and the document included a review of the evidence were evaluated using the AGREE II tool (5,6). Systematic reviews and meta-analyses were assessed for quality using the 'assessment of multiple systematic reviews' or 'AMSTAR' tool (7).

Guideline Selection for Adaptation

Guidelines appropriate for adaptation were selected in a two-step screening process. First, two physicians evaluated each guideline using two questions modified from the AGREE II instrument: Would you use this guideline? and Were the recommendations based on evidence

or expert opinion (5,6)? As a second level of screening, the quality of the remaining guidelines was assessed with the AGREE II instrument (5,6). These guidelines are described in Section 2, below. The process of adapting the recommendations is described in Section 3.

RESULTS

Literature Search Results

Of 7719 articles identified in the updated literature search, 168 were deemed relevant for a full article review. Of these, 16 articles not included in the NZGG 2009 systematic review met the inclusion criteria and were retained (3,8-23). In addition to the NICE 2005 and NZGG 2009 guidelines (2,3), six guidelines were found during the environmental scan (24-29). The American College of Chest Physicians (ACCP) published a series of evidence-based clinical practice guidelines for the management of patients with lung cancer. Four of these guidelines were included because they addressed at least one of the research questions (24-27). The other two guidelines were developed by SIGN and Australia (28,29). In the second updated literature search, one systematic review and two studies were included (30-32). Table 2 provides a summary of included articles for each research question.

Table 2 Summary of included articles for each research question.

Research Question	Guideline	Systematic review	Prospective studies	Retrospective studies
Signs / symptoms	5*	1	1	8**
Tests	7*	0	1	1
Risk factors	3*	0	0	0
Delay	4*	3	1	6**

*Some guidelines were relevant for more than one research question.
**Three articles addressed both the research question about signs or symptoms and the research question about the factors associated with delayed referral.

Study Design and Quality

Research Questions for Signs/Symptoms, Tests, and Risk Factors

Guidelines and Reviews

The NZGG 2009 guideline was based on the NICE 2005 guideline (2,3) and provided updated evidence since the NICE guideline for research questions about signs and symptoms as well as for diagnostic tests. The authors did not do a systematic review for the research question about risk factors, and their recommendations were essentially endorsed from the NICE recommendations with minor word changing.

NICE performed systematic reviews for these research questions, but the link of the evidence to the recommendations was not always clear (2). For example, it is unclear why certain risk factors for lung cancer were included in their recommendations and others were not. Presumably, the included risk factors are more established in the literature, but this is not specifically mentioned. They note that the literature is lacking to adequately address these research questions, especially within the context of primary care.

There were six guidelines, in addition to the NZGG 2009 and NICE 2005 guidelines, found during the environmental scan that addressed at least one of our research questions, were not cited in the NZGG or NICE guidelines (2,3) and included recommendations not found or different from those in either the NICE or NZGG guideline (24-29). The four guidelines developed by the ACCP that addressed at least one of the research questions did not provide lists or details of the included studies and did not assess the quality of the included studies, although each of the recommendations was followed by a grading of the supporting evidence (24-27). Kvale 2006

was published in the first edition of the ACCP clinical practice guidelines (25). Although MEDLINE was searched, only two terms were listed: "cough" and "lung neoplasms." Rivera and Mehta 2007, Spiro 2007, and Gould 2007 were published in the second addition of the ACCP clinical practice guidelines (24,26,27). Rivera and Mehta, and Gould searched more than one database and included their research questions as well as their inclusion and exclusion criteria (24,26). The search terms in MEDLINE and the inclusion and exclusion criteria were not outlined in the Spiro article (27).

SIGN 2005 included evidence summaries from their systematic review before each of their recommendations, and they included a grade of the strength of the evidence for each recommendation (29). They provided their search strategies for MEDLINE, but their inclusion and exclusion criteria were not clearly defined. This guideline addressed the management of patients with lung cancer and was not solely focused on the referral process; as such, whether the included studies were performed in the primary care setting was not a priority.

The Australian guidelines also covered a broad spectrum of care for patients with lung cancer from prevention and diagnosis to management (28). Therefore, the focus was not on the referral process, and studies were not selected on the basis of the primary care setting. They did not include their search strategy or their inclusion or exclusion criteria. They provided the strength of the level of evidence to support their recommendations, as well as the citations for each recommendation.

One systematic review by Stapley et al 2010 was included in the updated literature search since the NZGG search (30). Table 3 shows how this systematic review scored on each of the 11 AMSTAR items. This systematic review scored well, with eight of the 11 items meeting the AMSTAR criteria. The authors did not include all excluded studies and did not assess the likelihood of publication bias. Although a conflict of interest statement was included for the authors of the systematic review, conflict of interest statements were not acknowledged for the included studies.

Table 3. Evaluation of included publications using AMSTAR.

ITEM	Hanna et al. 2005 (12)	Olsson et al. 2009 (17)	Shapley et al. 2010 (30)	Singh et al. 2007 (19)
1. Was an 'a priori' design provided?	N	Y	Y	Y
2. Was there duplicate study selection and data extraction?	Can't answer	N	Y	N
3. Was a comprehensive literature search performed?	Y	N	Y	Y
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	N	Y	Y	Y
5. Was a list of studies (included and excluded) provided?	N	N	N	N
6. Were the characteristics of the included studies provided?	N	Y	Y	N
7. Was the scientific quality of the included studies assessed and documented?	N	Y	Y	N
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	N	Y	Y	N
9. Were the methods used to combine the findings of the studies appropriate?	NA	NA	Y	NA

ITEM	Hanna et al. 2005 (12)	Olsson et al. 2009 (17)	Shapley et al. 2010 (30)	Singh et al. 2007 (19)
10. Was the likelihood of publication bias assessed?	N	N	N	N
11. Was the conflict of interest stated?	N	N	N	N
TOTAL AMSTAR POINTS	1	5	8	3

Abbreviations: N, no; NA, not applicable; Y, yes.

Primary Studies

Of the 11 primary studies published since the NZGG search that addressed the first three research questions, nine had retrospective designs (Table 4)(8-11,13,14,16,21,22,31,32). None of these studies were performed in a primary care setting, and only two articles included patients with and without lung cancer and were blinded to the diagnostic results (11,13). The Working Group decided these primary studies would not significantly change the recommendations found in the eight evidence-based guidelines that provided recommendations for the first three research questions (2,3,24-29). Therefore, the Working Group decided to adapt the recommendations from these existing guidelines for use in Ontario.

Table 4: Study characteristics of included articles not included in the NZGG 2009 search.

Author	Study	Country	No. of Patients	No. of Patients with Lung Cancer (%)	Setting	Investigations Used	Consecutive Patients	Blinded
Ak et al 2007 (8)	Retrospective	Turkey	1340	1340	Secondary care	X-ray; Histopathologically confirmed	No	No
Beatty et al 2009 (9)	Retrospective	New Zealand	159	159	Secondary care	NR	No	No
Chandra et al 2009 (10)	Retrospective	India	165	165	Tertiary care	Cytologically or histologically confirmed	No	No
Choi et al 2008 (11)	Retrospective	Korea	955; 352 histologic-ally confirmed	127 (36%)	Secondary setting	ThinPrep sputum test versus conventional preparation; 352 histologically confirmed	No	Yes
Kemp et al 2007 (13)	Prospective	Canada	1123 with medical history or clinical symptoms suspicious of lung cancer	370 (33%)	Secondary care, Sponsored by Perceptronix Medical Inc.	LungSign sputum test versus conventional cytological or minimum of 3 mths follow-up	No	Yes
Koumarianou et al 2009 (14)	Retrospective	Greece	1906	1906 with non-small cell lung cancer	Cancer registry – mainly patients	Histologically or cytologically confirmed	No	No

Author	Study	Country	No. of Patients	No. of Patients with Lung Cancer (%)	Setting	Investigations Used	Consecutive Patients	Blinded
					from phase II/III trials			
Lo et al 2007 (15)	Program implementation and assessment	Canada	52	52	Primary and secondary care	X-ray	No	No
Lovgren et al 2008 (16)	Retrospective	Sweden	314	314	Secondary care	Cytology results available for 291	Yes	No
Rolke et al 2007 (18)	Retrospective	Norway	479	479	Secondary care	431 Histologically confirmed	Yes	No
Smith et al 2009 (20)	Retrospective	UK	360	360	Secondary care	NR	Yes	No
Thammakumpee et al 2007 (21)	Retrospective	Thailand	116	116 with small-cell lung cancer	Secondary care	X-ray; Histologically and/or cytologically confirmed	No	No
Thomas et al 2008 (22)	Retrospective	India	25	25 with pulmonary carcinoid tumours	Tertiary care	Bronchoscopy; all had biopsy	No	No
Uzun et al 2010 (31)	Prospective	Turkey	178 with hemoptysis	51 (29%)	Tertiary care	All X-ray, some bronchoscopy and/or CT scan; final diagnosis based on consensus	Yes	No
Yaman et al 2009 (32)	Retrospective	Turkey	109	109	Secondary care	Histopathologic-ally confirmed	No	No
Yilmaz et al 2008 (23)	Retrospective	Turkey	138	138 with non-small cell lung carcinoma	Secondary care	CT/PET; thoracotomy	Yes	No

Abbreviations: CT, computed tomography; mths, months; NR, not reported; PET, positron emission tomography.

Research Question about Delay in Referral

For the research question associated with delay, additional factors affecting delay beyond those mentioned in the NICE and NZGG guidelines were found in the SIGN guideline, the ACCP guideline by Spiro et al, three systematic reviews, and seven primary studies (Table 4)(2,3,10,12,15-20,23,27,29,32). Table 3 shows how the included systematic reviews scored on each of the 11 AMSTAR items. The overall scores were low for all the systematic reviews. Two of the systematic reviews did not include the characteristics of the included studies, nor did they assess the quality of the included studies (12,19). The one systematic review that did include characteristics and assessments of included studies searched only one electronic database (17).

Guideline Selection for Adaptation

Based on the two physicians' answers in the first level of screening, the recommendations from Spiro et al were felt to be too general (27). These recommendations were excluded when developing the recommendations for Ontario. The quality of the remaining guidelines from NICE, NZGG, the Australian National Health and Medical Research Council , the Scottish Intercollegiate Guidelines Network (SIGN) and the ACCP (includes Kvale, Rivera and Mehta, and Gould et al) was assessed with the AGREE II instrument (Table 5)(2,3,24-26,28,29).

Table 5. Results of AGREE II Tool quality rating of evidence-based guidelines.

Guideline	AGREE II Domain Scores					
	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigour of Development (%)	Clarity and Presentation (%)	Applicability (%)	Editorial Independence (%)
NICE 2005(2)	97.2	66.7	77.1	61.1	79.2	25.0
NZGG 2009 (3)	74.1	74.1	66.0	75.9	51.4	75.0
Australian 2004 (28)	80.6	94.4	74.0	86.1	27.1	58.3
SIGN 2005 (29)	61.1	81.5	81.9	96.3	47.2	30.6
ACCP (Kvale 2006) (25)	50.0	18.5	45.1	85.2	13.9	11.1
ACCP (Rivera and Mehta 2007) (26)	72.2	57.4	61.1	92.6	36.1	50.0
ACCP (Gould et al 2007) (24)	46.3	55.6	62.5	90.7	22.2	25.0

Abbreviations: ACCP, American College of Chest Physicians; NICE, National Institute for Health and Clinical Excellence; NZGG, New Zealand Guidelines Group; SIGN, Scottish Intercollegiate Guidelines Network.

The applicability and editorial independence were generally low and showed scores below 50% for five and four of the guidelines, respectively. Gould et al had a score of less than 50% for scope and purpose, and Kvale had scores below 50% for stakeholder involvement and rigour of development (24,25). The Working Group decided the Kvale recommendations should be excluded when formulating the recommendations for Ontario because four of six of their domain scores were below 50% (25). The recommendations for consideration can be found in Appendix 4.

Outcomes

What signs, symptoms and other clinical features are predictive of lung cancer?

Evidence from NICE 2005 and NZGG 2009

The systematic review conducted by NICE included three guidelines, only one of which provided a table of common signs and symptoms based on evidence from case series (2). These were not described in detail. The NICE systematic review of studies performed in secondary care settings also found one systematic review by Liedekerken et al (1997) that yielded little evidence to link prolonged cough with lung cancer (33). Nine additional studies were included in the NICE systematic review. Data from only two of the nine studies were collected from primary care records. Based on the results of the NICE systematic review, common signs and symptoms included cough (persistent or unexplained), chest and/or shoulder pain, dyspnea, hemoptysis, and weight loss (unexplained). Other signs and symptoms included finger clubbing, dysphagia, fever, hoarseness, pneumonia, superior vena cava obstruction, weakness, wheezing and stridor, and enlarged lymph nodes. Furthermore, patients may present with signs and/or symptoms of metastases.

The NZGG updated literature search from NICE included a case-control study by Hamilton et al (2005) and a case-series study by Jones et al (2007) that were not described

(34,35). Jones et al evaluated the association between hemoptysis and respiratory tract neoplasms, which included lung cancer but other respiratory tract cancers as well (35). This paper would have been excluded from our systematic review. Hamilton et al reported on a case-control study (n=247) and found loss of appetite, hemoptysis, dyspnea, loss of weight, fatigue, chest pain, second attendance with cough, and finger clubbing were independently associated with lung cancer (34).

Evidence from Newly Identified Reviews

In addition to the NICE and NZGG reports, three guidelines, developed by the ACCP, and one systematic review provided evidence to address this question (24,25,27,30). Kvale focused on the management of cough associated with lung tumours (25), and reported that a cough is found in greater than 65% of patients diagnosed with lung cancer and that dyspnea often accompanies the cough associated with lung cancer. Spiro et al conducted a systematic review and found the initial symptoms and signs of lung cancer, in order of most to least frequent, included cough, weight loss, dyspnea, chest pain, hemoptysis, bone pain, clubbing, fever, weakness, superior vena cava obstruction, dysphagia, and wheezing and stridor (27). They also provided information on the symptoms, signs, and laboratory tests that could be used in a standardized evaluation for systematic metastases, as well as a list of the paraneoplastic syndromes associated with lung cancer. They report that paraneoplastic syndromes may occur in 10% of patients with lung cancer. Gould et al performed a systematic review on the diagnosis and management of patients with pulmonary nodules (24). They did not distinguish between screen-detected nodules and nodules that were detected incidentally. In terms of follow-up of patients with pulmonary nodules, they found no evidence to suggest that extending the follow-up beyond two years would detect more malignant nodules or improve patient outcomes.

Shapley et al 2010 included studies that had a PPV of 5% or more for any sign or symptom as well as studies with PPVs less than of 5% for the same sign or symptom (30). The two articles included for lung cancer were already referenced in the NZGG guideline (34,35).

Evidence from Newly Identified Primary Studies

One prospective study and eight retrospective studies, beyond those mentioned by NICE or NZGG, of patients with lung cancer provided predictive information about the signs or symptoms for lung cancer (8-10,14,16,21,22,31,32). A prospective study by Uzun et al (2010), included consecutive patients with hemoptysis at a tertiary referral hospital (31). Thirty-two percent of patients with mild hemoptysis, 38% with moderate hemoptysis, 24% with severe hemoptysis and 13% with massive hemoptysis were diagnosed with lung cancer.

Ak et al (2007) compared symptom and sign presentation between young (<50 yrs, n=179) and older (≥50 yrs, n=1161) patients in a secondary care setting (8). Using multivariate analysis, exposure to occupational risk factors was a risk factor in the younger group, while in the older group, smoking was a risk factor. Chest pain was more common in younger patients, while cough and dyspnea were more common in older patients.

Beatty et al (2009) performed a retrospective review of 159 cases of primary lung cancer seen in an emergency department in Australia (9). Of those patients that were referred by their general practitioner (n=66), 47% presented with respiratory symptoms, 38% presented with hemoptysis, and 31% presented with no hemoptysis. Symptom duration varied from less than one week (35%, n=16) to greater than two months (33%, n=8).

Chandra et al (2009) reviewed 165 patients with lung cancer in a tertiary care setting (10). Major clinical features at the time of diagnosis of lung cancer included coughing (75.2%), shortness of breath (66.9%), weight loss (63.7%), chest pain (63.1%), hemoptysis (33.1%), hoarseness of voice (29.3%), excessive weakness/fatigue (26.8%), clubbing (22.9%), dysphagia (9.3%), and superior vena cava syndrome (8.0%).

Koumarianou et al (2009) reviewed the medical records of patients with non-small cell lung cancer (PS 0-3) (14). Most patients had been enrolled in phase II/III studies of cytotoxic chemotherapy combinations. They compared the symptom characteristics of 417 patients aged 70 years or more (elderly), 1374 patients aged 45-70 and 115 patients aged 45 years or less (young). The most commonly reported symptoms were hemoptysis, cough, and weight loss. Elderly patients presented with more symptoms such as pain, dyspnea, cough, and fatigue compared to younger patients.

Lovgren et al (2008) reviewed 314 patients diagnosed with primary lung cancer at a university hospital (16). Five of the most commonly reported first symptoms were cough, dyspnea, weight loss, fatigue, and thoracic pain. Four of the most common symptoms triggering health care system appointments included cough, dyspnea, and thoracic pain for men and women, and as a fourth symptom, neurological symptoms for women and haemoptysis for men.

Thammakumpee et al (2007) reviewed the symptoms of patients with small-cell lung cancer in Thailand in a secondary care setting (21). The symptoms and signs, in order of frequency, included cough, weight loss, dyspnea, chest pain, hemoptysis, hoarseness, superior vena cava syndrome, neurological syndrome, syndrome of inappropriate antidiuretic hormone, Cushing's syndrome, and massive hemoptysis.

Thomas et al (2008) reviewed the signs and symptoms of patients with pulmonary carcinoid tumours in India in a tertiary care setting (22). Only 25 patients were included in this study. Presenting symptoms or signs included hemoptysis, cough, breathlessness, chest pain, fever, and superior vena cava syndrome.

Yaman et al (2009) reviewed records of lung cancer patients at a speciality clinic (32). The percentage of first symptoms related to lung cancer grouped into five categories was 32% for cough, 21% for dyspnea, 11% for hemoptysis, 20% for chest pain and 16% for other first symptoms.

What is the diagnostic accuracy of investigations for lung cancer?

Evidence from NICE 2005 and NZGG 2009

The systematic review conducted by NICE included one systematic review with meta-analyses comparing the diagnostic accuracy of cytology, bronchoscopy, transthoracic needle aspirate, or biopsy (2). As well, three primary studies were included: two about chest radiography and one about blood work. Based on the studies reviewed, NICE concluded that a chest X-ray is the principal diagnostic investigation for lung cancer in primary care, that false-negative chest X-ray results do occur, and that sputum cytology is not a discriminatory investigation in symptomatic patients.

NZGG (2009) included complete blood count, chest X-ray, spirometry, and sputum cytology as investigations in their updated systematic review since NICE 2005 (3). In addition to NICE, they included one systematic review and two primary studies (34,36,37). Hamilton and Sharp (2004) suggested referral, despite a negative chest X-ray, should occur only if there is persistent hemopytsis and not for other symptoms, because the evidence is strongest only for persistent hemopytsis (36). For other symptoms negative for a chest X-ray, diagnoses other than lung cancer might be more likely and should be considered. They also emphasized that the experience of the doctor and the patient is an important factor in diagnostic assessment. However, in a more recent publication, they found that up to a quarter of lung cancer patients had negative chest X-rays taken in primary care for a variety of symptoms (37). This suggests that physicians should not over-rely on negative chest X-rays if there is a suspicion of lung cancer.

Using multivariate analysis, Hamilton et al (2005) found that an abnormal spirometric test and thrombocytosis were associated with lung cancer, each with a PPV of 1.6% (34).

Abnormal spirometric results remained significantly associated with lung cancer even after the exclusion of data in the last 180 days before diagnosis. They suggested that spirometric testing be performed in patients with dyspnea and no clear diagnosis. As well, thrombocytosis in symptomatic patients should raise a physician's suspicion of lung cancer.

Evidence from Newly Identified Reviews

Five guidelines in addition to the NICE and NZGG guidelines and that included systematic reviews provided information on the diagnostic accuracy of investigations for lung cancer (25-29). SIGN included one study that found that only 2% of 345 lung cancer patients presented with a normal chest X-ray (29). For CT scans, four studies were included, although none of them were in the primary care setting. SIGN found that CT scans have a good sensitivity (89%-100%) but low specificity (56%-63%) in differentiating malignant from benign solitary pulmonary nodules, which may be improved with serial scans. For sputum cytology, three studies showed a wide variation in sensitivity (10%-97%) in the diagnosis of lung cancer that was dependent on the techniques of sample collection. SIGN suggested sputum cytology should be reserved for cases with large central lesions where bronchoscopy or other diagnostic tests are contraindicated.

The ACCP guideline by Kvale included a systematic review and found that chest radiographs negative for lung cancer may show positive results with bronchoscopy or CT imaging (25). From their systematic review based on two primary studies, Spiro et al reported symptoms, signs, and laboratory tests that would be useful in screening patients for metastatic disease (27). Another ACCP guideline by Rivera and Mehta found a pooled sensitivity of 0.66 and pooled specificity of 0.99 based on 17 studies for sputum cytology (26). They found that sensitivity was highly variable across studies, and there was no clear explanation for this.

The guideline developed by the Australian National Health and Medical Research Council in 2004 included five articles about sputum cytology (28). They found that sensitivity increased with the number of samples obtained (50% with one sample to 90% with three or more samples) with centrally placed squamous cell carcinomas and lowest with peripheral tumours or centrally placed small cell carcinomas, and with the use of induced ultrasonic nebulised sputum or optimal processing. In an editorial (38), they reported a specificity of 97.9%

Evidence from Newly Identified Primary Studies

Only two studies were found in addition to the studies reported by NICE and NZGG (11,13). Kemp et al prospectively collected sputum samples from patients suspected of having lung cancer based on medical history or symptoms. Smears were assessed by conventional cytology (reference standard) or by using an automated technique (LungSign test) (13). LungSign showed a sensitivity of 40% and a specificity of 91%.

Choi et al retrospectively compared the diagnostic accuracy of sputum samples from a hospital using conventional preparation (CP) versus a ThinPrep method (TP) (11). The diagnosis of lung cancer was confirmed histologically. The sensitivity of TP and CP were 50.4% and 30.6%, respectively. The specificity was 99.1% with TP and 100.0% with CP.

What major, known risk factors are predictive of lung cancer?

Evidence from NICE 2005

The systematic review by NICE included four secondary studies and concluded that people with the following risk factors were at higher risk of developing lung cancer: current or previous tobacco smoking, smoking-related chronic obstructive pulmonary disease (COPD),

previous exposure to asbestos, or a previous history of cancer (especially head and neck cancer) (2). Other risk factors from the NICE systematic review and listed in the NZGG guideline included occupational exposure to dust or microscopic particles (e.g., wood dust, silica); a history of COPD, silicosis, or tuberculosis; a family history of cancer; or exposure to known carcinogens (e.g., radon, chromium, nickel) (2,3).

Evidence from Newly Identified Reviews

Two guidelines that included systematic reviews provided information addressing this question (25,29). The SIGN guideline included one prospective study that found 22% of patients diagnosed with lung cancer had coexistent COPD (29). The ACCP guideline by Kvale suggested the risk factors for lung cancer included tobacco smoking; passive cigarette smoke exposure; asbestos, radon, and selected other carcinogen exposure; COPD; and a family history of lung cancer (25).

Which factors are associated with delayed referral? Which factors influence delay by patient and which delay by provider? Does a delay in the time to consultation affect patient outcome?

Evidence from NICE 2005 and NZGG 2009

The systematic review conducted by the NZGG included seven primary studies about delay (3). The authors found that patients experiencing non-specific symptoms common in the primary care setting (e.g., cough, pain) were associated with patient delay. In addition, people with multiple medical problems or multiple consecutive investigations in primary care were associated with practitioner delay.

The NICE systematic review included two primary studies and reported that delay can occur when patients fail to recognize the significance of a symptom(s) such as a prolonged cough (2). Also, presentation with non-respiratory symptoms such as shoulder pain can increase the delay in diagnosis.

Evidence from Newly Identified Reviews

There were five systematic reviews, two of which included guidelines, in our updated literature search from NZGG that investigated the factors associated with delay (12,17,19,27,29). SIGN included two primary cohort studies (29). One study found no association between delayed referral and the stage of lung cancer, and another study found shorter delays were associated with poorer prognosis.

In addition to the factors affecting delay mentioned in the NZGG and NICE guidelines, Spiro et al suggested primary care physicians may fail to recognize the signs or symptoms of lung cancer in their patients (27). This may be due to the infrequent experience of seeing lung cancer patients in practice, as well as attributing the often common and non-specific symptoms to benign diseases.

Olsson et al (2009) performed a systematic review of timeliness of care for lung cancer patients (n=53 studies) (17). The median time from primary care referral to specialist ranged from 13 to 33 days across four studies. Factors associated with less timely care included atypical symptoms, co-morbid conditions, requirement for multiple diagnostic tests, and initial referral to a non-respiratory physician.

The Singh et al (2007) systematic review of diagnostic errors in cancer found that the factors associated with increased patient-mediated delay included the refusal of closer examination and patient beliefs about their health changes (19). Practitioner-mediated factors that increased delay included not recognizing symptoms, an insufficient or ineffective work-up

(e.g., performing numerous other procedures before biopsy), over-reliance on chest X-rays to diagnose lung cancer, and imaging (X-ray and CT scan) follow-up failure.

Hanna et al (2005) performed a systematic review of all cancers, assessing the two-week referral rule developed in the United Kingdom (12). They included two audits for lung cancer and found a high rate of adherence to the two-week referral guideline. They suggested that this may be attributed to the ability of referring clinicians to make a diagnosis on the basis of an abnormal chest radiograph.

Evidence from Newly Identified Primary Studies

Since the literature review conducted by the NZGG, only one prospective study was included (15). Lo et al (2007) implemented a Time to Treat Program in Ontario, Canada to reduce wait times (15). They developed a referral form to be completed by referring physicians and used a clerical facilitator to fast-track patients through a diagnostic pathway algorithm. The median wait time from suspicion of lung cancer to referral for specialist consultation decreased from 20 days to 6 days.

Our updated literature search since the NZGG guideline includes six retrospective studies that examined factors influencing delay (10,16,18,20,23,32). Chandra et al (2009) retrospectively reviewed patients with lung cancer in a tertiary care setting (10). They found that delay between the onset of symptoms to a confirmed diagnosis had no correlation with the presence of cough, shortness of breath, chest pain, hemoptysis, or hoarseness of voice. Delay in diagnosis was significantly higher in patients who had received antitubercular treatment initially (mean difference, 65.5 days; 95% confidence interval [CI] of difference, 24.5 to 106.6, p=0.002).

Lovgren et al (2008) reviewed 314 patients diagnosed with primary lung cancer at a university hospital (16). The presence of a lump and or resistance recorded in the medical records shortened the delay from first symptom reported to first visit at a health care system. Hemoptysis and appetite loss decreased the delay from first visit at a health care system to referral to a specialist.

Rolke et al (2007) prospectively recruited patients with primary lung cancer in Norway and retrospectively asked patients about symptom and referral history (18). Having an X-ray or CT scan of the chest prior to specialist referral did not affect delay from the general practitioner to the final diagnosis. Multivariate logistic analysis showed that the diagnosis of advanced tumour stage (odds ratio [OR], 0.49; 95% CI, 0.27 to 0.90) or poor performance status (OR, 0.48; 95% CI, 0.28 to 0.80) reduced referral delay.

Smith et al (2009) recruited consecutive patients with lung cancer and retrospectively asked about initial symptoms (20). Multiple linear regression analysis revealed independent factors associated with increased time before consulting such as living alone, a history of COPD, and longer pack-years of smoking. Hemoptysis, new onset of shortness of breath, cough, loss of appetite, history of chest infection, and renal failure were associated with earlier consulting.

Yaman et al (2009) reviewed lung cancer patients at a secondary care setting and found there was no relationship between age, gender, TNM classification, ECOG performance status, presence of endobronchial lesions, radiological localization of the lesion, family history of lung cancer and the intervals from first symptoms to admission or diagnosis (32). Also, there was no significant relationship between symptom type and the interval to admission to a specialist.

Yilmaz et al (2008) retrospectively collected delay history from all patients with primary lung cancer (23). The time from the onset of symptoms to the first visit to a physician or from first visit to physician to admission to hospital did not correlate with pathologic tumour stage.

DISCUSSION

Due to the paucity of evidence for lung cancer in the primary care setting, definitive conclusions could not be derived for the diagnostic accuracy of signs, symptoms, diagnostic tests, or risk factors associated with lung cancer. The Working Group agreed with the signs and symptoms of lung cancer listed in the NICE and NZGG guidelines, which are superior vena cava obstruction, stridor, hemoptysis, finger clubbing, enlarged lymph nodes, cough (persistent or unexplained), weight loss (unexplained), dyspnea, chest and/or shoulder pain, hoarseness, and an abnormal chest X-ray (2,3). Furthermore, patients might present with metastases. In addition, the Working Group chose to include dysphagia as a symptom of lung cancer because it was reported as a symptom for lung cancer in the NICE review and was found to be a major clinical symptom among lung cancer patients in a tertiary care setting (2,10). Furthermore, paraneoplastic syndromes were included by the Working Group, based on the review by Spiro et al that reported that paraneoplastic syndromes may occur in 10% of patients with lung cancer (27). Our literature review did not provide evidence for additional risk factors associated with lung cancer beyond those listed in the NICE or NZGG guidelines (2,3). In addition, no evidence was found to challenge the list of risk factors by suggesting that any item should be removed. Therefore, the Working Group agreed that the risk factors for lung cancer include current or previous smoking, COPD, previous exposure to asbestos, and a history of cancer (especially head and neck cancer). Other risk factors may include occupational exposure to dust or microscopic particles (e.g., wood dust, silica); past medical history of COPD, silicosis or tuberculosis; family history of cancer; exposure to known carcinogens (e.g., radon, chromium, nickel); and passive exposure to tobacco smoke.

The NICE and NZGG guidelines recommend ordering chest X-rays but urge physicians to refer if a chest X-ray is negative but there is still a high suspicion of lung cancer (2,3). This is because false negatives can occur with chest X-rays. In the updated search, two systematic reviews also report the high likelihood of false-negative results with chest X-rays (25,29).

NICE and NZGG do not report studies on the diagnostic accuracy of CT scans (2,3). As well, in the updated search there were few studies assessing the diagnostic accuracy of CT scans; therefore, no conclusions could be drawn (29).

NICE and NZGG do not recommend sputum cytology (2,3). The evidence from our updated systematic review suggests that, although the specificity is high, the sensitivity is highly variable (11,13,26,28,29).

Based on the interpretation of the evidence for diagnostic tests, the opinion of the Working Group is that chest X-rays should be ordered as a preliminary investigation for signs or symptoms of lung cancer. However, if a physician has a suspicion of lung cancer with a negative chest X-ray, a referral should be made. In addition, because sputum cytology shows variable sensitivity, the Working Group does not recommend sputum cytology as a primary investigation test for lung cancer.

The patient-related or family physician-related factors that may delay referral or the diagnosis of lung cancer found in the updated literature search since NZGG 2009 included a fear of a diagnosis of cancer, not recognizing the signs and symptoms suggestive of lung cancer, over-reliance on chest X-ray results to diagnose lung cancer, imaging follow-up failure, or initial referral to a non-respiratory physician (17,19,27).

Section 3 describes the adaptation of the identified guidelines and the development of recommendations from the evidence identified above.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, the Lung Cancer Referral Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest. Suzie Joanisse received a grant from CCO to develop a program to increase breast, colorectal, and cervical screening in Aboriginal communities.

Ranjan Sur owns a business by the name of R and M Sur Medicine Professional Corporation and received a research and development grant of $250,000 to develop the BrachyVision™ planning system for lung cancer brachytherapy. All other authors declared no conflicts of interest.

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REFERENCES

1. Cancercare.on.ca [Internet]. Toronto (ON): Cancer Care Ontario (CCO); 2011 [cited 2010 Aug 3].
2. National Collaborating Centre for Primary Care. Referral guidelines for suspected cancer. London: National Institute for Health and Clinical Excellence (NICE); 2005 Jun. Clinical Guideline No.: 27.
3. New Zealand Guidelines Group. Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities. Wellington (NZ): New Zealand Guidelines Group (NZGG); 2009.
4. Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12. Comment in: Ann Oncol. 2002 Sep;13(9):1507-9; author reply 1509.
5. The AGREE Collaboration, Cluzeau FA, Burgers JS, Brouwers M, Grol R, Mäkelä M, et al. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Safe Health Care. 2003;12(1):18-23.
6. Cancerview.ca [Internet]. (SAGE) Standards and guidelines evidence. Toronto (ON): Canada: Partnership Against Cancer; [cited 2010 MON Day#]. Available from: http://www.cancerview.ca.
7. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.
8. Ak G, Metintas M, Metintas S, Yildirim H, Erginel S, Alatas F. Lung cancer in individuals less than 50 years of age. Lung. 2007 Sep-Oct;185(5):279-86.
9. Beatty S, Stevens W, Stevens G, Kolbe J, Cox B. Lung cancer patients in New Zealand initially present to secondary care through the emergency department rather than by referral to a respiratory specialist. N Z Med J. 2009;122(1294):33-41.
10. Chandra S, Mohan A, Guleria R, Singh V, Yadav P. Delays during the diagnostic evaluation and treatment of lung cancer. Asian Pac J Cancer Prev. 2009 Jul-Sep;10(3):453-6.
11. Choi Y-D, Han C-W, Kim J-H, Oh I-J, Lee J-S, Nam J-H, et al. Effectiveness of sputum cytology using ThinPrep method for evaluation of lung cancer. Diagn Cytopathol. 2008 Mar;36(3):167-71.
12. Hanna SJ, Muneer A, Khalil KH. The 2-week wait for suspected cancer: Time for a rethink? Int J Clin Pract. 2005;59(11):1334-9.
13. Kemp RA, Reinders DM, Turic B. Detection of lung cancer by automated sputum cytometry. J Thorac Oncol. 2007 Nov;2(11):993-1000.
14. Koumarianou A, Fountzilas G, Kosmidis P, Klouvas G, Samantas E, Kalofonos C, et al. Non small cell lung cancer in the elderly: clinico-pathologic, management and outcome characteristics in comparison to younger patients. J Chemother. 2009 Nov;21(5):573-83.
15. Lo DS, Zeldin RA, Skrastins R, Fraser IM, Newman H, Monavvari A, et al. Time to treat: a system redesign focusing on decreasing the time from suspicion of lung cancer to diagnosis. J Thorac Oncol. 2007 Nov;2(11):1001-6.
16. Lovgren M, Levealahti H, Tishelman C, Runesdotter S, Hamberg K. Time spans from first symptom to treatment in patients with lung cancer--the influence of symptoms and demographic characteristics. Acta Oncol. 2008;47(3):397-405.
17. Olsson JK, Schultz EM, Gould MK. Timeliness of care in patients with lung cancer: A systematic review. Thorax. 2009;64(9):749-56.

18. Rolke HB, Bakke PS, Gallefoss F. Delays in the diagnostic pathways for primary pulmonary carcinoma in Southern Norway. Respir Med. 2007 Jun;101(6):1251-7.
19. Singh H, Sethi S, Raber M, Petersen LA. Errors in cancer diagnosis: current understanding and future directions. J Clin Oncol. 2007;25(31):5009-18.
20. Smith SM, Campbell NC, MacLeod U, Lee AJ, Raja A, Wyke S, et al. Factors contributing to the time taken to consult with symptoms of lung cancer: a cross-sectional study. Thorax. 2009 Jun;64(6):523-31.
21. Thammakumpee K, Juthong S, Viriyachaiyo V, Rittirak W, Tanomkiat W. Clinical manifestation and survival of patients with small-cell lung cancer. J Med Assoc Thai. 2007 Jul;90(7):1303-8.
22. Thomas R, Christopher DJ, Balamugesh T, Shah A. Clinico-pathologic study of pulmonary carcinoid tumours--a retrospective analysis and review of literature. Respir Med. 2008 Nov;102(11):1611-4.
23. Yilmaz A, Damadoglu E, Salturk C, Okur E, Tuncer LY, Halezeroglu S. Delays in the diagnosis and treatment of primary lung cancer: are longer delays associated with advanced pathological stage? Ups J Med Sci. 2008;113(3):287-96.
24. Gould MK, Fletcher J, Iannettoni MD, Lynch WR, Midthun DE, Naidich DP, et al. Evaluation of patients with pulmonary nodules: When is it lung cancer? ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132(3 Suppl):108S-30S.
25. Kvale PA. Chronic cough due to lung tumors: ACCP evidence-based clinical practice guidelines. Chest. 2006 Jan;129(1 Suppl):147S-53S.
26. Rivera MP, Mehta AC, American College of Chest Physicians. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007 Sep;132(3 Suppl):131S-48S.
27. Spiro SG, Gould MK, Colice GL, American College of Chest Physicians. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest. 2007 Sep;132(3 Suppl):149S-60S.
28. Australian Cancer Network Staff, Cancer Council Australia, Australian Cancer Network, National Health and Medical Research Council (Australia). Clinical practice guidelines for the prevention, diagnosis and management of lung cancer. Sydney (Australia): National Health and Medical Research Council (NHMRC); 2004.
29. Scottish Intercollegiate Guidelines Network. Management of patients with lung cancer: a national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2005.
30. Shapley M, Mansell G, Jordan JL, Jordan KP. Positive predictive values of ≥5% in primary care for cancer: systematic review. Br J Gen Pract. 2010 Sep;60(578):e366-77.
31. Uzun O, Atasoy Y, Findik S, Atici AG, Erkan L. A prospective evaluation of hemoptysis cases in a tertiary referral hospital. Clin Respir J. 2010 Jul;4(3):131-8.
32. Yaman N, Ozgen A, Celik P, Ozyurt BC, Nese N, Coskun AS, et al. Factors affecting the interval from diagnosis to treatment in patients with lung cancer. Tumori. 2009 Nov-Dec;95(6):702-5.
33. Liedekerken BM, Hoogendam A, Buntinx F, van der Weyden T, de Vet HC. Prolonged cough and lung cancer: the need for more general practice research to inform clinical decision-making. Br J Gen Pract. 1997 Aug;47(421):505.
34. Hamilton W, Peters TJ, Round A, Sharp D. What are the clinical features of lung cancer before the diagnosis is made? A population based case-control study. Thorax. 2005 Dec;60(12):1059-65.

35. Jones R, Latinovic R, Charlton J, Gulliford MC. Alarm symptoms in early diagnosis of cancer in primary care: cohort study using General Practice Research Database. Br Med J. 2007 May 19;334(7602):1040.
36. Hamilton W, Sharp D. Diagnosis of lung cancer in primary care: A structured review. Fam Pract. 2004;21(6):605-11.
37. Stapley S, Sharp D, Hamilton W. Negative chest X-rays in primary care patients with lung cancer. Br J Gen Pract. 2006 Aug;56(529):570-3.
38. Tockman MS, Mulshine JL. Sputum screening by quantitative microscopy: a new dawn for detection of lung cancer? Mayo Clin Proc. 1997 Aug;72(8):788-90.

Appendix 1. Members of the Lung Cancer Referral Working Group, Expert Panel, and Targeted Peer Reviewers.

Lung Cancer Referral Working Group	
Co-Chair: Sheila-Mae Young MD CCFP FCFP Regional Primary Care Lead, Cancer Care Ontario, Central East, ON	Co-Chair: Lisa Del Giudice MD CCFP FCFP Primary Care Practitioner Sunnybrook Family Practice Unit, Toronto, ON
Cheryl Levitt MBBCh CCFP FCFP Provincial Primary Care Lead Cancer Care Ontario, Toronto, ON	Marla Ash MD CCFP FCFP Regional Primary Care Lead, Cancer Care Ontario, Central, ON
Praveen Bansal MD CCFP FCFP Regional Primary Care Lead, Cancer Care Ontario, Central West and Mississauga Halton, ON	Andrew Robinson MD Medical Oncologist Sudbury Regional Hospital, Sudbury, ON
Roland Skrastins MD Respirologist Toronto East General Hospital, Toronto, ON	Yee Ung MD Radiation Oncologist Odette Cancer Centre, Toronto, ON
Robert Zeldin MD Thoracic Surgeon Toronto East General Hospital, Toronto, ON	Emily Vella PhD Research Coordinator Program in Evidence-based Care, Cancer Care Ontario, Hamilton, ON
Lung Cancer Referral Expert Panel	
Koop Alkema Provincial Primary Care and Cancer Network Regional Administrative Lead, ON	Hugh Langley Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON
Rob Annis Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON	Millie Litt Provincial Primary Care and Cancer Network Regional Administrative Lead, ON
Carole Beals Provincial Primary Care and Cancer Network Regional Administrative Lead, ON	Doina Lupea Program Manager Primary Care Cancer Care Ontario
Andrea Bezjak (conflict of interest not received) Lung Disease Site Group, CCO Princess Margaret Hospital, Toronto, ON	Richard Malthaner Lung Disease Site Group, CCO London Health Sciences Centre
Sandy Buchman Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON	Donna Maziak Lung Disease Site Group, CCO Program Director, Thoracic Surgery Ottawa Hospital, ON
Lynn Chappell Provincial Primary Care and Cancer Network Regional Administrative Lead, ON	Laura McDonald Provincial Primary Care and Cancer Network Regional Administrative Lead, ON
John Day Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON	Heather McLean Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON
Lee Donohue Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON	Alison McMullen Provincial Primary Care and Cancer Network Regional Administrative Lead, ON
Bill Evans Lung Disease Site Group, CCO Juravinski Cancer Centre, Hamilton, ON	Michael Mills Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON

Conrad Falkson Lung Disease Site Group, CCO Cancer Centre of Southeastern Ontario, Kingston General Hospital	Kim Mundy Provincial Primary Care and Cancer Network Regional Administrative Lead, ON
Mark Gaskin Provincial Primary Care and Cancer Network Regional Administrative Lead, ON	Julia Niblett Provincial Primary Care and Cancer Network Regional Administrative Lead, ON
Danusia Gzik Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON	Janice Owen Provincial Primary Care and Cancer Network Regional Administrative Lead, ON
Amanda Hey Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON	Rosanne Pegler Provincial Primary Care and Cancer Network Regional Administrative Lead, ON
Suzie Joanisse Provincial Primary Care and Cancer Network Regional Administrative Lead, ON	Carol Rand Provincial Primary Care and Cancer Network Regional Administrative Lead, ON
Sara Kaune Provincial Primary Care and Cancer Network Regional Administrative Lead, ON	Ranjan Sur Professor, Departments of Oncology and Medicine McMaster University, Hamilton, ON
Jaro Kotalik Lung Disease Site Group, CCO Director, Centre for Health Care Ethics Lakehead University, ON	Sophie Wilson Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON
Lung Cancer Referral Targeted Peer Reviewers	
Julian Dobranowski Associate Clinical Professor of Diagnostic Imaging McMaster University, Faculty of Health Sciences Hamilton, ON	Jeff Sisler Director, Primary Care Oncology Program, CancerCare Manitoba Associate Professor, Departments of Family Medicine and Internal Medicine, University of Manitoba
Anthony D'Urzo Associate Professor, Department of Family and Community Medicine, Faculty of Medicine, University of Toronto, ON	

Appendix 2. List of sites searched for the environmental scan.

CMA Infobase
The Physicians Query Database (National Cancer Institute)
National Guideline Clearing House
NICE (UK) – NICE Guidance
SIGN (UK) – SIGN Guidelines
ASCO (US) – ASCO Guidelines
NCCN (US) – NCCN home (consensus-based)
National Health and Medical Research Council (Aus) – Cancer Guidelines
New Zealand Guidelines Group - Guidelines

Canadian provincial cancer agencies:
BC Cancer Agency – Cancer management guidelines
Alberta Cancer Board – Treatment Guidelines
Saskatchewan Cancer Agency – Follow-up Guidelines
Cancer Care Manitoba – CCM Home
Cancer Care Nova Scotia - Guidelines

National cancer agencies:
NZ Cancer Control Trust
The Cancer Council Australia
National Cancer Control Initiative (AUS)
NHS (UK)

Organizations:
American College of Chest Physicians
Ontario Lung Association
American Thoracic Society – American Journal of Respiratory and Critical Care Medicine
Canadian Cancer Society

Appendix 3. Literature search strategies.

MEDLINE signs/symptoms

Database: Ovid MEDLINE(R) <1996 to February Week 3 2010> Search Strategy:

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1 exp "Sensitivity and Specificity"/ (257178)
2 false negative reactions/ or false positive reactions/ (13346)
3 (sensitivity or specificity or accura$).ab,ti. (474608)
4 diagnos$.ab,ti. (675617)
5 predictive value$.ab,ti. (33435)
6 reference value$.ab,ti. (5372)
7 ROC.ab,ti. (9736)
8 (likelihood adj ratio$1).ab,ti. (4454)
9 monitoring.tw. (135450)
10 (false adj (negative$1 or positive$1)).ab,ti. (24320)
11 (randomized controlled trial or controlled clinical trial).pt. (219134)
12 double-blind method/ or single-blind method/ (69713)
13 practice guideline.pt. (11637)
14 consensus development conference$.pt. (5176)
15 review.pt. (969050)
16 review.ab. (341939)
17 (meta-analysis or metaanalysis).ab. (16867)
18 meta-analysis.pt. (20815)
19 meta-analysis.ti. (10338)
20 (cohort adj stud$).ab,ti. (38966)
21 exp cohort studies/ (483039)
22 (single blind$3 or double blind$3 or triple blind$3).ab,ti. (55099)
23 or/1-22 (2632308)
24 letter.pt. (365247)
25 comment.pt. (309637)
26 editorial.pt. (170311)
27 or/24-26 (593853)
28 23 not 27 (2562958)
29 exp Respiratory Tract Neoplasms/ (78859)
30 Adenocarcinoma, Bronchiolo-Alveolar/ (795)
31 ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis)).tw. (55903)
32 or/29-31 (91728)
33 Cough/ (4973)
34 cough$.tw. (15116)
35 Dyspnea/ (6701)
36 dyspn$.tw. (14924)
37 short$ of breath.tw. (2272)
38 breathless$.tw. (1496)
39 Hemoptysis/ (1683)
40 (hemoptysis or haemoptysis).tw. (3018)
41 (blood$ adj2 (sputum or spit or spittle or phlegm)).ab,ti. (728)
42 Hoarseness/ (682)
43 hoarse$.tw. (1769)
44 chest pain/ or shoulder pain/ (6935)
45 ((chest or shoulder) adj3 pain$).tw. (13387)
46 Respiratory Sounds/ (3464)
47 wheez$.tw. (4956)

48 exp body weight changes/ (26256)
49 (weight adj1 (loss or gain or chang$)).tw. (41740)
50 Flushing/ (454)
51 ((face or facial) adj flushing).tw. (212)
52 Diarrhea/ (12803)
53 (diarrhea or diarrhoea).tw. (28506)
54 (Bronchitis/ or exp Pneumonia/) and Recurrence/ (531)
55 ((bronchitis or pneumonia) adj recur$).tw. (34)
56 "signs and symptoms"/ (37)
57 or/33-56 (137375)
58 28 and 32 and 57 (3064)
59 limit 58 to (english language and humans) (2171)
60 (200708: or 200709: or 20071: or 2008: or 2009: or 2010:).ed. (1755524)
61 59 and 60 (541)

EMBASE signs/symptoms
Database: EMBASE <1996 to 2010 Week 07>
Search Strategy:
---
1 "sensitivity and specificity"/ (61132)
2 false negative result/ or false positive result/ (5935)
3 (sensitivity or specificity or accura$).ab,ti. (447155)
4 diagnos$.ab,ti. (659380)
5 predictive value$.ab,ti. (32781)
6 reference value$.ab,ti. (5298)
7 ROC.ab,ti. (9233)
8 (likelihood adj ratio$1).ab,ti. (4206)
9 monitoring.tw. (132831)
10 (false adj (negative$1 or positive$1)).ab,ti. (23173)
11 double blind procedure/ or single blind procedure/ or triple blind procedure/ (64369)
12 exp controlled clinical trial/ (165121)
13 double blind procedure/ or single blind procedure/ or triple blind procedure/ (64369)
14 exp practice guideline/ (157434)
15 review.pt. (778874)
16 review.ab. (333674)
17 (meta-analysis or metaanalysis).ab. (16147)
18 Meta Analysis/ (33871)
19 meta-analysis.ti. (10280)
20 (cohort adj stud$).ab,ti. (37996)
21 cohort analysis/ (57607)
22 (single blind$3 or double blind$3 or triple blind$3).ab,ti. (56827)
23 or/1-22 (2157039)
24 letter.pt. (332953)
25 editorial.pt. (198989)
26 or/24-25 (531942)
27 23 not 26 (2107753)
28 exp Respiratory Tract Cancer/ (85473)
29 exp Respiratory Tract Tumor/ (101057)
30 ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis)).tw. (56184)
31 or/28-30 (108291)
32 coughing/ or irritative coughing/ (23756)
33 cough$.tw. (15124)

34 Dyspnea/ (33899)
35 dyspn$.tw. (14828)
36 short$ of breath.tw. (2271)
37 breathless$.tw. (1504)
38 Hemoptysis/ (5035)
39 (hemoptysis or haemoptysis).tw. (3053)
40 (blood$ adj2 (sputum or spit or spittle or phlegm)).ab,ti. (641)
41 Hoarseness/ (3141)
42 hoarse$.tw. (1854)
43 exp Pain/ and (chest or shoulder$).tw. (15220)
44 ((chest or shoulder) adj3 pain$).tw. (13510)
45 Wheezing/ (6922)
46 weight change/ or weight gain/ or weight reduction/ (62763)
47 (weight adj1 (loss or gain or chang$)).tw. (39434)
48 Flushing/ and (face or facial).tw. (297)
49 ((face or facial) adj flushing).tw. (211)
50 Diarrhea/ (64316)
51 (diarrhea or diarrhoea).tw. (26749)
52 (Bronchitis/ or exp Pneumonia/) and Recurrent Disease/ (1108)
53 ((bronchitis or pneumonia) adj recur$).tw. (33)
54 clinical feature/ or symptom/ (394982)
55 or/32-54 (578271)
56 and/27,31,55 (10014)
57 limit 56 to (human and english language) (8244)
58 (2007: or 2008: or 2009: or 2010:).ew. (1960406)
59 57 and 58 (3315)

MEDLINE tests

Database: Ovid MEDLINE(R) <1996 to February Week 3 2010> Search Strategy:

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1 Primary health care/ (26352)
2 Family physician/ (7730)
3 ((family or general) adj practitioner$).mp. (17461)
4 gp.mp. (14578)
5 family physician$.mp. (5085)
6 family doctor$.mp. (1844)
7 Family practice/ (28175)
8 ((family or general) adj practice$).mp. (36399)
9 primary care.mp. (35644)
10 primary health care.mp. (29333)
11 or/1-10 (98625)
12 meta-analysis/ (20815)
13 "review literature"/ (969050)
14 meta-analy$.mp. (36194)
15 metaanal$.mp. (972)
16 (systematic$ adj (review$ or overview$)).mp. (20607)
17 meta-analysis.pt. (20815)
18 review.pt. (969050)
19 review.ti. (89020)
20 or/12-19 (1012339)
21 "case reports [publication type]"/ (0)
22 letter.pt. (365247)
23 historical article.pt. (93482)
24 comment.pt. (309637)
25 editorial.pt. (170311)

26 or/21-25 (678519)
27 20 not 26 (978906)
28 exp "sensitivity and specificity"/ (257178)
29 (sensitivity or specificity).tw. (305303)
30 exp Diagnostic Errors/ (42087)
31 predictive value$.tw. (33435)
32 predictive value$ of test$.tw. (77)
33 ROC.tw. (9736)
34 (ROC adj (analys$ or area or auc or characteristic$ or curve$)).tw. (8197)
35 (false adj (negative or positive)).tw. (20791)
36 accuracy.tw. (96297)
37 reference value$.tw. (5372)
38 likelihood ratio$.tw. (4468)
39 ((pre-test or pretest) adj probability).tw. (716)
40 post-test probability.tw. (194)
41 Diagnosis, differential/ (156896)
42 Diagnostic tests, routine/ (3421)
43 or/28-42 (732409)
44 exp Lung Neoplasms/ (62936)
45 exp Lung neoplasms/di (7319)
46 exp Lung Neoplasms/bl, pa, di, ra, ri, us, ul [Blood, Pathology, Diagnosis, Radiography, Radionuclide Imaging, Ultrasonography, Ultrastructure] (32996)
47 exp Spirometry/ (4674)
48 exp Radiography, Thoracic/ (10130)
49 Sputum/cy (1231)
50 Tomography, X-ray Computed/ (133701)
51 cxr.mp. (567)
52 (chest adj X-ray$).mp. (7734)
53 (sputum adj cytolog$).mp. (258)
54 (cytolog$ adj sputum).mp. (11)
55 (CT adj scan$).mp. (27608)
56 exp Blood Cell Count/ (43206)
57 (CBC or FBC).mp. (1128)
58 exp thrombocytosis/ (1848)
59 thrombocytosis.mp. (1639)
60 C-reactive protein/ (15561)
61 c-reactive protein$.mp. (22996)
62 Blood sedimentation/ (2229)
63 erythrocyte sedimentation rate.mp. (3846)
64 or/47-63 (229500)
65 43 and 44 and 64 (3281)
66 limit 65 to (english language and humans) (2613)
67 (200708: or 200709: or 20071: or 2008: or 2009: or 2010:).ed. (1755524)
68 66 and 67 (775)

EMBASE tests

Database: EMBASE <1996 to 2010 Week 07>
Search Strategy:

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1 exp Primary health care/ (41348)
2 general practitioner/ (27507)
3 ((family or general) adj practitioner$).mp. (33901)
4 gp.mp. (23280)
5 Family physician/ (27507)
6 family physician$.mp. (5276)

7 family doctor$.mp. (1461)
8 general practice/ (17822)
9 ((family or general) adj practice$).mp. (23858)
10 primary care.mp. (32364)
11 primary health care.mp. (10931)
12 or/1-11 (108582)
13 Meta Analysis/ (33871)
14 "systematic review"/ (30835)
15 (meta-analy$ or metaanaly$).mp. (45121)
16 (systematic adj (review$ or overview$)).mp. (39408)
17 review.pt. (778874)
18 review.ti. (86948)
19 or/13-18 (848084)
20 letter.pt. (332953)
21 editorial.pt. (198989)
22 or/20-21 (531942)
23 19 not 22 (841566)
24 "sensitivity and specificity"/ (61132)
25 sensitivity.tw. (216861)
26 specificity.tw. (133140)
27 exp "prediction and forecasting"/ (289820)
28 predictive value$.tw. (32781)
29 predictive value$ of test$.tw. (74)
30 roc curve/ (2417)
31 (ROC adj (analys$ or area or auc or characteristic$ or curve$)).tw. (7784)
32 exp diagnostic error/ (23207)
33 (false adj (positive or negative)).tw. (19932)
34 diagnostic accuracy/ (118607)
35 accuracy.tw. (90057)
36 reference value/ (11181)
37 reference value$.tw. (5298)
38 likelihood ratio$.tw. (4223)
39 ((pre-test or pretest) adj probability).tw. (718)
40 post-test probability.tw. (182)
41 differential diagnosis/ (88178)
42 or/24-41 (801318)
43 exp thorax radiography/ (49040)
44 (chest adj X-ray$).mp. (7096)
45 cxr.mp. (592)
46 sputum cytodiagnosis/ (726)
47 (sputum adj cytolog$).mp. (312)
48 (cytolog$ adj sputum).mp. (38)
49 spirometry/ (8754)
50 spirometry.mp. (9472)
51 exp computer assisted tomography/ (238414)
52 (ct adj scan$).mp. (27280)
53 exp blood cell count/ (65723)
54 (CBC or FBC).mp. (998)
55 thrombocytosis.mp. or THROMBOCYTOSIS/ (2185)
56 c-reactive protein.mp. or C Reactive Protein/ (33758)
57 erythrocyte sedimentation rate/ (9503)
58 erythrocyte sedimentation rate.mp. (10136)
59 or/43-58 (371380)
60 exp Respiratory Tract Tumor/ (101057)
61 42 and 59 and 60 (6257)

62 limit 61 to (human and english language) (5065)
63 (2007: or 2008: or 2009: or 2010:).ew. (1960406)
64 62 and 63 (1878)

MEDLINE risk factors

Database: Ovid MEDLINE(R) <1996 to February Week 3 2010> Search Strategy:

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1 meta-Analysis as topic/ (7854)
2 meta analysis.pt. (20815)
3 (meta analy$ or metaanaly$).tw. (24735)
4 (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw. (21090)
5 (systematic adj (review$ or overview?)).tw. (19541)
6 (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw. (25295)
7 or/1-6 (58753)
8 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab. (19163)
9 (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab. (12995)
10 (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab. (18337)
11 (study adj selection).ab. (4140)
12 10 or 11 (19500)
13 review.pt. (969050)
14 12 and 13 (12893)
15 7 or 8 or 9 or 14 (73671)
16 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. (772629)
17 15 not 16 (69887)
18 limit 17 to (english language and humans) (60155)
19 exp Respiratory Tract Neoplasms/ (78859)
20 Adenocarcinoma, Bronchiolo-Alveolar/ (795)
21 ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis)).tw. (55903)
22 exp Lung Neoplasms/ (62936)
23 exp Bronchial Neoplasms/ (19941)
24 exp Carcinoma, Bronchogenic/ or exp Carcinoma, Small Cell/ (23676)
25 exp Carcinoma, Non-Small-Cell Lung/ or exp Carcinoma, Bronchogenic/ or exp Carcinoma, Small Cell/ (23676)
26 or/19-25 (92832)
27 18 and 26 (1098)
28 (200406: or 200407: or 200408: or 200409: or 20041: or 2005: or 2006: or 2007: or 2008: or 2009: or 2010:).ed. (3719911)
29 27 and 28 (675)

EMBASE risk factors

Database: EMBASE <1996 to 2010 Week 08>

Search Strategy:

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1 exp Meta Analysis/ or exp "Systematic Review"/ (49212)
2 (meta analy$ or metaanaly$).tw. (24549)
3 (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw. (20607)

4 (systematic adj (review$ or overview?)).tw. (19078)
5 exp "Review"/ or review.pt. (782579)
6 (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab. (68816)
7 (study adj selection).ab. (5220)
8 5 and (6 or 7) (23763)
9 or/1-4,8 (77888)
10 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab. (14532)
11 (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab. (10146)
12 9 or 10 or 11 (85530)
13 (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/ (912302)
14 12 not 13 (77569)
15 limit 14 to (human and english language) (62319)
16 exp Respiratory Tract Cancer/ (85763)
17 exp Respiratory Tract Tumor/ (101409)
18 ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis)).tw. (56365)
19 exp lung tumor/ (82442)
20 exp bronchus tumor/ (1962)
21 exp lung carcinoma/ (40823)
22 exp lung non small cell cancer/ (22789)
23 exp small cell carcinoma/ (1628)
24 or/16-23 (109737)
25 15 and 24 (1966)
26 (2004: or 2005: or 2006: or 2007: or 2008: or 2009: or 2010:).ew. (3733765)
27 25 and 26 (1412)

MEDLINE delay

Database: Ovid MEDLINE(R) <1996 to February Week 3 2010> Search Strategy:

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1 (lung adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$)).mp. (72095)
2 exp respiratory tract neoplasms/ (78859)
3 1 or 2 (89545)
4 (delay$ adj3 practitioner$).mp. (32)
5 (delay$ adj3 diagnos$).mp. (7680)
6 diagnos$ delay$.mp. (851)
7 diagnos$ early.mp. (1283)
8 early diagnosis/ (5519)
9 earl$ diagnosis.mp. (25481)
10 earl$ detection.mp. (17519)
11 earl$ presentation.mp. (370)
12 earl$ symptom$.mp. (1070)
13 exp health behavior/ (48048)
14 exp attitude to health/ (156459)
15 (delay$ adj3 patient$).mp. (5360)
16 or/4-15 (221476)
17 "referral and consultation"/ (22446)
18 referral$.mp. (48091)
19 late$ referral$.mp. (290)
20 earl$ referral$.mp. (731)
21 or/17-20 (48091)

22 Disease progression/ (63334)
23 Time factors/ (378374)
24 Physician's practice patterns/ (24905)
25 or/17-24 (502786)
26 3 and 16 and 25 (324)
27 limit 26 to (english language and humans) (276)
28 (200708: or 200709: or 20071: or 2008: or 2009: or 2010:).ed. (1755524)
29 27 and 28 (91)

EMBASE delay

Database: EMBASE <1996 to 2010 Week 07>
Search Strategy:

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1 exp Lung Cancer/di [Diagnosis] (16047)
2 exp lung cancer/ (78320)
3 (lung adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$)).tw. (49515)
4 or/1-3 (85222)
5 Cancer diagnosis/ (43817)
6 early diagnosis/ (34719)
7 earl$ diagnosis.tw. (21124)
8 diagnos$ earl$.tw. (1569)
9 Delayed Diagnosis/ (1531)
10 (delay$ adj3 diagnos$).tw. (7691)
11 diagnos$ delay$.tw. (861)
12 (delay$ adj3 practitioner$).tw. (22)
13 exp Patient attitude/ (100071)
14 Attitude to health/ or Attitude to illness/ (4401)
15 earl$ detection.tw. (16186)
16 detect$ earl$.tw. (3013)
17 earl$ presentation.tw. (359)
18 earl$ symptom$.tw. (1060)
19 or/5-18 (207084)
20 patient referral/ (26907)
21 referral$.tw. (30325)
22 earl$ referral$.tw. (697)
23 late$ referral$.tw. (260)
24 or/20-23 (46360)
25 Time factors/ (53844)
26 exp disease course/ (796755)
27 clinical practice/ (86307)
28 or/20-27 (953739)
29 4 and 19 and 28 (3330)
30 limit 29 to (human and english language) (2810)
31 (2007: or 2008: or 2009: or 2010:).ew. (1960406)
32 30 and 31 (1138)

Appendix 4. Recommendations to adapt from existing guidelines.

Appendix 4 Table 1. Recommendations from existing guidelines.

NZGG 2009[1]	NICE 2005[2]	SIGN 2005[3]	Australian 2004[4]	ACCP 2007[5]
General Recommendations				
	A patient who presents with symptoms suggestive of lung cancer should be referred to a team specialising in the management of lung cancer, depending on local arrangements. (D)		All individuals with suspected lung cancer should be referred to a specialist with expertise in the management of lung disease for an opinion. (IV)	
When to Order a Chest X-ray				
A person should be referred urgently for a chest X-ray if they have (C): • unexplained haemoptysis OR • any of the following unexplained, persistent (lasting more than 3 weeks or less than 3 weeks in people with known risk factors†) symptoms and signs: -chest &/or shoulder pain -shortness of breath -weight loss/loss of appetite -abnormal chest signs – hoarseness –finger clubbing –cervical and/or supraclavicular lymphadenopathy –cough –features suggestive of	An urgent referral for a chest X-ray should be made when a patient presents with (D): • haemoptysis, or • any of the following unexplained persistent (that is, lasting more than 3 weeks) symptoms and signs: - chest and/or shoulder pain - dyspnea - weight loss - chest signs - hoarseness - finger clubbing -cervical &/or supraclavicular lymphadenopathy - cough with or without any of the above - features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin).	Patients should be referred urgently for a chest X-ray if they have experienced unexplained or persistent haemoptysis. (D) Patients should be referred for a chest X-ray if any of the following symptoms persist for more than three weeks without an obvious cause (D): • cough • chest/shoulder pain • dyspnea • weight loss • chest signs • hoarseness • finger clubbing • Features suggestive of metastases from lung cancer (e.g., brain, bone, liver or skin) • Persistent cervical/supraclavicular lymphadenopathy A chest X-ray should be		

NZGG 2009[1]	NICE 2005[2]	SIGN 2005[3]	Australian 2004[4]	ACCP 2007[5]
metastasis from a lung cancer (e.g., in brain, bone, liver or skin) †Current or ex-smokers, smoking-related chronic obstructive pulmonary disease, previous exposure to asbestos, history of cancer (especially head and neck cancer)	A report should be made back to the referring primary healthcare professional within 5 days of referral. Unexplained changes in existing symptoms in patients with underlying chronic respiratory problems should prompt an urgent referral for chest X-ray.(D) In individuals with a history of asbestos exposure and recent onset of chest pain, shortness of breath or unexplained systemic symptoms, lung cancer should be considered and a chest X-ray arranged. If this indicates a pleural effusion, pleural mass or any suspicious lung pathology, an urgent referral should be made. (C)	performed on all patients being investigated for the possibility of lung cancer (D).		
When to Order CT Scans				
		Contrast enhanced CT scanning of the chest and abdomen is recommended in all patients with suspected lung cancer, regardless of chest X-ray results. (D) A tissue diagnosis should not be inferred from CT appearances alone. (D) CT scanning should be performed prior to further		

NZGG 2009[1]	NICE 2005[2]	SIGN 2005[3]	Australian 2004[4]	ACCP 2007[5]
		diagnostic investigations, including bronchoscopy, and the results used to guide the investigation that is most likely to provide both a diagnosis and stage the disease to the highest level. (D)		
When to Order Sputum Cytology				
Sputum cytology is not recommended for the investigation of lung cancer (✓)		Sputum cytology should only be used in patients with large central lesions, where bronchoscopy or other diagnostic tests are deemed unsafe. (D)	Sputum cytology is recommended to help establish a positive diagnosis of lung cancer in individuals with a central pulmonary mass. (III)	In patients suspected of having lung cancer, who present with a central lesion with or without radiographic evidence of metastatic disease, in whom a semi-invasive procedure such as bronchoscopy or transthoracic needle aspiration might pose a higher risk, sputum cytology is recommended as an acceptable method of establishing the diagnosis. However, the sensitivity of sputum cytology varies by the location of the lung cancer. It is recommended that further testing be performed with a nondiagnostic sputum cytology test if the suspicion of lung cancer remains. (1C) (Rivera and Mehta 2007)
What to Do After Receiving Results of X-ray				
A person should be referred urgently to a specialist if they have a normal chest X-ray, but there is a high suspicion of lung cancer (C)	If the chest X-ray is normal, but there is a high suspicion of lung cancer, patients should be offered an urgent referral. (D)	Even with a normal chest X-ray, patients who have experienced unexplained, non-specific symptoms, e.g., fatigue potentially attributable to lung cancer,		In every patient with an SPN, we recommend that clinicians estimate the pretest probability of malignancy either qualitatively by using their clinical judgment or

NZGG 2009[1]	NICE 2005[2]	SIGN 2005[3]	Australian 2004[4]	ACCP 2007[5]
A person with risk factors* for lung cancer who has consolidation on an initial chest X-ray should have a repeat chest X-ray within 6 weeks to confirm resolution (✓) *Current or ex-smokers, smoking-related chronic obstructive pulmonary disease, previous exposure to asbestos, history of cancer (especially head and neck cancer)		for more than six weeks should be referred urgently to a respiratory physician. (D)		quantitatively by using a validated model. (1C) (Gould et al 2007) In a patient with an SPN that is stable on imaging tests for at least 2 years, we suggest that no additional diagnostic evaluation be performed, except for patients with pure ground-glass opacities on CT, for whom a longer duration of annual follow-up should be considered. (2C) (Gould et al 2007)
Patients with Risk Factors				
	Patients in the following categories have a higher risk of developing lung cancer (C): are current or ex-smokers • have smoking-related chronic obstructive pulmonary disease (COPD) • have been exposed to asbestos • have a previous history of cancer (especially head and neck). An urgent referral for a chest X-ray or to a team specialising in the management of lung cancer should be made as for other patients but may be considered sooner, for	A chest X-ray should be performed in patients with COPD who develop new symptoms (especially weight loss) that might be attributable to lung cancer. (✓)		

NZGG 2009[1]	NICE 2005[2]	SIGN 2005[3]	Australian 2004[4]	ACCP 2007[5]
	example if symptoms or signs have lasted for less than 3 weeks.			
When to Urgently/Immediately Refer				
A person should be referred urgently to a specialist if they have (C): • persistent haemoptysis and are smokers or ex-smokers aged 40 years or older • a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation)	An urgent referral should be made for any of the following (D): • persistent haemoptysis in smokers or ex-smokers who are aged 40 years and older • a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation). Immediate referral should be considered for the following (C): Immediate referral should be considered for the following: signs of superior vena caval obstruction • (swelling of the face and/or neck with fixed elevation of jugular venous pressure) • stridor	Patients should be referred urgently to a chest physician if they have any of the following (D): • Persistent hemoptysis in smokers or ex-smokers over 40 years of age • A chest X-ray suggestive or suspicious of lung cancer (including pleural effusion and slowly resolving consolidation) Signs of superior vena caval obstruction (swelling of the face and or neck with fixed elevation of jugular • venous pressure) • Stridor (emergency referral)		
Referral Process				
The smoking status of all patients should be recorded and regularly updated in the practice notes (✓)		Patients should be offered tailored, clear and accurate information, including an indication of the expected time scale of the referral process (✓). Verbal and written communication between		

NZGG 2009[1]	NICE 2005[2]	SIGN 2005[3]	Australian 2004[4]	ACCP 2007[5]
		health professionals should include information regarding what the patient has been told about their diagnosis, investigation, treatment and prognosis (✓). Clinicians should consider using different approaches for conveying information depending upon patients' preferences (✓) e.g.: • Verbal (from different healthcare professionals) Written (high quality • information sheets and leaflets) Details of appropriate websites • Recorded audio tapes of the consultation and discussion.		
Timelines				
After urgent referral for chest X-ray, the chest X-ray should be completed and reported within one week (✓)		Patients referred to a respiratory physician should be seen promptly, ideally within two weeks (✓)		

Abbreviations: ACCP, American College of Chest Physicians; NICE, National Institute for Health and Clinical Excellence; NZGG, New Zealand Guidelines Group; SIGN, Scottish Intercollegiate Guidelines Network.

[1] **See Table 2 (below) for Grading explanations**

[2] **See Table 3 (below) for Grading and Evidence explanations**

[3] **See Table 4 (below) for Grading and Evidence explanations**

[4] **See Table 5 (below) for Evidence explanations**

[5] **See Table 6 (below) for Grading of the Evidence and Recommendations**

Appendix 4 Table 2. Grading of NZGG 2009 recommendations.

Recommendations	
The recommendation is supported by good evidence (based on a number of studies that are valid, consistent, applicable and clinically relevant)	A
The recommendation is supported by fair evidence (based on studies that are valid, but there are some concerns about the volume, consistency, applicability and clinical relevance of the evidence that may cause some uncertainty but are not likely to be overturned by other evidence)	B
The recommendation is supported by international expert opinion	C
Grades indicate the strength of the supporting evidence rather than the importance of the evidence	

Good Practice Points	
Where no evidence is available, best practice recommendations are made based on the experience of the Guideline Development Team, or feedback from consultation within New Zealand	✓

Appendix 4 Table 3. Details of levels of evidence and grading of NICE 2005 recommendations

Levels of evidence

Hierarchy of evidence	
Ia	Systematic review or meta-analysis of randomised controlled trials
Ib	At least one randomised controlled trial
IIa	At least one well-designed controlled study without randomization
IIb	At least one well-designed quasi-experimental study, such as a cohort study
III	Well-designed non-experimental descriptive studies, case-control studies, and case series
IV	Expert committee reports, opinions and/or clinical experience of respected authorities
NICE	NICE guidelines or Health Technology Appraisal programme

Grades of recommendation

Grading of recommendations	
A	Based directly on level I evidence
B	Based directly on level II evidence or extrapolated from level I evidence
C	Based directly on level III evidence or extrapolated from level I or level II evidence
D	Based directly on level IV evidence or extrapolated from level I, level II, or level III evidence
A NICE	Recommendation taken from NICE guideline or Technology Appraisal
GPP	Good practice point based on the clinical experience of the GDG

Levels of evidence for studies of the accuracy of diagnostic tests for NICE 2005

Levels of evidence/Type of evidence	
Ia	Systematic review (with homogeneity)[†] of level-1 studies[‡]
Ib	Level-1 studies[‡]
II	Level-2 studies[§] Systematic reviews of level-2 studies
III	Level-3 studies[§§] Systematic reviews of level-3 studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience without explicit critical experience, based on physiology, bench research or 'first principles.'

†Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

‡Level-1 studies are studies that use a blind comparison of the test with a validation reference standard (gold standard) in a sample of patients that reflects the population to whom the test would apply.

§Level-2 studies are studies that have only one of the following: narrow population (the sample does not reflect the population to whom the test would apply), use a poor reference standard (defined as that where a 'test' is included in the 'reference', or where the 'testing' affects the 'reference'), the comparison between the test and reference standard is not blind or case-control studies.

§§Level-3 studies are studies that have at least two or three of the features listed above§.

Classification of recommendations for studies of the accuracy of diagnostic tests

Class Level of evidence	
A (DS)	Studies with level of evidence Ia or Ib
B (DS)	Studies with level of evidence II
C (DS)	Studies with level of evidence III
D (DS)	Based on studies with level of evidence IV

(DS – diagnostic studies).

Appendix 4 Table 4. Details of levels of evidence and grading of SIGN 2005 recommendations.

Levels of Evidence For SIGN

1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g., case reports, case series
4	Expert opinion

Grades of Recommendations for SIGN

A	At least one meta-analysis, systematic review of RCTs, or RCT rates as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rates as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rates as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
✓	Recommended best practice based on the clinical experience of the guideline development group

Appendix 4 Table 5. Designation of levels of evidence for the Australian 2004 Guideline.

I	Evidence obtained from a systematic review of all relevant randomized controlled trials.
II	Evidence obtained from at least one properly designed randomized controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

(In effect we listed all level III – as III regardless of category.)
These levels of evidence ratings have been adapted from: US Preventive Services Task Force., Guide to clinical preventive services: an assessment of the effectiveness of 169 interventions. M Fisher, Editor. Baltimore, Maryland: Williams and Williams, Baltimore; 1989.

Appendix 4 Table 6. Grading of the Evidence and Recommendations for ACCP Guidelines.

Quality of Evidence Scale

High	RCTs without important limitations or overwhelming evidence from observational studies*
Moderate	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies*
Low or very low	Observational studies or case series

*Although the determination of magnitude of the effect based on observational studies is often a matter of judgment, we offer the following suggested rule to assist this decision: a large effect would be a relative risk > 2 (risk ratio < 0.5) [which would justify moving from weak to moderate], and a very large effect is a relative risk > 5 (risk ratio < 0.2) [which would justify moving from weak to strong]. There is some theoretical justification in the statistical literature for these thresholds (the magnitude of effect that is unlikely or very unlikely to be due to residual confounding after adjusted analysis). However, once the decision is made, authors should be explicit in justifying their decisions.

Relationship of Strength of the Supporting Evidence to the Balance to Risks and Burdens

	Balance of benefits to Risks and Burdens			
Quality of Evidence	**Benefits outweigh risks/burdens**	**Risks/burdens outweigh benefits**	**Evenly balanced**	**Uncertain**
High	1A	1A	2A	
Moderate	1B	1B	2B	
Low or very low	1C	1C	2C	2C

Appendix 4. References.

- Australian National Health and Medical Research Council. Clinical practice guidelines for the prevention, diagnosis and management of lung cancer [Internet]. Sydney, Australia: The Cancer Council Network; 2004 [cited 2010 Mar 5]. Available from: http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp97.pdf.
- Gould MK, Fletcher J, Iannettoni MD, Lynch WR, Midthun DE, Naidich DP, et al. Evaluation of patients with pulmonary nodules: When is it lung cancer? ACCP evidence-based clinical practice guidelines. 2nd ed. Chest. 2007;132(3 Suppl):108S-130S.
- National Institute for Health and Clinical Excellence. Referral guidelines for suspected cancer [Internet]. London: National Institute for Health and Clinical Excellence; 2005 [cited 2010 Feb 4]. Available from http://www.nice.org.uk/CG027.
- New Zealand Guidelines Group. Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities [Internet]. Wellington, NZ: New Zealand Guidelines Group (NZGG); 2009 [cited 2010 Feb 4]. Available from: http://www.nice.org.uk/Guidance/CG27.
- Rivera MP, Mehta AC, American College of Chest Physicians. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines. 2nd ed. Chest. 2007 Sep;132(3 Suppl):131S-48S.
- Scottish Intercollegiate Guidelines Network. Management of patients with lung cancer: a national clinical guideline [Internet]. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network (SIGN); 2005 [cited 2010 Mar 5]. Available from: http://www.guidelines.gov/browse/archive.aspx?type=2.

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Evidence-Based Series 24-2: Section 3

Referral of Suspected Lung Cancer by Family Physicians and Other Primary Care Providers: EBS Development Methods and External Review Process

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A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: August 29, 2011

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- **Section 1: Guideline Recommendations**. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- **Section 2: Evidentiary Base.** Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- **Section 3: EBS Development Methods and External Review Process**. Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Provincial Primary Care and Cancer Network of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on primary care referral for suspected lung cancer, developed through review of an updated evidentiary base since the National Institute for Health and Clinical Excellence (NICE) 2005 and New Zealand Guidelines Group (NZGG) 2009 guidelines, an adaptation of existing guidelines, consensus of the Lung Cancer Referral Working Group, and input from external review participants in Ontario (3,4).

Development of the Recommendations

The recommendations from NZGG 2009, Suspected Cancer in Primary Care: Guidelines for Investigation, Referral and Reducing Ethnic Disparities (available from http://www.nzgg.org.nz/guidelines/dsp_guideline_popup.cfm?guidelineID=158); NICE 2005, Referral guidelines for suspected cancer (available from http://www.nice.org.uk/Guidance/CG27); the American College of Chest Physicians' Evidence-based Clinical Practice Guidelines (Gould et at 2007, Rivera and Mehta 2007); the Australian National Health and Medical Research Council 2004 (available from http://www.nhmrc.gov.au/publications/synopses/cp97syn.htm); and the Scottish Intercollegiate Guidelines Network (SIGN) 2005 (available from http://www.sign.ac.uk/guidelines/fulltext/80/index.html) were considered during the adaptation process (see Section 2: Appendix 4) (3-8). The updated evidentiary base was also considered. The evidentiary base consisted mainly of case series retrospective studies.

The Working Group held a teleconference to develop the recommendations through informal consensus. Each of the recommendations in Appendix 4 was discussed taking into consideration any evidence found in the systematic review. The recommendations were written and approved by all members during the meeting. The following content details the results of how the recommendations were generated.

The recommended wait times from the guidelines were all based on consensus. Therefore, all recommended wait times in this document were based on the expert opinion of this Working Group to be feasible in Ontario.

The Working Group felt the general recommendations from NICE 2005 and Australia 2005 were too general and needed to specifically mention the Diagnostic Assessment Programs (3,5). These recommendations could be covered in other recommendations.

For the indications for referral to the emergency department, the Working Group adapted the recommendation from the NICE guidelines for immediate referral (3). The Working

group chose to add massive hemoptysis based on common practice in Ontario as well as the Time-to-Treat Program (9).

For indications for chest X-ray, the working group choose to use the wording from the recommendation from the NZGG guidelines for urgent referral for a chest X-ray (4). Based on expert opinion, the position was that, for unexplained finger clubbing, features suggestive of metastasis from a lung cancer (e.g., brain, bone, liver, skin), and suspicious lymphadenopathy, the three-week time frame was not required for referral for a chest X-ray. The Working Group chose to include dysphagia as an indicator for a chest X-ray because it was reported in the NICE review as a symptom of lung cancer and was found to be a major clinical symptom among lung cancer patients in a tertiary care setting (3,10). Furthermore, paraneoplastic syndromes were included as indications for chest X-ray based on the review by Spiro et al (2007) that reported that paraneoplastic syndromes may occur in 10% of patients with lung cancer (11).

For patients with underlying chronic respiratory problems, the Working Group chose to adapt the recommendation from NICE (3). In addition, the list of risk factors was broadened to include all risk factors summarized by the NZGG, based on the review by NICE (4).

The recommendations for the indications for a CT scan were based on expert opinion. SIGN does provide some recommendations, but the evidence is weak (8). Therefore, the Working Group developed their own recommendations.

The recommendations varied between guidelines as to whether sputum cytology should be performed (4,5,7,8). The updated literature search found high specificity but variable sensitivity of sputum cytology in detecting lung cancer (5,7,8,12,13). Therefore, the Working Group endorsed the recommendation from the NZGG referral guidelines (4).

The recommendation for follow-up to consolidation on a chest X-ray was adapted from the NZGG referral guideline, which was based on the experience of their guideline development team (4). The Working Group chose to modify the NZGG recommendation by including all patients rather than specifying only patients with risk factors for lung cancer. In addition to consolidation, the Working Group also included unexplained pleural effusion based on their experience in their practices.

A recommendation for follow-up of solitary pulmonary nodules on imaging tests, adapted from the American College of Chest Physicians' Clinical Practice Guidelines for pulmonary nodules (6), was initially included. However, after internal review, the Working Group chose to remove this recommendation because patients with a solitary pulmonary nodule, independent of size, would be referred to a specialist.

The indications for referral to a specialist were adapted from the NZGG and NICE referral guidelines, which were based on expert opinion (3,4). Additional abnormal chest X-ray results were included from the Time-to-Treat Program (9). An unexplained elevated diaphragm was included based on the suggestion of an Expert Panel member. As well, information that should be provided to the specialist was taken from the Time-to-Treat Program (9).

The recommendations to reduce diagnostic delay were taken from evidence found in the NZGG and NICE guidelines, as well as from the updated literature search (11,14,15).

Development of One-Page Algorithms

One-page algorithms were developed to provide a quick reference guide for PCPs and/or educational material for patients. Currently, CCO does not have a general template for algorithm design that can be used for representing guideline information. Therefore, a search for algorithm designs from the following well-recognized, international guideline developers commonly used by the PEBC was conducted.

The search indicated that a variety of designs were being used to disseminate guideline information. From this list, the most commonly used designs were the Condensed Summary, the Flow Chart, and the Sectioned List. Consequently, these were used as models for

representing the information. The Microsoft Visio 2007 drawing and diagramming software was used to develop the sample algorithm designs. A questionnaire using Survey Monkey[1] (http://www.surveymonkey.com/) was developed and sent to the Expert Panel members for their feedback. Specifically, the questionnaire was used to assess which algorithm style was preferred by Expert Panel members, how it would be utilized (i.e., to make professional decisions or for patient education), and whether any modifications needed to be made to any of the layouts. The data from this survey is shown in Table 1.

Table 1. Responses to five items on the expert panel algorithm questionnaire.

		Reviewer Ratings (N=7)				
Question		**Flow Chart**	**Sectioned List**		**Condensed Summary**	
1. Rank the two best algorithm styles in order of preference		1,1,1,1,2,2,2	1,1,2		1,2,2,2	
2. If you prefer the Flow Chart algorithm style, which paper layout would you use? (Check one)		**Horizontal**	**Vertical**		**Either is okay**	
		16.7%	66.7%		16.7%	
		Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
3. I would make use of this algorithm layout in my professional decisions	Flow Chart	0	0	0	6	1
	Sectioned List	0	1	1	5	0
	Condensed Summary	0	1	1	4	0
4. I would make use of this algorithm layout for patient education.	Flow Chart	1	3	0	3	0
	Sectioned List	1	3	0	2	0
	Condensed Summary	1	4	1	1	0
5. Do you prefer to use another algorithm style that is not represented here?		**yes**		**no**		
		0%		100%		

Based on the results of the algorithm survey, the Expert Panel preferred the horizontal flow chart design. This design was used to create the algorithm in Section 1.

Lung Cancer Referral Expert Panel Review

Key issues raised by the guideline Expert Panel and the Working Group responses (immediately below) included the following:

- I believe FPs want "just in time delivery" of information. So when they get a chest x-ray report that suggests the presence of lung cancer, they might want to have an electronic decision support tool that tells them what set of tests need to be done and how to make a referral to an appropriate specialist for further workup.
    - The recommendation, "Decision-support tools should be readily available to assist FPs and other PCPs." was added under the recommendations to reduce diagnostic delay.

[1] Qadir S. Algorithm Feedback. http:www.surveymonkey.com/s/XMHDTXY (last visited 2010 Nov 18).

- I wonder if there should be a comment about possibly using high dose steroids if time to diagnosis might be delayed? That is if there is a long distance to an ER in a remote area for example or a delay in getting appropriate investigations or specialist care.
    - The Working Group felt this was beyond the scope of this document.
- Some of the recommendations lack clarity on points that could lead to overuse or underuse of referral. E.g. 'suspicious lymphadenopathy'...could this be defined? I believe NICE 2005 uses cervical and supraclavicular. Some definition of 'suspicious' as it relates to known lymph drainage patterns would be helpful.
    - The Working Group chose not to qualify lymphadenopathy, believing that all patients with lymphadenopathy should receive a chest X-ray.
- Features suggestive of metastatic lung cancer (e.g., in brain, bone, liver or skin): numerous patients present with metastatic disease before the primary is known; the presence of metastatic disease should lead to a chest x-ray as lung cancer commonly presents first with evidence of metastasis.
    - The recommendation was changed to “features suggestive of metastatic lung cancer that metastasize elsewhere and cancer that metastasized to the lung.”
- A more specific definition for 'chest signs' is needed
    - We have inserted hyperlinks to provide examples, references or explanations of conditions/signs/symptoms.
- All smokers cough, so it is the onset of a new cough or the change in a cough and it has to last for some period of time, as suggested 3 weeks
    - The Working Group decided against including the word ‘new’ because we have the word ‘unexplained’ in the recommendation.
- ...But what are the guidelines criteria for 'high suspicion' in this guideline? Is it haemoptysis? Is it weight loss/ loss of appetite? A big difference. It may be worthwhile to state 'in consultation with the radiologist' in this section.
    - The Working Group chose not to include ‘in consultation with the radiologist’ because FPs and other PCPs that have a high suspicion of lung cancer would be inclined to consult with the radiologist.
- Is a CT scan always necessary after a highly suspicious CXR, or can some patients go directly to the surgeon?
    - The Working Group agreed that patients should always have a chest computerized tomography (CT) scan after a suspicious chest X-ray; however, the ordering physician will depend on locally available resources.
- Indications for chest CT scan: should include the patient with symptoms of pneumonia whose chest x-ray fails to clear after a two-week course of antibiotic therapy
    - Non-resolving consolidation or effusion despite treatment was included as an example of an abnormal chest X-ray that raises suspicion of lung cancer.
- I suspect that if a work up was done for suspected lung cancer and was negative, yet no cytology was done, the physician may (inappropriately) be faulted and be subjected to a College or malpractice complaint.
    - The Working Group chose not to change their recommendation for sputum cytology based on the opinion of the respirologist, Dr. R. Skrastins.
- Sputum cytology: it is still a useful test for centrally arising tumours, particularly if squamous in histology.
    - The Working Group chose not to change their recommendation for sputum cytology based on the opinion of the respirologist, Dr. R. Skrastins.
- I think physicians might interpret that only individuals with risk factors for lung cancer should have a follow up chest X-ray. I would opt for a statement that is more general - that a person with consolidation should have a follow up chest X-ray.

    - The Working Group removed ‘risk factors for lung cancer’ from the recommendation under follow-up to diagnostic investigations.
- Six weeks is too long an interval. Chest x-ray should be repeated after a 2 week course of antibiotics.
    - The Working Group decided not to change this recommendation, based on their own clinical experiences.
- I don't see why you have differentiated between 'non-peripheral mass or nodule in smoker', 'peripheral nodule or mass in smoker' and 'nodule or mass in non-smoker'. Why not simply say 'mass or nodule'.
    - The Working Group reworded the recommendation to “a nodule or mass.”
- With pertinent information with referral, many facilities are able to retrieve the previous images by picture archiving and communication systems (PACS), so even including the phrase (with accompanying films and/or electronic copies or stating where previous images were done).
    - The recommendation was changed to “All efforts should be made for pre-existing imaging results including chest X-rays and CT scans (films and digital images should be available at the time of consultation).”
- Some suggested rewording: Family physicians and other primary care providers should include all relevant information regarding risk factors, presentation, diagnostic test results and co-morbidities in their referral letters and should ask patients to help retrieve electronic copies of their imaging tests to bring to specialist appointments and/ or provide the consultant/DAP with the site of where previous images were taken to facilitate PACS retrieval.
    - To reflect that co-morbidities should be included in the referral letter, the recommendation was changed to “All relevant other medical conditions and medications taken by patient.”
- Mention if early diagnosis will affect outcome.
    - The Working Group felt they could not speak to this issue due to the lack of evidence.
- Define delay.
    - The Working Group felt this was not necessary since studies measure different intervals between the onset of symptoms and a definitive diagnosis.
- What is appropriate education? Who will do it?
    - This recommendation was changed to “There should be appropriate educational tools developed and disseminated that highlight the signs and symptoms of lung cancer for FPs and other PCPs and for patients.”
- I’m not sure what ‘low threshold of suspicion’ means. Does this mean they should refer lots, or refer sceptically? I’m not sure everyone will interpret this phrase the same way.
    - Reworded the recommendation to “FPs and other PCPs should have a high index of suspicion with a low threshold for investigation of suspected lung cancer in ordering chest X-rays and referral to lung cancer specialists or the DAP.”
- I think it important to give a footnote to the timelines to state these are 'based on expert opinion. Clinical judgement and access to resources need also to be considered.'
    - The Working Group chose not to make this change. Physicians can refer to the full guideline if they want more information.
- Add elevated diaphragm to the box that lists descriptors of a chest x-ray that may be suggestive or suspicious of lung cancer.
    - The Working Group decided to add ‘elevated diaphragm’ to the list of descriptors of a chest X-ray that may be suggestive or suspicious of lung cancer.

PEBC Director’s Review

Prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by the Director of the PEBC, Dr. Melissa Brouwers, with expertise in methodological issues. The key issues raised by the Director and the Working Group responses (italicized) were the following:

- The questions do not lend themselves to actionable recommendations for the most part. The answers to the questions would be statements of facts. Also, the role of primary care here – except in being the intended audience – is a bit unclear.
  - *The questions have been reworded to address these issues.*
- More detail is need for the rationale behind wait times and the nature of studies that were included in the NICE 2005 guideline.
  - *More detail is provided to address these concerns.*
- Explain under the methods section that the NICE 2005 and NZGG 2009 guidelines were chosen a priori and the reasons why. Also, explain why an environmental scan of guidelines was performed.
  - *These concerns were explained more thoroughly in the document.*
- The discussion should include statements about what the working group believed were the most appropriate signs, symptoms and diagnostic tests for lung cancer.
  - *These were included in the discussion.*
- More detail is needed about how the consensus was achieved when developing the recommendations.
  - *This section was expanded.*

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC's Director, the Lung Cancer Referral Working Group circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the Lung Cancer Referral Working Group.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review May 19, 2011)

QUESTIONS
Overall question:
In patients presenting to primary care services with signs and/or symptoms of lung cancer, what should the referral process include?
The following questions are the factors considered in answering the overall question:

What signs, symptoms and other clinical features are predictive of lung cancer?
What is the diagnostic accuracy of investigations for lung cancer?
What major, known risk factors are predictive of lung cancer?
Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers? Does a delay in the time to consultation affect patient outcome?

TARGET POPULATION
Patients presenting in primary care settings comprise the target population. This guideline does not provide recommendations for patients in a screening program.

INTENDED USERS
This guideline is targeted to family physicians (FPs), general practitioners, emergency room physicians, other primary care providers (PCPs) (nurse practitioners, registered nurses, and physician assistants), respirologists, thoracic surgeons, and radiologists. For the purposes of this document, we have referred to FPs, general practitioners, emergency room physicians, and other PCPs as 'FPs and other PCPs'.

RECOMMENDATIONS
The following recommendations were adapted from the New Zealand Guidelines Group (NZGG) guideline Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities and the National Institute for Health and Clinical Excellence (NICE 2005), Referral guidelines for suspected cancer (3,4). The recommendations below reflect the integration of the NZGG 2009 and NICE 2005 recommendations, an updated systematic review of the research evidence since the NZGG 2009 or NICE 2005 guidelines, and consensus by the PEBC Primary Care Working Group for Referral for Suspected Lung Cancer (see Section 2: Appendix 1) (3,4).

Special consideration for these recommendations:

Factors that Increase the Risk of Lung Cancer
The following factors have been shown to increase the risk of lung cancer and will be referred to in the recommendations below: • Current or previous smoker or second-hand exposure to tobacco smoke • History of chronic obstructive pulmonary disease • Previous exposure to asbestos or other known carcinogens (e.g., radon, chromium, nickel) • Occupational exposure to dust or microscopic particles (e.g., wood dust, silica) • Personal or family history of cancer (especially lung, head and neck cancer) • Silicosis, tuberculosis

Indications for Referral to the Emergency Department
A person should be referred to the Emergency Department for the following: • Signs of superior vena cava obstruction • Stridor • Massive hemoptysis
Indications for Chest X-ray
A person should have a chest X-ray within two working days if they present with any of the following: • hemoptysis • new finger clubbing • suspicious lymphadenopathy • dysphagia

- features suggestive of lung cancer that has metastasized elsewhere or other cancers that have metastasized to the lung
- features suggestive of paraneoplastic syndromes

OR

any of the following unexplained signs or symptoms lasting more than three weeks (patients with known risk factors may be considered sooner):

- cough
- weight loss/loss of appetite
- shortness of breath
- chest and/or shoulder pain
- abnormal chest signs
- hoarseness

Patients with underlying chronic respiratory problems should have a chest X-ray within two weeks if they have unexplained changes in existing symptoms.

The requisition for a chest X-ray should include the presenting history, including all signs and symptoms suspicious of lung cancer and all risk factors.

Chest X-rays should be completed, reviewed and reported on by the radiologist, and the report read by the FP or other PCPs within two weeks of being ordered.

Indications for Chest CT scan

A person should have a chest CT scan within two weeks if they have any of the following:

- an abnormal chest X-ray that raises suspicion of lung cancer
- a normal chest X-ray, but there is a high suspicion of lung cancer, based on clinical judgement

The ordering physician (i.e., FP or other PCPs, specialist, radiologist, or Diagnostic Assessment Program [DAP]) will depend on locally available resources and processes for expedited CT scans.

Sputum Cytology

Sputum cytology is not recommended for the investigation of suspected lung cancer.

Follow-up to diagnostic investigations

A person who has consolidation or unexplained pleural effusion on an initial chest X-ray should be treated and have a chest X-ray repeated within six weeks to confirm resolution.

Indications for Referral to a Specialist (Respirologist or Thoracic Surgeon) or DAP

Patients should be referred and expect a consultation to a specialist or where locally available to the DAP within one to two weeks if they have any of the following:

- Persistent hemoptysis
- A chest X-ray suggestive or suspicious of lung cancer including:
    - A nodule or mass
    - Multiple pulmonary nodules
    - Non-resolving pleural effusion
    - Mediastinal or contralateral hilar adenopathy
    - Interstitial infiltrates
    - Slowly or non-resolving pneumonia or consolidation
    - Fibroapical disease suggesting possible tuberculosis
    - Unexplained elevated diaphragm
- A normal chest X-ray, but there is a high suspicion of lung cancer, based on clinical judgement

If promptly accessible, a chest CT scan can be simultaneously ordered with the referral while awaiting the specialist's consultation. This will depend upon locally available resources.

To expedite the diagnosis and avoid duplication of investigations, at a minimum, the following information should be provided to the specialist:

- History of patient, including all risk factors and signs or symptoms suspicious of lung cancer
- All efforts should be made for pre-existing imaging results, including chest X-rays and CT scans (films and digital images should be available at the time of consultation)
- All relevant other medical conditions and medications taken by patient
- All recent blood work

Recommendations to Reduce Diagnostic Delay

There should be appropriate educational tools developed and disseminated that highlight the signs and symptoms of lung cancer for FPs and other PCPs and for patients.

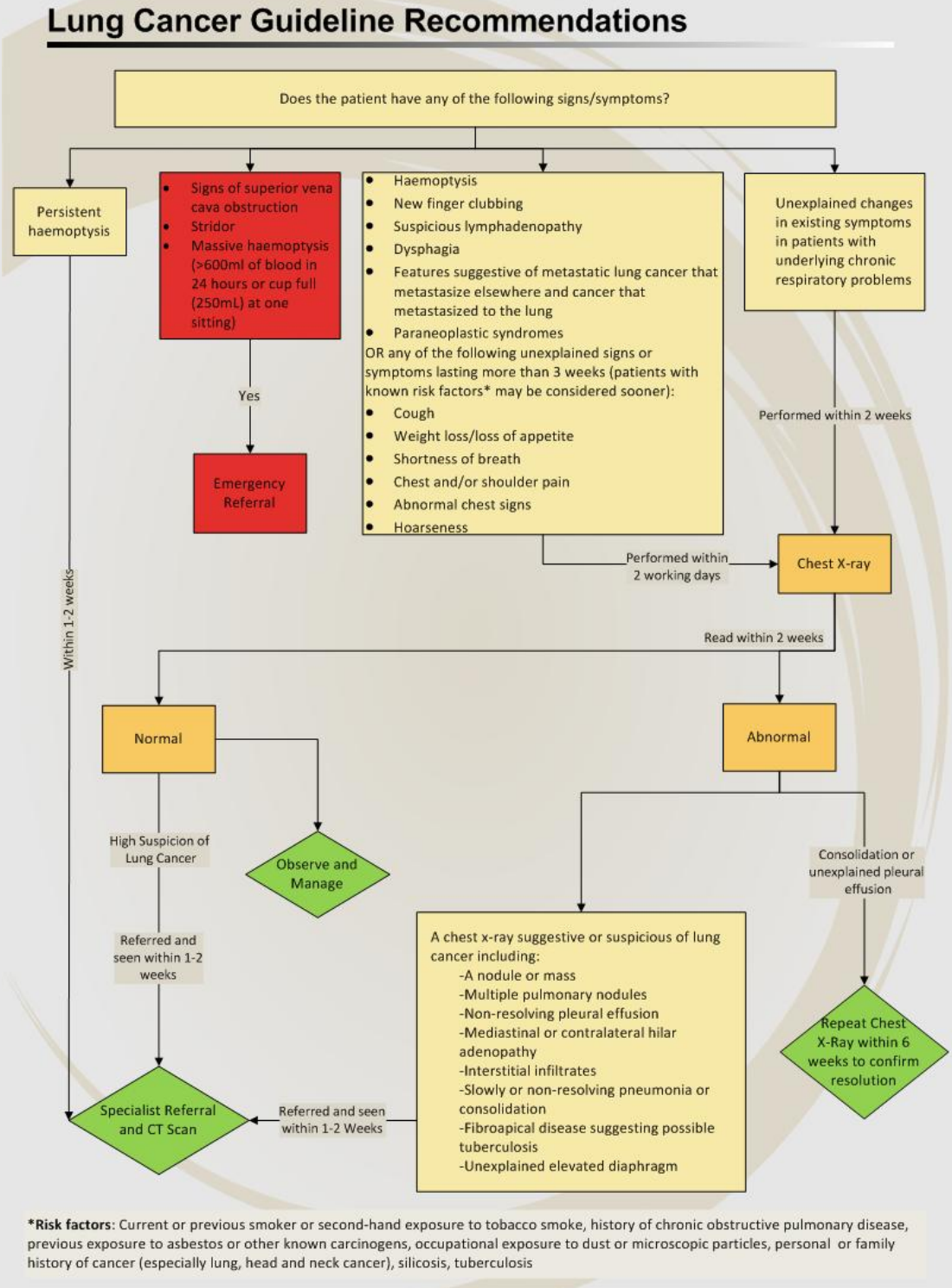
FPs and other PCPs should have a high index of suspicion with a low threshold for investigation of suspected lung cancer in ordering chest x-rays and referral to lung cancer specialists or the DAP. Decision support tools should be readily available to assist FPs and other PCPs.

FPs and other PCPs should include as much information as possible in their referral letters and should ask patients to help retrieve electronic copies of their imaging tests to bring to specialist appointments.

Counselling of patients should occur to address common fears and concerns.

Public health and other health agencies should work with local community leaders to address challenges, such as lower levels of education or demographic discrepancies in communities with high rates of lung cancer or known delays in lung cancer diagnosis.

ALGORITHM


Lung Cancer Guideline Recommendations
Does the patient have any of the following signs/symptoms?
Persistent haemoptysis
Signs of superior vena cava obstruction
Stridor
Massive haemoptysis (>600ml of blood in 24 hours or cup full (250mL) at one sitting)
Haemoptysis
New finger clubbing
Suspicious lymphadenopathy
Dysphagia
Features suggestive of metastatic lung cancer that metastasize elsewhere and cancer that metastasized to the lung
Paraneoplastic syndromes
OR any of the following unexplained signs or symptoms lasting more than 3 weeks (patients with known risk factors* may be considered sooner):
Cough
Weight loss/loss of appetite
Shortness of breath
Chest and/or shoulder pain
Abnormal chest signs
Hoarseness
Unexplained changes in existing symptoms in patients with underlying chronic respiratory problems
Yes
Emergency Referral
Performed within 2 weeks
Performed within 2 working days
Chest X-ray
Within 1-2 weeks
Read within 2 weeks
Normal
Abnormal
High Suspicion of Lung Cancer
Observe and Manage
Consolidation or unexplained pleural effusion
Referred and seen within 1-2 weeks
A chest x-ray suggestive or suspicious of lung cancer including:
-A nodule or mass
-Multiple pulmonary nodules
-Non-resolving pleural effusion
-Mediastinal or contralateral hilar adenopathy
-Interstitial infiltrates
-Slowly or non-resolving pneumonia or consolidation
-Fibroapical disease suggesting possible tuberculosis
-Unexplained elevated diaphragm
Repeat Chest X-Ray within 6 weeks to confirm resolution
Specialist Referral and CT Scan
Referred and seen within 1-2 Weeks
*Risk factors: Current or previous smoker or second-hand exposure to tobacco smoke, history of chronic obstructive pulmonary disease, previous exposure to asbestos or other known carcinogens, occupational exposure to dust or microscopic particles, personal or family history of cancer (especially lung, head and neck cancer), silicosis, tuberculosis

KEY EVIDENCE

- Many of these recommendations were adapted or endorsed from the NZGG 2009 or NICE 2005 recommendations (3,4). Signs and symptoms listed in the NZGG 2009 or NICE 2005 recommendations were derived from their systematic reviews which mainly included case-series studies (3,4). The development of the recommendations in this guideline can be found in Section 3 of this report.

- There was no evidence found on wait times and their effects on patient outcomes. Therefore, all wait times were chosen by the Working Group because they considered them to be achievable targets in the Ontario health care system.

- The list of risk factors was broadened to include all risk factors summarized by NZGG 2009 based on the review by NICE 2005 (3,4).

<u>Indications for Referral to Emergency Department</u>

- This recommendation was adapted from the NICE 2005 guidelines for immediate referral. Massive hemoptysis was included based on common practice in Ontario as well as the Time-to-Treat Program (9).

<u>Indications for Chest X-ray</u>

- This recommendation was adapted from the NZGG 2009 guidelines for urgent referral for a chest X-ray (4). Based on expert opinion, it was felt that, for new finger clubbing, features suggestive of lung cancer that has metastasized elsewhere or other cancers that have metastasized to the lung, and suspicious lymphadenopathy, the three-week time frame was not required for referral for a chest X-ray. The Working Group chose to include dysphagia as an indicator for a chest X-ray because it was reported in the NICE 2005 review as a symptom of lung cancer and was found to be a major clinical symptom among lung cancer patients in a tertiary care setting (3,10). Furthermore, paraneoplastic syndromes were included as indications for chest X-ray based on the review by Spiro et al 2007 that reported that paraneoplastic syndromes may occur in 10% of patients with lung cancer (11).

- For patients with underlying chronic respiratory problems, the Working Group chose to adapt the recommendation from NICE 2005 (3).

<u>Indications for CT Scan</u>

- There was little evidence to inform these recommendations, therefore the Working Group decided to develop their own recommendations based on experiences within their own practices.

<u>Sputum Cytology</u>

- The updated literature search found high specificity but variable sensitivity of sputum cytology in detecting lung cancer (5,7,8,12,13). Therefore, this recommendation was endorsed from the NZGG 2009 referral guidelines (4).

<u>Follow-up to Diagnostic Investigations</u>

- The recommendation for follow-up to consolidation on a chest X-ray was adapted from the NZGG 2009 referral guideline which was based on the

experience of their guideline development team (4). The Working Group chose to modify the NZGG's 2009 recommendation by including all patients rather than specifying only patients with risk factors for lung cancer. In addition to consolidation, the Working Group also included unexplained pleural effusion based on their experience in their practices.

Indications for Referral to a Specialist (Respirologist or Thoracic Surgeon) or the DAP

- These recommendations were adapted from the NZGG 2009 and NICE 2005 referral guidelines which were based on expert opinion (3,4). Additional abnormal chest X-ray results were included from the Time-to-Treat Program (9). Unexplained elevated diaphragm was included based on the suggestion of an expert panel member.

Recommendations to Reduce Diagnostic Delay

- There is evidence to suggest that the following may delay the diagnosis of lung cancer (3,4,11,14,15):
  - Patient Related Delay:
- patient's lack of appreciation regarding the association of symptoms with lung cancer
- fear of cancer diagnosis

  - Family Physician related delay:
- not recognizing signs and symptoms suggestive of lung cancer
- co-morbidity of conditions increased delay
- multiple consecutive investigations in primary care
- over-reliance on chest X-ray results to diagnose lung cancer
- imaging follow-up failure
- initial referral to a non-respiratory physician

Algorithm

- The process used to develop this algorithm can be found in Section 3.

FUTURE RESEARCH

Further studies could be designed to investigate the diagnostic performance of signs, symptoms, or tests for lung cancer in the primary care setting. In addition, studies are needed to determine which educational initiatives would be best at decreasing practitioner or patient-related delay.

GLOSSARY

Abnormal Chest Signs

e.g., crackles or wheezes

Abnormal Chest X-ray that Raises Suspicion of Lung Cancer

e.g., nodule(s), infiltrates, non-resolving consolidation or effusion despite treatment

Features Suggestive of Metastatic Disease

Family physicians can refer to the American College of Chest Physicians (ACCP) Clinical Practice Guidelines for features of a standardized evaluation for systematic

metastases (available at: http://chestjournal.chestpubs.org/content/132/3_suppl/149S.full.pdf)(11)

Massive Hemoptysis
>600 mL of blood in 24 hours or one cup full of blood (250 mL) at one sitting
Features Suggestive of Paraneoplastic Syndromes
Family physicians can refer to the ACCP Clinical Practice Guidelines for a list of paraneoplastic syndromes associated with lung cancer (available at: http://chestjournal.chestpubs.org/content/132/3_suppl/149S.full.pdf)(11)

Signs of Superior Vena Cava Obstruction
Swelling of the face and or neck with fixed elevation of jugular venous pressure

Methods

Targeted Peer Review: During the guideline development process, seven targeted peer reviewers from Ontario and Manitoba considered to be clinical and/or methodological experts on the topic were identified by the Lung Cancer Referral Working Group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on May 19, 2011. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Lung Cancer Referral Working Group reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All health care professionals with an interest in lung cancer including family physicians, thoracic surgeons and radiologists in the PEBC database were contacted by email to inform them of the survey. Also, members of the Canadian Cancer Society, the Nurses Practitioner Association of Ontario, the Ontario College of Family Physicians, the Ontario Hospital Association, the Ontario Medical Association, and the Uniting Primary Care and Oncology Leads at Cancer Care Manitoba were invited to review this guideline. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on May 19, 2011. The consultation period ended on June 20, 2011. The Lung Cancer Referral Working Group reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received from three reviewers. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	0	1	2
2. Rate the guideline presentation.	0	0	0	1	2
3. Rate the guideline recommendations.	0	0	1	0	2
4. Rate the completeness of reporting.	0	0	0	1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	1	1	1
6. Rate the overall quality of the guideline report.	0	0	1	1	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	1	0	2
8. I would recommend this guideline for use in practice.	0	0	1	0	2

9. What are the barriers or enablers to the implementation of this guideline report?
The targeted peer reviewers indicated that the document is informative and not too lengthy. They mentioned that algorithms should be readily available at point of care, not just on the CCO website. Also, the recommendations should be coordinated with diagnostic imaging departments and specialists/hospital care. Furthermore, a validation study to evaluate effectiveness is needed.

Table 3. Summary of Written Comments by targeted peer reviewers and Modifications/Actions Taken

Summary of Written Comments	*Modifications/Actions/Comments*
1. I would harmonize the three weeks of symptoms versus the two weeks of worsening in patients with chronic symptoms. It's unduly confusing to have different time thresholds. Doing X-rays for every flare up of COPD may not be warranted. I'd recommend both recommendations be harmonized at three weeks.	For patients with underlying chronic respiratory problems and unexplained changes in existing symptoms, the working group chose to change the timeframe to "have a X-ray from two weeks to three weeks."
2. I would also include criteria for referral based on CT scan results, unless you are sure you want every CT scan ordered to be accompanied by specialist referral. In practice, I suspect CTs are often ordered without such referral.	The recommendation "If the CT scan is entirely negative, then further referral to a specialist can be cancelled." was added.

Professional Consultation: One-hundred and fifteen of 428 (27%) responses were received. Key results of the feedback survey are summarized in Table 4.

Table 4. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	*0*	***5***	*13*	*51*	*30*
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	*4*	*3*	*15*	*33*	*44*
3. I would recommend this guideline for use in practice.	*1*	*4*	*15*	*34*	*46*

4. What are the barriers or enablers to the implementation of this guideline report?
The professional consultants stated that the recommendations are simple to use and are very practical, and that the algorithm is useful and a great teaching aid for students. They mentioned that there are resource issues with obtaining a CT because they are not always accessible/available and not always possible to be completed in two weeks, especially in rural areas. There are also resource issues in terms of access to specialists and demand for services. They also noted the lack of evidence to support the recommendations and believed that more patient awareness may also help.

Table 5. Summary of Written Comments by professional consultants and Modifications/Actions Taken.

Summary of Written Comments	*Modifications/Actions/Comments*
1. I would have added "severe dyspnea or hypoxia" to the list of indications for referral to the Emergency Department.	The working group chose not to add severe dyspnea or hypoxia because the definition of severe would have to be explained.
2. I would argue that in most cases someone with chest pain should go to emergency room and not be sent for a chest X-ray in three weeks. I imagine most family physicians know this though.	The working group chose to exclude chest pain as an indicator for referral to the emergency room, because it would indicate cardiac concerns and not lung cancer.
3. I think it is hard to justify insisting on a chest X-ray within two days for finger clubbing (which has likely arisen over months).	The working group decided that new finger clubbing should prompt a chest X-ray. There is no point confusing things by saying "for this presentation of lung cancer, two days is appropriate, and for this presentation, two weeks."

	Clubbing does mean something has been going on for a while, but it does not mean non-resectable (curable disease).
4. I would suggest that something needs to be added to "suspicious adenopathy". It needs to be qualified as lower neck or supraclavicular.	The working group felt that "suspicious" covered the location of the lymphadenopathy.
5. I have some concerns about the indications for chest X-ray. I believe that there are circumstances where a low risk individual could have a cough for more than three weeks (e.g. viral/post-viral/asthma) where the degree of suspicion would be sufficiently low that a chest X-ray would not be ordered. This guideline would introduce an "absolute" recommendation which may lead to a lot more chest X-rays being done in low risk people. Similarly, I don't believe that every patient with "shoulder pain" for three weeks or more requires a chest X-ray. Obviously a 60 year old smoker would be managed quite differently from a 20 year old, non-smoking baseball pitcher.	The working group felt that the term "unexplained" addressed this concern and chose to underline this word to emphasize it in the recommendation.
6. The guideline states that the requisition for chest X-ray should include all signs and symptoms and risk factors for chest X-ray. This seems to me to be an unfair expectation. It is unclear that this would be of much help to radiologists over and above a brief summary statement that listed the main symptoms.	The working group agreed and chose to modify this recommendation to "The requisition for a chest X-ray should include the presenting history, including signs and symptoms suspicious of lung cancer and whether risk factors exist."
7. Many reviewers felt that a chest X-ray report should be available and read by the family physician within a few days of being ordered and that two weeks is an excessive delay.	The working group chose to decrease the time frame to one week.
8. CT's are not available within two weeks in many rural places; patients need to travel >300 km.	The working group chose not to change the time frame of two weeks. The emerging DAPs should help achieve this time frame. Also, a statement that "These guidelines are also intended for policymakers in helping PCPs achieve the target wait times." was added.
9. It would be useful to have algorithms based on some of the symptom presentations that we struggle with - e.g. "approach to patient with hemoptysis and normal chest X-ray", "approach to a pleural effusion in the absence of obvious cause on chest X-ray", and "follow-up strategy for an incidental pulmonary nodule (I think that the radiologists have recommendations on this topic and this might be referred to in this document)".	The working group decided not to include this as these decisions are not made by FPs and other PCPs.

10. DAPs would certainly make it easier. Continuing to generate awareness of the DAP to family physicians in the various local health integration networks would also be helpful (maybe acknowledge them in the document)	A description of a DAP was added to the glossary.
11. Access to specialty care is still a problem and a delaying factor. The treating physician will not treat without a "tissue diagnosis" and in the very ill this can be a difficult problem to resolve. The early finding of positive sputum cytology can help move everything along faster.	The working group chose not to modify the recommendation based on the evidence that sputum cytology has high specificity but variable sensitivity.
12. Consolidations in the lung may be associated with fever or not. If there is a fever then there is likely an infection requiring antibiotics and follow up to ensure complete clearing. There could still be an underlying cancer hence the need to ensure complete clearing. If there is a consolidation without fever then I would recommend proceeding to a CT scan immediately. So I would add "...has a fever and consolidation...should be treated with antibiotics and have... To confirm complete resolution". It is important to emphasize complete resolution as too often incomplete resolution leads to a second or third course of antibiotics.	The working group chose not to include fever as a criterion because cancers can cause fever. Also, the working group decided not to include treatment options for pneumonia and effusions and left that decision to the FP and other PCPs based on their clinical judgement. The working group decided to include the word "complete" resolution.
13. For referral of "nodule", if we referred every nodule before a CT scan, then specialists would be overwhelmed.	The recommendation "If the CT scan is entirely negative, then further referral to a specialist can be cancelled." was added.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Lung Cancer Referral Expert Panel and the Director of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12. Comment in: Ann Oncol. 2002 Sep;13(9):1507-9; author reply 1509.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the Practice Guidelines Development Cycle: the role of practitioner feedback. J Clin Oncol. 1998 Mar;16(3):1226-31.
3. National Collaborating Centre for Primary Care. Referral guidelines for suspected cancer. London: National Institute for Health and Clinical Excellence (NICE); 2005 Jun. Clinical Guideline No.: 27.
4. New Zealand Guidelines Group. Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities. Wellington (NZ): New Zealand Guidelines Group (NZGG); 2009.
5. Australian Cancer Network Staff, Cancer Council Australia, Australian Cancer Network, National Health and Medical Research Council (Australia). Clinical practice guidelines for the prevention, diagnosis and management of lung cancer. Sydney (Australia): National Health and Medical Research Council (NHMRC); 2004.
6. Gould MK, Fletcher J, Iannettoni MD, Lynch WR, Midthun DE, Naidich DP, et al. Evaluation of patients with pulmonary nodules: When is it lung cancer? ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132(3 Suppl):108S-30S.
7. Rivera MP, Mehta AC, American College of Chest Physicians. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007 Sep;132(3 Suppl):131S-48S.
8. Scottish Intercollegiate Guidelines Network. Management of patients with lung cancer: a national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2005.
9. Lo DS, Zeldin RA, Skrastins R, Fraser IM, Newman H, Monavvari A, et al. Time to treat: a system redesign focusing on decreasing the time from suspicion of lung cancer to diagnosis. J Thorac Oncol. 2007 Nov;2(11):1001-6.
10. Chandra S, Mohan A, Guleria R, Singh V, Yadav P. Delays during the diagnostic evaluation and treatment of lung cancer. Asian Pac J Cancer Prev. 2009 Jul-Sep;10(3):453-6.
11. Spiro SG, Gould MK, Colice GL, American College of Chest Physicians. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest. 2007 Sep;132(3 Suppl):149S-60S.
12. Choi Y-D, Han C-W, Kim J-H, Oh I-J, Lee J-S, Nam J-H, et al. Effectiveness of sputum cytology using ThinPrep method for evaluation of lung cancer. Diagn Cytopathol. 2008 Mar;36(3):167-71.
13. Kemp RA, Reinders DM, Turic B. Detection of lung cancer by automated sputum cytometry. J Thorac Oncol. 2007 Nov;2(11):993-1000.
14. Olsson JK, Schultz EM, Gould MK. Timeliness of care in patients with lung cancer: A systematic review. Thorax. 2009;64(9):749-56.
15. Singh H, Sethi S, Raber M, Petersen LA. Errors in cancer diagnosis: current understanding and future directions. J Clin Oncol. 2007;25(31):5009-18.

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Evidence-Based Series 24-2: Section 4

Referral of Suspected Lung Cancer by Family Physicians and Other Primary Care Providers: Evidentiary Base

Document Review Summary

L. Del Giudice, G. Darling, C. Zwaal, and Members of the Referral of Suspected Lung Cancer Expert Panel

January 6, 2019

The 2011 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2011, and updated in 2019.

In March 2018, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (CZ) conducted an updated search of the literature. Two clinical experts (LD and GD) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. Members of the Referral of Suspected Lung Cancer Expert Panel (Appendix 1) endorsed the recommendations found in Section 1 (Clinical Practice Guideline) on January 6, 2019.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

In patients presenting to primary care services with signs and/or symptoms of lung cancer, what should the referral process include?
The following questions are the factors considered in answering the overall question:

1. What signs, symptoms and other clinical features are predictive of lung cancer?
2. What is the diagnostic accuracy of investigations for lung cancer?
3. What major, known risk factors are predictive of lung cancer?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers? Does a delay in the time to consultation affect patient outcome?

Literature Search and New Evidence

The literature search strategy is shown in Appendix 2. The updated search (January 2011 to May 2018) yielded 6 practice guidelines, 65 systematic reviews, 2 randomized controlled trials, and 33 non-randomized trials. Brief results of these searches are shown in the Document Summary and Review Tool. The evidence is summarized below in Tables 1 to 5.

Impact on the Guideline and Its Recommendations

The new evidence essentially supports the existing recommendations. The updated search to May 2018 provided new data to add more issues to the list of factors that can increase the risk of lung cancer. As well, new data gave more factors to add to the list of indications for chest X-ray.

The original guideline indicated that some unexplained signs and symptoms should last for three weeks before referral to an X-ray. It was believed by the clinical experts that X-rays are minimally invasive and that three weeks is not needed before referring an individual. As well, patients with underlying chronic respiratory problems should be referred to an X-ray as soon as possible.

The original guideline also indicated that a person who had consolidation or unexplained pleural effusion on an initial chest X-ray should be treated and have a chest X-ray repeated in six weeks to confirm complete resolution. The clinical experts believed that four weeks is more reasonable.

The clinical experts also believed that after reading through the new evidence that the epidemiology is changing and believed that it was important to add a comment to the recommendations stating that there is an increasing number of non-smokers and young people with cancer and that lung cancer can happen at any age and risk factors should preclude any person based on age alone.

The new data support existing recommendations. However some issues were identified and added to the risk factors of lung cancer and the signs and symptoms for referral to X-ray.

Hence, the Referral of Suspected Lung Cancer Expert Panel ENDORSED the 2011 recommendations (with additional factors and referral time changes) on Referral of Suspected Lung Cancer by Family Physicians and Other Primary Care Providers.

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Document Review Tool

Number and Title of Document under Review	**Guideline 24-2 Referral of Suspected Lung Cancer by Family Physicians and Other Primary Care Providers**
Original Report Date	August 29, 2011
Date Assessed (by DSG or Clinical Program Chairs)	December 11, 2017
Health Research Methodologist	Caroline Zwaal
Clinical Experts	Dr. Lisa Del Giudice Dr. Gail Darling
Approval Date and Review Outcome (once completed)	ENDORSE January 6, 2019

Research Questions:
In patients presenting to primary care services with signs and/or symptoms of lung cancer, what should the referral process include?
The following questions are the factors considered in answering the overall question:

1. What signs, symptoms and other clinical features are predictive of lung cancer?
2. What is the diagnostic accuracy of investigations for lung cancer?
3. What major, known risk factors are predictive of lung cancer?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers? Does a delay in the time to consultation affect patient outcome?

Target Population:
Patients presenting in primary care settings comprise the target population. This guideline does not provide recommendations for patients in a screening program.

Study Section Criteria:
No changes to the inclusion or exclusion criteria

Inclusion Criteria:
Guidelines were included if they addressed at least one of our research questions, were not cited in the NZGG 2009 or NICE 2005 guidelines, and included recommendations not found or different from those in either the NICE 2005 or NZGG 2009 guidelines.
For the clinical question about the predictive characteristics of signs or symptoms, all prospective or retrospective case series or cohort or case control studies of symptom recognition/identification for lung cancer were included. Studies conducted in the secondary care setting that provided predictive information about signs/symptoms for suspected lung cancer were included when limited evidence was available from the primary care setting. Screening studies were excluded because they include asymptomatic patients. This report focuses on patients presenting to primary care with signs or symptoms of lung cancer.
All diagnostic studies in which symptomatic primary care patients underwent one or more investigations including complete blood count, chest X-ray, spirometry, sputum cytology and CT scan were sought. If limited evidence was available from the primary care setting, studies

conducted in secondary care settings were included if they provided diagnostic information for suspected lung cancer for the specified investigations. Screening studies were excluded. For the clinical questions concerning risk factors and delay in referral, a search for practice guidelines, systematic reviews (with meta-analyses), and systematic reviews (without meta-analyses) was performed. If these articles did not definitively answer the particular clinical question, then searches for randomized phase III trials and randomized phase II trials followed by prospective or retrospective case series or cohort or case-control studies were performed. If information from systematic reviews definitively answered the question(s), then articles from the time of publication of the systematic review and onwards were retrieved.

Exclusion Criteria:
Publications in a language other than English were not eligible because of lack of funding for translation. Non-systematic reviews, abstracts, case studies, letters, editorials, and commentaries were excluded.

Search Details:
Guideline Search: 34 found
Full text review: 6
Included: 6

Search Details:

Question 1: What signs, symptoms and other clinical features are predictive of lung cancer?
Searched EMBASE and MEDLINE: May 22, 2018
Limited to 2011 to 2018; English only
Search strategy identical to that used for original 2011 guideline

Retrieval:
Study search: 2926 citations

Title and abstract review:
Guidelines: 0 relevant citations
Systematic reviews: relevant citations
RCTs: 10 relevant citations
Non-RCT: 115 relevant citations
Full text review:
Systematic reviews: 10 relevant
RCTs: 2 relevant
Non-RCT: 24
Included:
Systematic reviews: 3
RCTs: 0
Non-RCT: 6
Excluded:
Non-systematic reviews, abstracts, case studies, letters, editorials, commentaries and non-English studies were excluded.

Question 2: What is the diagnostic accuracy of investigations for lung cancer?
Searched EMBASE and MEDLINE: May 24, 2018

Limited to 2011 to 2018; English only
Search strategy identical to that used for original 2011 guideline

Retrieval:
Study search: 3577 citations

Title and abstract review:
Guidelines: 0 relevant citations
Systematic reviews: 2 relevant citations
RCTs: 0 relevant citations
Non-RCT: 50
Full text review:
Guidelines: 3
Systematic reviews: 2 relevant
RCTs: 0 relevant
Non-RCT: 9
Included:
Guidelines: 0
Systematic reviews: 1
RCTs: 0
Non-RCT: 6
Excluded:
Non-systematic reviews, abstracts, case studies, letters, editorials, commentaries and non-English studies were excluded.

Question 3: What major, known risk factors are predictive of lung cancer?
Searched EMBASE and MEDLINE: June 11, 2018
Limited to 2011 to 2018; English only
Search strategy identical to that used for original 2011 guideline

Retrieval:
Study search: 3166 citations

Title and abstract review:
Guidelines: 5 relevant citations
Systematic reviews: 42 relevant citations
RCTs: 46 relevant citations
Non-RCT: 20 relevant citations
Full text review:
Guidelines: 3
Systematic reviews: 10 relevant
RCTs: 1 relevant
Non-RCT: 7
Included:
Guidelines: 0
Systematic reviews: 60
RCTs: 0
Non-RCT: 4
Excluded:

Non-systematic reviews, abstracts, case studies, letters, editorials, commentaries and non-English studies were excluded.

Question 4: Which factors are associated with delayed referral?
Searched EMBASE and MEDLINE: May 23, 2018
Limited to 2011 to 2018; English only
Search strategy identical to that used for original 2011 guideline

Retrieval:
Study search: 676 citations

Title and abstract review:
Guidelines: 0 relevant citations
Systematic reviews: 4 relevant citations
RCTs: 6 relevant citations
Non-RCT: 52 relevant citations
Full text review:
Guidelines: 3
Systematic reviews: 2 relevant
RCTs: 3 relevant
Non-RCT: 24 relevant
Included:
Guidelines: 0
Systematic reviews: 1
RCTs: 2
Non-RCT: 17
Excluded:
Non-systematic reviews, abstracts, case studies, letters, editorials, commentaries and non-English studies were excluded.

Summary of new evidence:
Please see Evidence Tables below
Clinical Expert Interest Declaration:

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No, with some modifications.
2. Does the newly identified evidence support the existing recommendations?	Yes

3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes, plus some additional information
Review Outcome as recommended by the Clinical Expert	Endorse with modifications.
If outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	N/A
DSG/Expert Panel Commentary	

Evidence Tables

Table 1. Recommendation Summary of Relevant Guidelines (since 2011)

Reference	Search dates	Recommendations
NCCN Guideline (1) Small cell lung cancer 2018 Question 1	None provided but updated yearly	Signs and symptoms due to local primary growth • Cough –endobronchial irritation, bronchial compression • Hemoptysis –usually central or cavitary lesion • Wheezing –partially obstruction endobronchial lesion • Fever -post –obstructive pneumonia • Dyspnea -bronchia obstruction, pneumonia, pleural effusion Signs and symptoms due to primary tumor invasion or regional lymphatic metastases • Hoarseness –let vocal chard paralysis due to tumor invasion or lymphadenopathy in the aorta-pulmonary window • Hemidiaphragm elevation –due to phrenic nerve compression • Dysphagia –due to esophageal compression • Chest pain –involvement of pleura or chest wall, often dull and non-localized • Superior cava syndrome • Pericardial effusion and tamponade • Cervical or supraclavicular lymph node enlargement
Suspected Cancer: Recognition and Referral (2) Year: 2015 Developer organization: National Institute for Health and Care Excellence Question 1	28 May 2012 and 8 June 2015.	• Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they: have chest X-ray findings that suggest lung cancer or are aged 40 and over with unexplained haemoptysis. [new 2015] • Offer an urgent chest X-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over if they have 2 or more of the following unexplained symptoms, or if they have ever smoked and have 1 or more of the following unexplained symptoms: cough, fatigue, shortness of breath, chest pain, weight loss, appetite loss. [new 2015] • Consider an urgent chest X-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following: persistent or recurrent

Reference	Search dates	Recommendations
		chest infection, finger clubbing, supraclavicular lymphadenopathy or persistent cervical lymphadenopathy, chest signs consistent with lung cancer, thrombocytosis. [new 2015] • Discussion with a specialist (for example, by telephone or email) should be considered if there is uncertainty about the interpretation of symptoms and signs, and whether a referral is needed. This may also enable the primary healthcare professional to communicate their concerns and a sense of urgency to secondary healthcare professionals when symptoms are not classical. [2005] • Put in place local arrangements to ensure that letters about non-urgent referrals are assessed by the specialist, so that the person can be seen more urgently if necessary. [2005] • Put in place local arrangements to ensure that there is a maximum waiting period for non-urgent referrals, in accordance with national targets and local arrangements. [2005] • Include all appropriate information in referral correspondence, including whether the referral is urgent or non-urgent. [2005] • Use local referral proformas if these are in use. [2005] • Once the decision to refer has been made, make sure that the referral is made within 1 working day. [2005]
Combined Endobronchial and Esophageal Endosonography for the Diagnosis and Staging of Lung Cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in Cooperation With the European Respiratory Society (ERS) and the European Society	1990-October 2013. A few important studies published after the search period was included.	• For mediastinal nodal staging in patients with suspected or proven non-small-cell lung cancer (NSCLC) with abnormal mediastinal and/or hilar nodes at computed tomography (CT) and/or positron emission tomography (PET), endosonography is recommended over surgical staging as the initial procedure (Recommendation grade A). The combination of endobronchial ultrasound with real-time guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic (esophageal) ultrasound with fine needle aspiration, with use of a gastrointestinal (EUS-FNA) or EBUS (EUS-B-FNA) scope, is preferred over either test alone (Recommendation grade C). If the combination of EBUS and EUS-(B) is not available, we suggest that EBUS alone is acceptable (Recommendation grade C). Subsequent surgical staging is recommended, when endosonography does not show malignant nodal involvement (Recommendation grade B).

Reference	Search dates	Recommendations
of Thoracic Surgeons (3) (ESTS) Year: 2015 Question 2		• For diagnostic purposes, in patients with a centrally located lung tumor that is not visible at conventional bronchoscopy, endosonography is suggested, provided the tumor is located immediately adjacent to the larger airways (EBUS) or esophagus (EUS-(B)) (Recommendation grade D).
Management of Lung Cancer: A National Clinical Guideline (4) Year: 2014 Developer organization: Scottish Intercollegiate Guidelines Network Question 2	2005-2012	• A chest X-ray should be performed on all patients being investigated for the possibility of lung cancer. • Contrast enhanced CT scanning of the chest and abdomen is recommended in all patients with suspected lung cancer, regardless of chest X-ray results. • A tissue diagnosis should not be inferred from CT appearances alone. • Contrast enhanced CT scanning of the chest and abdomen should be performed prior to further diagnostic investigations, including bronchoscopy, and the results used to guide the investigation that is most likely to provide both a diagnosis and stage the disease to the highest level. • FDG PET-CT scanning may be used to investigate patients presenting with solitary lung lesions but histological/cytological confirmation of results will still be required. • Visible tumours should be sampled using more than one technique to optimize sensitivity. • Bronchoscopy may provide a diagnosis for peripheral lesions, although percutaneous FNA biopsy is the preferred approach. • Sputum cytology should only be used in patients with large central lesions, where bronchoscopy or other diagnostic tests are deemed unsafe.
Establishing the Diagnosis of Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (5) Year: 2013	July 2004-July 2011	• In patients suspected of having small cell lung cancer (SCLC) based on the radiographic and clinical findings, it is recommended that the diagnosis be confirmed by the least invasive method (sputum cytology, thoracentesis, fi ne needle aspiration [FNA], bronchoscopy including transbronchial needle aspiration [TBNA]), as dictated by the patient's presentation • In patients suspected of having lung cancer, if sputum cytology is done but is negative for carcinoma, it is recommended that further testing be performed • In patients suspected of having lung cancer, who have a central lesion, bronchoscopy is recommended to confirm the diagnosis. However, it is recommended that further testing be performed if bronchoscopy results are nondiagnostic and suspicion of lung cancer remains

Reference	Search dates	Recommendations
Question 2		• In patients suspected of having lung cancer, the diagnosis of non-small cell lung cancer made on cytology (sputum, TTNA, bronchoscopic specimens, or pleural fluid) is reliable. However, it is recommended that adequate tissue be obtained to accurately define the histologic type and to perform molecular analysis when applicable • The possibility of an erroneous diagnosis of SCLC on a cytology specimen must be kept in mind if the clinical presentation or clinical course is not consistent with that of SCLC. In such a case, it is recommended that further testing be performed to establish a definitive cell type
NCCN Guideline Non-small cell lung cancer, 2018 (6) -after incidental finding of nodule suspicious for lung cancer Question 3	None provided but updated yearly	Risk assessment Patient factors • Age • Smoking history • Previous cancer history • Family history • Occupational exposures • Other lung diseases (COPD, pulmonary fibrosis) • Exposure to infection or risk factors or history suggestive of infection Radiologic factors • Size, shape and density of the pulmonary nodule • Associated parenchymal abnormalities • PDG avidity on PET imaging

Table 2. Studies that examined signs and symptoms of lung cancer

Systematic Reviews

Study	Search details	Inclusion criteria	Intervention/ comparison	Results
Latimer, 2015 (7) Lung Cancer: Diagnosis, Treatment Principles, and Screening	PubMed, Clinical Inquiries, the Cochrane database, the USPSTF and Ovid. Relied heavily on the ACCP 2013 lung cancer evidence-based guidelines. Used references from recent review articles from UptoDate and American Family Physician. Search dates: January through March 2014.	Could not find number of studies found/included/excluded	Clinical presentation of patients with lung cancer (vs. healthy controls)	Patients with lung cancer are almost always symptomatic at diagnosis. Symptoms can be caused by the primary tumor (e.g., cough, hemoptysis); intrathoracic spread (e.g., Horner syndrome, superior vena cava obstruction); and distant metastases (e.g., bone pain). Two individual symptoms that significantly increase the likelihood of lung cancer are digital clubbing and hemoptysis. Other independent predictors of lung cancer include loss of appetite, weight loss, fatigue, dyspnea, chest or rib pain, and an increasing number of visits to evaluate persistent cough. Patients rarely present with only one symptom, and the positive predictive value is higher when two or more symptoms are reported. Lung cancer should be highly suspected in any patient older than 40 years with risk factors and symptoms.
Mitchell, 2015 (8) Risk factors for emergency presentation with lung and colorectal cancers	MEDLINE, EMBASE, CINAHL, EBM Reviews, Science and Social Sciences Citation Indexes, Conference Proceedings Citation Index Science and Conference Proceedings Citation Index-Social Science and Humanities.	Studies of any design assessing factors associated with diagnosis of colorectal or lung cancer via EP, or describing an intervention to impact on EP. Studies involving previously diagnosed cancer patients, assessing only referral	Identify patient and practitioner factors that influence cancer diagnosis via emergency presentation (EP)	Older patient age was associated with EP for lung and colorectal cancers (OR 1.11–11.03 and 1.19–5.85, respectively). Women were more at risk of EP for lung cancer. Higher deprivation increased the likelihood of lung cancer EP. Lack of a regular source of primary care, and lower primary care use were positively associated with EP. Only three studies considered practitioner

	Searches were undertaken from 1996 to 2014. No language restrictions were applied. 22 studies with over 200 000 EPs were included from 927 articles identified, most providing strong evidence. Five were graded 'insufficient', primarily due to missing information rather than methodological weakness.	pathway effectiveness, outcomes related to diagnosis or post-EP management were excluded. The population was individual or groups of adult patients or primary care practitioners. Two authors independently screened studies for inclusion.		factors, two involving diagnostic tests. No conclusive evidence was found.
Shim, 2014 (9) A systematic review of symptomatic diagnosis of lung cancer	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. 6037 papers were retrieved, 11 studies were included (5 quantitative and 6 qualitative).	Quantitative study design (reported diagnostic values for the symptom, sign or test) or qualitative study design (described initial symptoms); only adult populations recruited from hospitals, outpatient clinic, specialist clinic, specific community or general public; the group with the positive outcome must have a confirmed diagnosis of lung cancer; must be written in English, German, Spanish, Malay or Chinese.	Identify symptoms that are independently associated with lung cancer (LC) and to identify the key methodological issues relating to symptomatic diagnosis research in LC.	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.

Cohort Studies

Study	Type of Study	Population	Outcomes of Interest	Brief Results
Baburao, 2015 (10) Clinic-pathological profile and haematological abnormalities associated with lung cancer in Bangalore, India	Prospective	96 newly diagnosed lung cancer patients 72 male, 24 female. Age range 40-90 with majority between 61-80	Evaluate clinical and pathological profile and haematological abnormalities associated with lung cancer	The most frequent symptom was cough (86.4%) followed by loss of weight and appetite (65.6%) and dyspnea (64.5%). The most common radiological presentation was a mass lesion (55%). Distant metastasis at presentation was seen in 53.1% patients. Anaemia was seen in 61.4% of patients, leucocytosis in 36.4%, thrombocytosis in 14.5% and eosinophilia in 19.7% of patients. Haematological abnormalities were more commonly seen in non-small cell lung cancer. Majority of male patients were farmers (75%) and all the female patients were housewives and passive smokers. Most of the female patients also had an exposure to fire wood smoke.
Walter, 2015 (11) Symptoms and other factors associated with time to diagnosis and stage of lung cancer	Prospective cohort study	Patients that were referred with symptoms suggestive of lung cancer; Among 963 pts. 15.9% were diagnosed with primary lung cancer, 5.9% with other thoracic malignancies and 78.2% with non-malignant conditions.	Symptom and patient factors that influence time to lung cancer diagnosis and stage at diagnosis (19.5% response rate to symptom questionnaire)	Half the cohort had an isolated first symptom (475, 49.3%); synchronous first symptoms were common. Haemoptysis, reported by 21.6% of cases, was the only initial symptom associated with cancer. Diagnostic intervals were shorter for cancer than non-cancer diagnoses (91 vs 124 days, P=0.037) and for late-stage than early-stage cancer (106 vs 168 days, P=0.02). Chest/shoulder pain was the only first symptom with a shorter diagnostic interval for cancer compared with non-cancer diagnoses (P=0.003). Haemoptysis is the strongest symptom predictor of lung cancer but occurs in only a fifth of patients.
Ades, 2014 (12) Symptom lead time distribution in lung cancer	Retrospective	247 lung cancer cases and 1235 matched controls in Devon, UK.	Symptom incidence in cases and controls prior to diagnosis, symptom lead time (SLT) distribution (the	Symptom incidence in LC cases was higher than in controls 2 years before diagnosis, accelerating markedly in the last 6 months. The median SLT was under 3 months, mean 5.3 months [95% credible interval (CrI) 4.5–6.1].

natural history and prospects for early diagnosis			time between symptom presentation and diagnosis), stage at diagnosis	An earlier stage at diagnosis was observed in patients identified through chest X-ray from primary care. Most symptoms preceded clinical diagnosis by a few months. Isolated cough picks up 64.8% of cases but would also lead to investigations in 29.5% of controls. Haemoptysis is highly specific (present in 1.5% of controls), but would identify only 20% of cases Individuals with undiagnosed lung cancer attend general practice with suggestive but non-specific symptoms more often than matched controls, but the great majority of the excess attendances precede the diagnosis date by a only few months.
Gonzalez-Barcala, 2014 (13) Symptoms and Reason for a Medical Visit in Lung Cancer Patients	Retrospective	All patients diagnosed with lung cancer in the Pontevedra Health Area over a period of three years; 358 pts. With a mean age of 68.7 years and 87% were males	Symptoms of lung cancer	The most common initial symptoms were, constitutional in 30.4%, cough in 20.9%, and chest pain in 12%. The most frequent reason for the consultation was dyspnea in 22.1%, an incidental finding in 15.4%, and haemoptysis in 12.8%. There was a moderate association (correlation coefficient = 0.495) between the initial symptoms and the consulting symptom.
Iyen-Omofoman, 2013 (14) Using socio-demographic and early clinical features in general practice to identify people with lung cancer earlier	Retrospective	12 074 cases of lung cancer (40+ years old) and 120 731 controls in a large general practice database	Identify socio-demographic and early clinical features predictive of lung cancer	Clinical and socio-demographic features that were independently associated with lung cancer were patients' age, sex, socioeconomic status and smoking history. From 4 to 12 months before diagnosis, multivariate model of factors associated with lung cancer: cough (OR: 1.63 (1.53 to 1.75)), haemoptysis (OR: 8.70 (6.75 to 11.20), dyspnoea (OR: 1.41 (1.29 to 1.55), weight loss (OR: 2.66 (2.16 to 3.29), lower respiratory tract infections (OR: 1.56 (1.38 to 1.76), non-specific chest infections (OR: 1.55 (1.44 to 1.68), chest pain (OR: 1.39 (1.28 to 1.51)) hoarseness (OR: 1.79 (1.28 to 2.49)) upper

				respiratory tract infections (OR: 1.15 (1.02 to 1.30)) and chronic obstructive pulmonary disease (OR: 1.61 (1.46 to 1.78))
Cakar, 2011 (15) The prognostic value of thrombocytosis in newly diagnosed lung cancer patients: a retrospective analysis	Retrospective	260 patients diagnosed with lung cancer	Thrombocytosis as a prognostic factor	There were no statistically significant differences between histological subgroups (small cell/SCLC and non-small cell/NSCLC) according to age, disease stage and gender. Sixty-six (25.38%) patients had thrombocytosis before starting treatment. We found no relationship between thrombocytosis and disease stage, gender, age, PS and thrombotic episodes. Thrombocytosis was significantly correlated only with weight loss (p=0.011) and paraneoplastic syndromes (p=0.027). OS was shorter in the thrombocytosis group, but without statistical significance. PFS and DFS did not differ between thrombocytemic and non-thrombocytemic patients.

Table 3. Studies that examined the diagnostic accuracy of lung cancer tests

Systematic Reviews

Study	**Search Details**	**Inclusion Criteria**	**Intervention /Comparison**	**Results**
Madsen, 2016 (16) Clinical utility of F-18 FDG PET-CT in the initial evaluation of lung cancer	Search terms included the combination of multiple synonyms for PET, PETCT, and lung cancer. Covered the PubMed, Embase, and Cochrane databases from January 2003 to the search date and was limited to papers in English, Danish, Swedish, and Norwegian. The Medical Research Library of Odense	Articles that described the use of F-18 FDG PET-CT in the clinical situations that were covered by PICO-questions. For all excluded papers, a record was kept to	Clinical usefulness of positron emission tomography-computed tomography (PET-CT) in regards to the diagnosis, staging and	-PET-CT can rule out malignancy in most solitary pulmonary nodules due to high sensitivity (recommendation level A). With few exceptions, solitary pulmonary nodules can safely be considered benign if the PET-CT scan is negative. Exceptions consist of small and non-solid solitary nodules. -PET-CT reduces the number of futile treatment trials (recommendation level A). No curative-intent treatment should be commenced until a PET-CT scan has excluded occult distant metastases. -The sensitivity of PET-CT in general is insufficient to rule out mediastinal lymph node metastasis

	University Hospital performed the searches on October 23 2013, resulting in 4,208 records including 918 reviews, of which 139 met the predefined criteria.	document why the paper was excluded in case this would later become relevant.	evaluation of lung cancer	(recommendation level A). In general, lymph node metastasis in the mediastinum cannot be ruled out on the basis of a negative PET-CT, and confirmative invasive staging should be performed in most patients before mediastinal metastasis is confirmed or ruled out.

Cohort Studies

Study	Study Type	Population	Outcomes of Interest	Results
Feng, 2017 (17) Retrospective analysis for the false positive diagnosis of PET-CT scan in lung cancer patients	Retrospective	754 patients diagnosed with lung cancer via PET-CT	Determine diagnostic accuracy and false positive rate of PET-CT in lung cancer	705/754 cases were pathologically confirmed as lung cancer. The diagnostic accuracy of PET-CT was 93.5%, and the false positive rate was 6.50%. Among the false positives, inflammatory pseudotumor (42.86%) and tuberculoma (36.74%) were the most pathological types. In the positive detection group, adenocarcinoma (57.16%) and squamous carcinoma (33.19%) were the main pathological types. 68.09% of the lung cancer patients were at the advanced stages. The false positive rate was related with age, diabetes, interleukin-6 level, and T-spot test.
Zheng, 2015 (18) 68Ga-NOTA-PRGD2 PET/CT for Integrin Imaging in Patients with Lung Cancer	Prospective	Ninety-one patients (48 men and 43 women; age, 22–82 years) with suspected lung lesions on CT were enrolled with informed consent	Determine diagnostic accuracy of Ga-NOTA-PRGD2 PET/CT for lung cancer	The standardized uptake values of proven malignancies were significantly higher than those of the benign ones. With an average standardized uptake value of greater than 1.3 being considered malignant, the sensitivity, specificity, and accuracy of 68GaNOTA-PRGD2 PET/CT in diagnosing lung cancer were 83.8% (57/68), 91.3% (21/23), and 85.7% (78/91), respectively. The diagnostic value of 68Ga-NOTA-PRGD2 for lung cancer is comparable to that of 18F-FDG PET/CT. However, 68Ga-NOTA-PRGD2 PET/CT is more specific than 18F-FDG PET/CT in assessing lymph node metastasis, with positive and negative predictive values of 90.0% (27/30) and 93.8% (121/129), respectively, whereas those of 18F-FDG PET/CT were 30.2% (29/96) and 90.5% (57/63), respectively.

De Vries, 2015 (19) Integration of electronic nose technology with spirometry: validation of a new approach for exhaled breath analysis	Prospective	Thirty-seven asthmatics (41 ± 14.2 years), 31 COPD patients (66 ± 8.4 years), 31 lung cancer patients (63 ± 10.8 years) and 45 healthy controls (41 ± 12.5 years)	Determine and optimize the technical performance and diagnostic accuracy of breath analysis linked to routine spirometry	SpiroNose could adequately distinguish between controls, asthma, COPD and lung cancer patients with cross-validation values ranging between 78–88%. No correlation was found between sensor readings and exhaled volume, humidity and temperature. Breathprints from patients with lung cancer and healthy controls were very well distinguished ($p < 0.001$) and a crossvalidated accuracy value of 88% was achieved with an ROC-AUC of 0.95 ± 0.11. Breathprints of COPD patients could also be discriminated from those of lung cancer patients ($p = 0.002$; CVV: 80%). When excluding those lung cancer patients with comorbid COPD from the latter analysis, the COPD and lung cancer patients could still be distinguished ($p < 0.001$) with a cross-validated accuracy of 87%.
Hubers, 2012 (20) Prolonged sampling of spontaneous sputum improves sensitivity of hypermethylation analysis for lung cancer	Prospective	53 lung cancer patients and 47 chronic obstructive pulmonary disease patients as controls	Determine diagnostic accuracy of sputum collected over nine successive days, in three canisters, one for three consecutive days. (1 canister for days 1-3, 4-6, 7-9)	Analysis of each canister separately showed hypermethylation of RASSF1A, APC and/or CYGB in samples I, II and III, in 43%, 40% and 47% of cases, respectively. In control samples, these numbers were 4%, 2% and 4%, respectively. Cumulative analysis for days 1-6 and days 1-9 revealed an increase in sensitivity to 53% and 64%, and specificity of 94% and 91%, respectively. Sputum collected over multiple successive days results in a gain in sensitivity for the detection of lung cancer, at the expense of a small loss in specificity.
Harders, 2012 (21) Limited value of 99mTc depreotide single photon emission CT compared with CT for the evaluation of	Prospective	60 males and 80 females with a mean age of 64 years (range, 34–83 years) participated in the study. 137 participants had a mean smoking	Examine whether a contrast-enhanced MDCT scan supplied with an additional non-contrast enhanced high-resolution CT scan, or a newer but more expensive ^{99m}Tc depreotide single photon emission CT	Overall sensitivity, specificity and diagnostic accuracy of CT were 97%, 30% and 84%, respectively. Overall sensitivity, specificity and diagnostic accuracy of ^{99m}Tc depreotide SPECT were 94%, 58% and 76%, respectively. For indeterminate lesions sensitivity, specificity and diagnostic accuracy of ^{99m}Tc depreotide SPECT were 71%, 68% and 69%, respectively. Both CT and ^{99m}Tc depreotide SPECT made valuable contributions to the evaluation of pulmonary lesions. ^{99m}Tc depreotide SPECT results were not superior to CT results and did not contribute further to the diagnostic work-up. Regarding indeterminate lesions, ^{99m}Tc depreotide SPECT sensitivity was too low.

pulmonary lesions		history of 31 pack-years.	(SPECT) scan, was the better first-choice examination for the work-up of pulmonary lesions.	
Guerra, 2012 (22) Respiratory gated PET/CT in a European multicentre retrospective study: added diagnostic value in detection and characterization of lung lesions	Retrospective	155 patients (89 men, 66 women, mean age 63.9 ±11.1 years) from 5 European centres that underwent 3- D and 4-D PET/CT from February 2007 to December 2010	Evaluate the added diagnostic value of respiratory gated (4-D) positron emission tomography/computed tomography (PET/CT) in lung lesion detection/characterization	In 34 of 50 (68 %) 3-D equivocal lesions follow-up data were available and the presence of malignancy was confirmed in 21 of 34 (61.8 %) lesions, while in 13 of 34 (38.2 %) was excluded. In 31 of these 34 controlled lesions, 20 of 34 (58.8 %) and 11 of 34 (32.4 %) were correctly classified by 4-D PET/CT as positive and negative, respectively; 3 of 34 (8.8 %) remained equivocal. With equivocal lesions classified as positive, the overall accuracy of 3-D and 4-D was 85.7 and 92.8 %, respectively, while the same figures were 80.5 and 94.2 % when equivocal lesions were classified as negative. The respiratory gated PET/CT technique is a valuable clinical tool in diagnosing lung lesions, improving quantification and confidence in reporting, reducing 3-D undetermined findings and increasing the overall accuracy in lung lesion detection and characterization.

Table 4. Studies that examined risk factors for lung cancer

Systematic Reviews

Risk Factor	**Study**	**Search Details**	**Inclusion Criteria/ Comparison**	**Results**
Previous lung disease/ Infection 9 Reviews	Qu, 2017 (23) Asthma and the risk of lung cancer: a meta-analysis	Two authors (YLQ and JL) searched the titles and abstracts obtained from the initial electronic search for potentially relevant studies for full review.	(1) study design: prospective cohort study, cross-sectional study, and longitudinal study; (2) population: individuals without lung cancer; (3) exposure:	Asthma was significantly associated with the increased risk of lung cancer (odds ratio (OR) = 1.44; 95% confidence interval (CI) 1.31–1.59; P < 0.00001; I^2 = 83%). Additionally, asthma patients without smoking also had the increased lung cancer risk (OR = 1.28; 95% CI 1.10–1.50; P = 0.002; I^2 = 0%). In the subgroup analysis of race, both Caucasians and Asians with

		Two authors (YLQ and LXZ) then assessed the full text of the retrieved studies to determine whether the study met the inclusion criteria. 884 potential studies; 18 included.	asthma or wheeze; (4) comparison: individuals without asthma or wheeze; (5) outcome: relative risk, hazard ratio or OR with corresponding 95% CI of lung cancer risk in overall population and in non-smokers. If serial studies of the same population from the same group were reported, the largest study was included. Reviews, meta-analyses, letters, and editorial articles were all excluded.	asthma showed the same results. In the stratified analysis by gender, both male and female patients with asthma showed the increased risk of lung cancer (OR = 1.38; 95% CI 1.31–1.46; P < 0.00001; I^2 = 24%; OR = 1.68; 95% CI 1.45–1.95; P < 0.00001; I^2 = 63%). However, asthma was not significantly associated with lung adenocarcinoma risk (OR = 1.01; 95% CI 0.69–1.50; P = 0.95; I^2 = 45%). In the stratified analysis by asthma definition, significant associations were found between asthma and lung cancer in self-reported subgroup (OR = 1.23; 95% CI 1.03–1.48; P = 0.02; I^2 = 53%), questionnaire subgroup (OR = 1.32; 95% CI 1.12–1.57; P = 0.001; I^2 = 0%), and register databases subgroup (OR = 1.60; 95% CI 1.42–1.79; P < 0.00001; I^2 = 91%). However, no significant association was observed in physician-diagnosed asthma subgroup (OR = 1.26; 95% CI 0.96–1.65; P = 0.10; I^2 = 0%).
	Mouronte-Roibas, 2016 (24) COPD, emphysema and the onset of lung cancer. A systematic review	Literature search was performed on Pubmed (Medline) employing a combination of MeSH terms ("Lung Neoplasms" AND "Pulmonary Disease, Chronic Obstructive"). Articles were published between 01/01/2000 and 30/05/2016 and published in English or Spanish.	a) cohort studies, case control studies, systematic reviews or meta-analysis; b) sample size of at least 500 individuals; c) COPD patients older than 35 years, with a cumulated tobacco consumption higher than 10 pack/years and with an obstructive spirometry; d) emphysema diagnosis could be either	Both COPD and emphysema seem to increase the risk of developing lung cancer, being this risk higher for smokers with heavier tobacco consumption. These results emphasize the need for physicians to perform spirometries in current and former smokers and lung image tests when needed in order to identify COPD and emphysema and thus select patients at higher risk of developing lung cancer. COPD prevalence in patients with lung cancer ranges from 28.4 to 39.8% in studies specifically designed to assess the relationship between COPD and lung cancer. This percentage is higher when the study includes selected populations to be screened for lung cancer (66%) since these patients are older and have smoked more pack-years. Sanchez-Salcedo et al. observed a Hazard Ratio (HR) of 4.52 (95% CI 2.5–8.18)

	11 studies were included	qualitative or quantitative evaluations of computed tomography imaging; e) lung cancer diagnosis must be anatomopathological .	for COPD patients compared with non- COPD patients. Regarding histological types of lung cancer, 98% of lung cancers in COPD patients are non-small cell lung cancers. Emphysema is present in 47–76% of lung cancer patients and increases with higher tobacco consumption.
Zhai, 2015 (25) HPV and lung cancer risk: A meta-analysis	MEDLINE (PubMed), EMBASE (OVID) and Web of Science were searched to find relevant publications up to March 2014, using the search terms “lung cancer”, “human papillomavirus”, “HPV” and combinations thereof. The search was limited to studies that had been conducted on human subjects and written in English. Meeting abstracts were excluded because of limited data they offered. Reference lists of the retrieved articles, reviews and editorials were also screened to find all additional eligible studies.	(1) case-control, cross-sectional or cohort studies compared HPV infection in lung tissue among LC patients and non-cancer controls; (2) HPV types were specified; (3) histological diagnosis of cases and controls were established; (4) HPV detection was based on DNA; (5) no restrictions based on patients’ nationality, ethnicity or gender; (6) there were no pediatric subjects included; (7) sufficient information was provided to calculate odds ratio with 95% confidence intervals; (8) when an overlap of patients was found in several studies, only the study with the largest sample size and detailed	The pooled results showed that HPV infection was associated with LC (OR = 5.67, 95% CI: 3.09–10.40, P < 0.001). Similar results were also observed in HPV16 and/or HPV18 (HPV16/18) infection analyses (OR = 6.02, 95% CI: 3.22–11.28, P < 0.001). HPV16/18 was significantly associated with lung squamous cell carcinoma (SCC) (OR = 9.78, 95% CI: 6.28–15.22, P < 0.001), while the pooled OR was 3.69 in lung adenocarcinoma (95% CI: 0.99–13.71, P = 0.052). Our results suggest that lung tissue with HPV infection has a strong association with LC, and especially, HPV16/18 infection significantly increases SCC risk, which indicates a potential pathogenesis link between HPV and LC.

	9 publications were included from 287 potential studies.	information was included.	
Hua-Feng, 2015 (26) A meta-analysis of the association between Chlamydia pneumoniae infection and lung cancer risk	Medline, EMBASE, Web of Science, and China National Knowledge Infrastructure (CNKI) databases were searched for publications related to the association between pneumonia infection and lung cancer risk. All potential relevant studies were assessed in detail, as well as the references of the included articles in order to identify additional suitable studies. 13 publications were included.	(1) Study design was limited to prospective cohort study or retrospective case-control study; (2) the patients were pathology clinical confirmed lung cancer; (3) the controls were relative healthy people with no diagnosis of any cancer; (4) the C. pneumoniae infection rate can be extracted from the included individual study. Only studies published in English and Chinese were considered.	The pooled results indicated that the C. pneumoniae infection significant increased the risk of lung cancer OR = 2.07 (95% CI: 1.43-2.99) by random effect model. And for serum IgG, 12 publications reported the IgG positive rate in lung cancer patients and relative healthy controls. The pooled OR was 2.22 (95% CI: 1.41-3.50) by using the random effects model which indicated that the IgG positive rate was significantly higher in lung cancer patients than that of healthy controls. The sensitivity analysis indicated the pooled OR was not sensitive to a single study. However, Begger's funnel plot and Egger's line regression analysis indicated significant publications bias for this meta-analysis. Conclusions: According to the present published data, C. pneumoniae infection may increase the risk of lung cancer. However, for its significant publications and heterogeneity among the included studies, the conclusion should be interpreted cautiously.
Huang, 2015 (27) Associated Links Among Smoking, Chronic Obstructive	Pooled analysis of 24 case-control studies in the International Lung Cancer Consortium (ILCCO) that in total included 4346 SCLC cases and 37,942 cancer-free controls.	1) Subjects had histologically confirmed SCLC cases; 2) Used a structured questionnaire to evaluate lifestyle; 3) Provided an intact study protocol.	Significant dose–response relationships of SCLC risk were observed for all quantitative smoking variables. Smoking pack-years were associated with a sharper increase of SCLC risk for pack-years ranged 0 to approximately 50. The former smokers with longer cessation showed a 43% (quit for 5–9 years) to 89% (quit for ≥20 years) declined SCLC risk vs. subjects who had quit smoking less than 5 years. Compared with non-

Pulmonary Disease, and Small Cell Lung Cancer: A Pooled Analysis in the International Lung Cancer Consortium	24 studies were determined to be relevant to the topics: 1) exposure–response relationships between SCLC risk and smoking indicators, including cumulative smoking, age of initiation, and time since quitting smoking; 2) the association between physician diagnosis of COPD and SCLC risk; and 3) the interaction and mediation effects of COPD and cigarette smoking on SCLC risk.	Among the 24 studies, two were cohort studies and the remaining 22 were case-control design.	COPD subjects, smoking behaviors showed a significantly higher effect on SCLC risk among COPD subjects, and further, COPD patients showed a 1.86-fold higher risk of SCLC. Furthermore, smoking behaviors on SCLC risk were significantly mediated through COPD which accounted for 0.70% to 7.55% of total effects. COPD status was independently associated with SCLC risk (OR, 1.86, 95% CI 1.61–2.16, P < 0.001) with adjustment for age, gender, and smoking pack-years. Overall, less than 10% of smoking's risk effect on SCLC was mediated through COPD.
Rosenberger, 2012 (28) Asthma and lung cancer risk: a systematic investigation by the International Lung Cancer Consortium	Searched 'PubMed' and other databases via the 'Deutsches Institut fu¨r Medizinische Dokumentation und Information' for further publications concerning the epidemiology, etiology, classification or history of asthma or allergies or inflammation and LC up to 27 October 2010 and references to	–Sufficient study design (no serious methodical problems) –Considered asthma independent from other respiratory diseases (in particular: chronic bronchitis, emphysema, tuberculosis). However, asthma and hay fever (or any other atopic/allergic non-pulmonary disease) might be considered in co-occurrence.	The overall LC relative risk (RR) associated with asthma was 1.28 [95% confidence intervals (CIs) = 1.16–1.41] but with large heterogeneity (I^2 = 73%, P < 0.001) between studies. Among ILCCO studies, an increased risk was found for squamous cell (RR = 1.69, 95%, CI = 1.26–2.26) and for small-cell carcinoma (RR = 1.71, 95% CI = 0.99–2.95) but was weaker for adenocarcinoma (RR = 1.09, 95% CI = 0.88–1.36). The increased LC risk was strongest in the 2 years after asthma diagnosis (RR = 2.13, 95% CI = 1.09–4.17) but subjects diagnosed with asthma over 10 years prior had no or little increased LC risk (RR = 1.10, 95% CI = 0.94–1.30). Because the increased incidence of LC was chiefly observed in small cell and squamous cell lung carcinomas, primarily within 2 years of asthma diagnosis and because the association was weak among never smokers, the

		identify relevant study reports. Pooled analysis of 16 participating ILLCCO studies compared to 36 previously published studies.	–Considered incidence or mortality of LC independent from cancer of other sites (i.p. overall cancer), except the combination of lung and pleura. –Any available estimate of odds ratio (OR), relative risk (RR) or hazard ratio (HR).	association may not reflect a causal effect of asthma on the risk of LC.
	Brenner, 2012 (29) Previous Lung Diseases and Lung Cancer Risk: A Pooled Analysis From the International Lung Cancer Consortium	Pooled analysis of studies in the International Lung Cancer Consortium. 17 out of 52 studies including 24,607 cases and 81,829 controls, mainly conducted in Europe and North America, were included (1984–2011).	Included in the International Lung Cancer Consortium and relevant to the topic.	A history of emphysema conferred a 2.44-fold increased risk of lung cancer (95% confidence interval (CI): 1.64, 3.62 (16 studies)). A history of chronic bronchitis conferred a relative risk of 1.47 (95% CI: 1.29, 1.68 (13 studies)). Tuberculosis (relative risk = 1.48, 95% CI: 1.17, 1.87 (16 studies)) and pneumonia (relative risk = 1.57, 95% CI: 1.22, 2.01 (12 studies)) were also associated with lung cancer risk. Among never smokers, elevated risks were observed for emphysema, pneumonia, and tuberculosis.
	Brenner, 2011 (30) Previous Lung Diseases and Lung Cancer Risk: A Systematic Review and Meta-Analysis	MEDLINE database was searched from January 1960 to August 2010 to obtain a list of publications containing risk estimates describing the association between lung cancer and previous lung diseases	-Estimates were adjusted for smoking status, estimates for individual conditions were reported, estimates were based on the diagnosis (rather than just symptoms) and a diagnostic cut point was provided that	A previous history of COPD, chronic bronchitis or emphysema conferred relative risks (RR) of 2.22 (95% confidence interval (CI): 1.66, 2.97) (from 16 studies), 1.52 (95% CI: 1.25, 1.84) (from 23 studies) and 2.04 (95% CI: 1.72, 2.41) (from 20 studies), respectively, and for all these diseases combined 1.80 (95% CI: 1.60, 2.11) (from 39 studies). The RR of lung cancer for subjects with a previous history of pneumonia was 1.43 (95% CI: 1.22–1.68) (from 22 studies) and for subjects with a previous history of tuberculosis was 1.76 (95% CI = 1.49,

		including COPD, emphysema, chronic bronchitis, pneumonia and tuberculosis. 39 studies included.	could be used to combine the studies. -What previous lung conditions are risk factors for developing lung cancer?	2.08), (from 30 studies). Effects were attenuated when restricting analysis to never smokers only for COPD/emphysema/chronic bronchitis (RR = 1.22, 0.97–1.53), however remained significant for pneumonia 1.36 (95% CI: 1.10, 1.69) (from 8 studies) and tuberculosis 1.90 (95% CI: 1.45, 2.50) (from 11 studies).
	Zhan, 2011 (31) Chlamydia pneumoniae infection and lung cancer risk: A meta-analysis	The electronic databases PubMed, Embase, Web of Science and CNKI were searched; Data were extracted and analyzed independently by two investigators. Ultimately, 12 studies, involving 2595 lung cancer cases and 2585 controls from four prospective studies and eight retrospective studies were included.	(1) Evaluating the association between C. pneumoniae infection and lung cancer risk; (2) case–control studies; and (3) and supply the numbers (or percentage) of positivity for C. pneumoniae antibody in lung cancer cases and controls, respectively.	People exposed to C. pneumoniae infection had an odds ratio (OR) of 1.48 (95% confidence interval (CI), 1.32–1.67) for lung cancer risk, relative to those not exposed. C. pneumoniae infection was clearly identified as a risk factor for lung cancer in both prospective studies (OR, 1.16; 95% CI, 1.00–1.36) and retrospective studies (OR, 2.17; 95% CI, 1.79–2.63) and in both IgA ≥ 16 cutoff group (OR, 1.22; 95% CI, 1.06–1.41) and the IgA ≥ 64 cutoff group (OR, 2.35; 95% CI, 1.88–2.93). In conclusion, C. pneumoniae infection is associated with an increased risk for lung cancer; higher titre may be a better predictor of lung cancer risk.
Other non-lung related diseases and medical conditions 9 Reviews	Lin, 2017 (32) Blood lipids profile and lung cancer risk in a meta-analysis of prospective cohort studies	Searched articles published on PubMed, Cochrane Library, Web of Science, EBSCO, Ovid, CNKI, VIP, and WANGFANG MED through August 2016, using the following keywords: ‘‘lipids,’’ ‘‘cholesterol,’’ ‘‘triglyceride,’’ ‘‘lung neoplasms,’’ ‘‘lung cancer,’’ ‘‘risk,’’	(1) Exposure factors were levels of lipids in blood serum or plasma, language is limited to English and Chinese; (2) studies designed as a prospective cohort study; (3) the outcome of interest was lung cancer; (4) relative risk (RR), odds risk, or hazard ratio estimates	Analysis of 18,111 lung cancer cases among 1,832,880 participants showed that serum total cholesterol levels were inversely associated with lung cancer risk (RR = 0.93, 95% confidence interval [CI]: 0.85–1.03). Further analysis considered the lag time and excluded the effects of preclinical cancer, with totally 1,239,948 participants and 14,052 lung cancer cases, found a significantly inverse association between total cholesterol and lung cancer risk (RR = 0.89, 95% CI: 0.83–0.94). Analysis of 3067 lung cancer cases among 59,242 participants found that the high-density lipoprotein cholesterol levels (RR = 0.76, 95% CI: 0.59–0.97) was negatively associated with lung cancer risk

		‘‘prevalence,’’ ‘‘incidence,’’ and ‘‘prospective cohort studies.’’ Reference lists from retrieved articles were also used to identify any potentially relevant studies. 9 studies were included from 10 500 relevant literatures searched.	with 95% confidence intervals (CIs).	and 4673 lung cancer cases among 685,852 participants showed that the total triglyceride (RR = 1.68, 95% CI: 1.44– 1.96) was positively associated with lung cancer risk.
	Wu, 2016 (33) Systemic lupus erythematous increased lung cancer risk: Evidence from a meta-analysis	PubMed, Cochrane Library, EMBASE, Chinese National Knowledge Infrastructure, and WANFANG databases were searched for relevant published articles (last search update was May 18 2015). Search terms “lung cancer,” “lung tumor,” “systemic lupus erythematosus,” and “SLE” were used individually and in various combinations. Bibliographies were checked for other relevant publications.	1) Case-control or cohort study on the association between SLE and lung cancer risk; 2) Sufficient published data for estimating the odds ratio with 95% confidence interval. Studies were excluded if one of the following exists: (1) Not relevant to SLE or lung cancer, (2) animal studies, (3) editorials, reviews and abstracts, and (4) overlapping of studies.	All 12 studies, involving a total of 57,890 SLE patients were included in the meta-analysis. A statistically significant association between SLE and lung cancer risk was found. The data showed that SLE patients had an increased lung cancer risk (OR = 1.60; 95% CI: 1.44–1.77; P < 0.00001). In the subgroup analysis of study design, population and hospital based studies also showed an increased lung cancer risks (OR = 1.68; 95% CI: 1.49–1.89; P < 0.00001; OR = 1.38; 95% CI: 1.12–1.69; P = 0.002). In the subgroup analysis of follow-up duration, significant results were observed in the study with more than 10 years (OR = 1.72; 95% CI: 1.08–2.73; P = 0.02) and < 10 years (OR = 1.59; 95% CI: 1.43–1.77; P < 0.00001), respectively. In addition, studies with large and small sample size also showed an increased lung cancer risk (OR = 1.58; 95% CI: 1.42–1.76; P < 0.00001; OR = 1.76; 95% CI: 1.16–2.67; P = 0.007). This meta-analysis suggested that SLE was associated with an increased lung cancer risk.

		12 studies were included.		
	Zeng, 2016 (34) Periodontal Disease and Incident Lung Cancer Risk: A Meta-Analysis of Cohort Studies	PubMed, Scopus, and ScienceDirect were searched to identify all relevant studies published in English up to June 10, 2015 using the following search terms: ("periodontal disease" OR periodontitis OR "periodontal attachment loss" OR "periodontal pocket" OR "alveolar bone loss" OR "clinical attachment loss") AND (lung AND cancer). Reference lists of included studies, relevant review articles, and editorials were also screened for additional studies. Five cohort studies were included from 119 records	1) prospective cohort, retrospective cohort, or nest case-control studies published as full-text articles; 2) exposure of interest was periodontal disease; 3) endpoint of interest was incident lung cancer (including incidence rate and cancer mortality); and 4) adjusted risk ratios (RRs), incidence density ratios, or hazard ratios (HRs) and associated 95% confidence intervals (95% CIs), or the numbers of events that could calculate them, were reported.	Five cohort studies involving 321,420 participants in this meta-analysis. Summary estimates based on adjusted data showed that periodontal disease was associated with a significant risk of lung cancer (HR = 1.24, 95% CI = 1.13 to 1.36; I^2 = 30%). Moreover, alcohol consumption, a common risk factor of periodontal disease and lung cancer, was also adjusted for in these four studies, and analysis in the current study showed a 1.32-fold increase in lung cancer incidence. No publication bias was detected. Subgroup analysis indicated that the association of periodontal disease and lung cancer remained significant in the female population.
	Simon, 2015 (35)	MEDLINE, BIOSIS Previews, Embase, Derwent Drug File and	(1) Observational study design, (2) reported malignancy outcomes in	Seven of these reported SIRs for overall malignancy; eight for lymphoma, melanoma, and lung, colorectal and breast cancer; seven for prostate cancer; and four

	Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis	SciSearch databases were searched using specified search terms: cancer or tumor, tumour, malign* and rheumatoid arthritis or RA, and epidemiolog* or inciden*, population, observation, retrospective or occurren*. A total of nine publications met the inclusion criteria from 136 articles identified	patients with RA and a general population, (3) enrolled more than 100 patients, (4) included only patients older than 18 years of age, (5) covered any geographic region, (6) written in English, (7) Published 1 January 2008-30 November 2014.	for cervical cancer. Compared with those in the general population, the SIR estimates for patients with RA suggest a modest increased risk in overall malignancy, as previously observed. Patients with RA continued to show an increased risk of lymphoma and lung cancer compared with the general population. Overall, SIR estimates for colorectal and breast cancers continued to show a decrease in risk, whereas cervical cancer, prostate cancer and melanoma appeared to show no consistent trend in risk among patients with RA compared with the general population.
	Hasegawa, 2014 (36) Human papilloma virus in non-small cell lung cancer in never smokers: A systematic review of the literature	Performed a systematic search of MEDLINE database using PubMed for articles of HPV infection in human subjects with NSCLC up to September 2012. All searches were limited to human studies and the English language. 46 eligible articles.	Included studies that used the lung tissue of patients diagnosed by histopathology to have primary NSCLC and excluded studies that used blood samples. The polymerase chain reaction (PCR) as the primary HPV detection method was included in our analysis. Studies using alternative detection methods were excluded.	The HPV prevalence was 28.1% (95% confidence interval (CI) 26.6–30.3%), 8.4% (95% CI 7.1–9.9%) and 21.3% (95% CI 15.2–28.4%), respectively. Eleven studies from East Asia (N = 1110) and 4 from Europe (N = 569) provided information on smoking status. The number of never smoker was 392 patients (33.9%) in East Asia and 54 patients (14.8%) in Europe. The HPV prevalence in East Asian countries was similar between never and ever smokers (33.9% vs 39.2%, P = 0.080). Based on the literature confirming the presence of HPV in lung cancer in never smokers, the virus plays a role in carcinogenesis in the disease. There were different patterns of HPV prevalence between Asian and European countries in the never smokers as well as in ever smokers.

	Hou, 2013 (37)	Comprehensive search of PubMed, Embase, the Web of Science, and Google Scholar. Also reviewed three major Chinese databases, including the China Knowledge Resource Integrated (CNKI) database, the WanFang database, and the VIP database. The final literature search was conducted on May 23, 2013 65 publications were included from 224 articles identified.	First, the article had to include the continent and region of the study, the number of HIV cases, and the number of lung cancer cases. Second, follow-up for lung cancer should start after the diagnosis of HIV was made or the onset of AIDS. Third, the article should have been published in English or Chinese.	Lung cancer risk was greater among HIV-infected individuals compared with the general population. SIRs or adjusted IRRs were 1.5–3.4 in Europe, 0.7–6.9 in the USA, and 5.0 in Africa. Most, but not all studies did not observe a significant change in the incidence and risk of lung cancer between the pre-HAART and HAART eras. In most studies, the risk of lung cancer was higher among women, younger individuals, and injection drug users (IDUs), but the incidence of lung cancer was higher among men and the elderly. No significant trend in lung cancer risk across CD4 cell count categories was reported among the selected articles.
	Onishi, 2013 (38) Cancer Incidence in Systemic Sclerosis: Meta-Analysis of Population-Based Cohort Studies	Medline, Scopus, CINAHL, Web of Science, and Cochrane were searched from January 1966 through May 2012. Review articles and the reference lists from studies were included in the review. Only full-text articles were selected, and the search was not subject to language restrictions.	1) population-based cohort studies of patients adult patients with SSc 2) data on cancer incidence was obtained from cancer registers 3) the number of patients was reported, as well as the exact number of cancers occurring in the cohort during followup, expected cancer incidence rates for a matched background	The pooled SIR for the incidence of cancer overall was 1.41 (95% confidence interval [95% CI] 1.18–1.68), and significant heterogeneity was observed as a consequence of variability in the participants, outcome, study design, and risk of bias among the studies. Men had a significantly higher pooled SIR (1.85 [95% CI 1.49–2.31]) than women (SIR 1.33 [95% CI 1.18–1.49]) ($P < 0.01$), and stratification for sex eliminated heterogeneity, which indicates that variability among the studies greatly contributed to differences between the sexes. There were no differences between limited cutaneous SSc and diffuse cutaneous SSc ($P = 0.77$). Significant increases were observed in the risk of cancer of the lung.

		Six articles met criteria and were included in the meta-analysis from 6 769 search results.	population, and/or ratios of observed-to-expected cancers with 95% confidence intervals (95% CIs).	
	Lee, 2013 (39) Diabetes mellitus as an independent risk factor for lung cancer: A meta-analysis of observational studies	PubMed, EMBASE and the Cochrane Library were searched for observational studies regarding the association between diabetes and lung cancer conducted prior to September 2012. Overall search strategy included terms for diabetes, cancer, outcomes and study design. 34 studies (24 manuscripts) from 7442 identified articles	(1) the study design was based on case– control or cohort studies; (2) the study evaluated the association between diabetes and cancer risk and (3) relative risk (RR) in cohort studies or odds ratios (OR) in case–control studies, and their 95% confidence intervals (CIs) (or data to calculate them), were reported.	Diabetes was significantly associated with increased risk of lung cancer compared with non-diabetic controls when limiting to studies adjusting for smoking status (RR, 1.11; 95% CI, 1.02–1.20; I^2 = 46.1%). This association disappeared when the analysis was restricted to studies not adjusting for smoking status (RR, 0.99; 95% CI, 0.88–1.11; I^2 = 96.7%). When stratifying by sex, an increased risk of lung cancer was present in diabetic women (RR, 1.14; 95% CI, 1.09–1.20; I^2 = 0%), while there was no association in diabetic men (RR, 1.07; 95% CI, 0.89–1.28; I^2 = 96.6%). Among diabetic women, significantly increased risks of lung cancer were found in the following subgroups: cohort studies (RR, 1.14; 95% CI, 1.08–1.20; I^2 = 0%), studies controlling for major confounding variables such as age, smoking and alcohol (RR, 1.19; 95% CI, 1.00–1.43; I^2 = 23.1%), studies with long-term follow-up (RR, 1.14; 95% CI, 1.08–1.20; I^2 = 0%), and high-quality studies assessed by the Newcastle–Ottawa Scale.
	Bonifazi, 2013 (40) Systemic sclerosis (scleroderma) and cancer risk: systematic review and meta-analysis	Searched MEDLINE and Embase for all original articles of observational studies on cancer incidence in scleroderma patients without language restriction published up to December 2011. Two independent	(i) cohort study of patients with scleroderma reporting relative risk or any ratio comparing the observed with the expected numbers of cancer cases in general population and the corresponding CIs or sufficient	Compared with the general population, the summary RR to develop all invasive cancers in scleroderma patients was 1.75 (95% CI 1.41, 2.18). The results for selected cancer sites indicated a strong association with lung cancer (RR 4.35; 95% CI 2.08, 9.09), and a significant increased risk also for haematological neoplasms (RR 2.24; 95% CI 1.53, 3.29). The histological pattern was evaluated in six of eight studies investigating lung cancer risk and it appeared to be fairly heterogeneous, yielding a similar predominance

	of observational studies	authors reviewed all titles/abstracts and retrieved detailed full-text of potentially relevant articles to identify studies. From 1597 articles initially identified, 16 original studies, involving more than 7000 patients, were included in the present review.	information to calculate them; (ii) case-control study of cancer estimating the odds ratios relative to scleroderma; (iii) studies reporting histologically confirmed cancer cases; (iv) studies with diagnosis of cancer following the diagnosis of systemic sclerosis; when a study included cancer cases diagnosed both before and after the onset of scleroderma, we considered data for the latter group only.	of adenocarcinoma (32%) and squamous cell carcinoma (32%). The remaining cases were small cell lung cancer, undifferentiated non-small cell cancer and oat cell carcinoma, while bronchioloalveolar cell carcinoma was reported in only one patient. Out of 13 cohort studies, 7 were judged to have low risk of bias, 3 medium and 3 high. All case-control studies were deemed to have low risk of bias. The present meta-analysis, the first on scleroderma and cancer risk, provides definite estimates on the association between scleroderma and cancer.
Silica 4 Reviews	Boffetta, 2017 (41) Exposure to silicon carbide and cancer risk: a systematic review	Searched PubMed, Embase, and Scopus from inception to December 31, 2015 to identify observational studies examining associations of silicon carbide exposures and cancer outcomes. Used the keywords “silicon carbide” “carborundum,” “dust/adverse effects,” “silicon/adverse effects” AND	-Must be observational study -Must be human study and contain human health data -No language restrictions	We identified two studies of SiC production workers and several studies of users. The studies of production workers indicated an increased risk of lung cancer. The increased risk was restricted to workers with elevated dust exposure and, in the most informative study from Norway, was linked to estimated cristobalite exposure, a form of crystalline silica. Increased risk was not linked to SiC particles, once cristobalite exposure was controlled for. Studies of SiC users in various industries did not reveal an increased risk of lung cancer.

		"neoplasms" or "occupational disease." Reference lists were also searched. 363 documents were identified following the search. The included articles comprised seven cohort studies (four of which referred to the same population of production workers from Norway), one case–control study, and four studies based on routine statistics.		
	Poinen-Rughooputh, 2016 (42) Occupational exposure to silica dust and risk of lung cancer: an updated meta-analysis of epidemiological studies	MEDLINE and EMBASE databases were searched from January 1982 through 29 April 2016 using the search terms "lung cancer", "silica", "silicosis", "risk"," incidence" and "mortality" to identify epidemiological studies which evaluated the relationship between silica exposure and lung cancer in workers,	The article had to have been published in English; the study had to be cohort, case-control or proportional mortality study design; lung cancer should have been reported as a major outcome; reported original results along with confidence intervals in the form of standardized mortality ratio, standardized	The risk of lung cancer was found to be elevated in both silicotics and non-silicotics. The pooled standardized mortality ratio (SMR) was 2.32 with a 95 % confidence interval (95 % CI) of 1.91–2.81 and 1.78 (95 % CI 1.07–2.96) respectively. The pooled standardized incidence ratio (SIR) was 2.49 (95 % CI 1.87–3.33) and 1.18 (95 % CI 0.86–1.62) respectively. Subgroup analysis showed that workers in the mining industry had the highest risk of lung cancer with a pooled SMR of 1.48 (95 % CI 1.18–1.86) and the weakest association was seen in potteries with a pooled SMR of 1.14 (95 % CI 1.05–1.23). A positive exposure-response relation was found between cumulative silica exposure and risk of lung cancer.

		irrespective of their silicotic status 85 studies included from 227 initial records identified.	incidence ratio, odds ratio, proportional mortality ratio, mortality odds ratio or relative risk with their corresponding 95% CI.	
	Gamble, 2011 (43) Crystalline silica and Lung cancer: A critical review of the occupational epidemiology literature of exposure-response studies testing this hypothesis	E-R analyses in 18 studies from eight countries with about 2000 lung cancer cases and the same database used by IARC (2009).	Individual studies of silica-exposed workers with quantitative estimates of exposure, including studies considered by IARC (IARC, 2009) and the pooled analysis (Steenland; Mannetje et al., 2001).	Strength of association is consistently weak in the majority of studies. At the highest exposure level the mean relative risk (RR) is 1.5; four studies have strong associations (RRs>2), three have moderate strong associations (RRs 1.5–2.0), six have weak-negligible associations (RRs 1–1.5), and five have no associations (RRs ≤1.0). Weight of evidence from occupational epidemiology does not support a causal association of lung cancer and silica exposure, which is contrary to the IARC conclusion using essentially the same data.
	Erren, 2011 (44) Meta-analyses of published epidemiological studies, 1979-2006, point to open causal questions in silica-silicosis-lung cancer research.	Published in English, provided estimates of relative risk (RR) of lung cancer, and the corresponding confidence interval (CI) or sufficient data to calculate the latter, for silicotics and/or non-silicotics. 14 studies in addition to 23 investigations	Updated earlier meta-analyses of silicosis and lung cancer and compared the results with 2009 meta-analysis of risks in individuals without silicosis	In silicotics, lung cancer risks were found to be doubled in 38 studies (**FE:** RR = 2.1; 95% CI = 2.0-2.3). In non-silicotics, eight studies without smoking adjustment suggested marginally elevated risks (**FE:** RR = 1.2; 95% CI = 1.1-1.3; **RE:** RR = 1.2; 95% CI =1.0-1.4) but three studies which were controlled for smoking showed null results (FE and **RE:** RR = 1.0; 95% CI = 0.8-1.3). Heterogeneity was substantial but could be linked to study characteristics, like sector of industry, and other second-level data in meta-regression. As no excess was observed for other smoking-related effects in studies of lung cancer among non-silicates, smoking was not considered to be an important confounder or modifier.

		were found to be eligible for meta-analysis.		
Occupational: Mining 1 Review	Taeger, 2015 (45) Lung cancer among coal miners, ore miners and quarrymen: smoking-adjusted risk estimates from the synergy pooled analysis of case–control studies	This analysis was based on 15 609 lung cancer cases and 18 531 controls from the epidemiological SYNERGY database. 14 studies were included that were conducted in 20 study centers in Europe, Canada, and New Zealand between 1985–2010 and restricted the analysis to men, because ever working as a miner was reported by one woman only.	Only study subjects without missing values in any of the analysis variables were eligible.	Ever working as miner or quarryman (690 cases, 436 controls) was associated with an elevated odds ratio (OR) of 1.55 [95% confidence interval (95% CI) 1.34–1.79] for lung cancer. Ore miners (53 cases, 24 controls) had a higher OR (2.34, 95% CI 1.36-4.03) than quarrymen (67 cases, 39 controls; OR 1.92, 95% CI 1.21–3.05) and coal miners (442 cases, 297 controls; OR 1.40, 95% CI 1.18–1.67), but CI overlapped. We did not observe trends by duration of exposure or time since last exposure.
Occupational: Painting 1 Review	Guha, 2011 (46) Lung Cancer Risk in Painters: A Meta-Analysis	PubMed and the reference lists of pertinent publications were searched and reviewed. Data from 47 independent cohort, record linkage and case-control studies (74 total) was used.	All epidemiologic studies included in the previous *IARC Monographs* were considered, published in any language, describing lung cancer in painters; published between 1989 and August 2009.	74 total reports included > 11,000 incident cases or deaths from lung cancer among painters. The summary relative risk for lung cancer in painters was 1.35 (95% confidence interval) and 1.35 after controlling for smoking. The relative risk was higher in never smokers and persisted when restricted to studies that adjusted for other occupational exposures. These results support the conclusion that occupational exposures in painters are casually associated with the risk of lung cancer.

Occupational: Organic Dust (agriculture, meat industry, sawmills, woodworking) 2 Reviews	Peters, 2012 (47) Occupational exposure to organic dust increases lung cancer risk in the general population	Contains pooled data from 11 population or hospital based case-control studies conducted between 1985 and 2005 in 12 European countries and Canada. Altogether, these studies include 13479 lung cancer cases and 16510 controls	Current smokers were people who had smoked at least 1 cigarette per day for at least 1 year, and included those who had stopped smoking in the last 2 years before diagnosis/interview. For all subjects, detailed lifetime occupational and smoking history is available assessing of exposure was done using a newly developed general population job-exposure matrix(JEM) which assigns no, low, or high exposure to organic dust, endotoxic and contact with animals or fresh animal products).	29 573 patients from the SYNERGY population were analyzed. Occupational organic dust exposure was associated with increased lung cancer risk. The second to the fourth quartile of cumulative exposure showed significant risk estimates ranging from 1.12 to 1.24 in a dose-dependent manner ($p<0.001$). This association remained in the highest quartile after restricting analyses to subjects without chronic obstructive pulmonary disease or asthma. No association was observed between lung cancer and exposure to endotoxin or contact with animals or animal products.
	Seidler, 2013 (48) Systematic review and quantification of respiratory cancer risk for occupational exposure to hexavalent chromium	The search terms refer to ‘‘cancer’’ and its synonyms in order to gather as many relevant studies as possible. PubMed was searched from 1947 to December 31, 2010. Medline was searched to identify populations with occupational risk of exposure to	The studies needed to report risk estimates for more than one level of cumulative occupational Cr(VI) exposure (according to AGS 2008), and have adjusted for potential confounding by smoking, the most critical confounding factor in studies on respiratory cancers.	Based on different estimates for the exposure effect, the absolute excess risk was found to be ‘‘acceptable’’ (less than 4 per 10,000 according to the German Committee on Hazardous Substances, ‘‘AGS’’) at a Cr(VI) concentration of 0.1 $\mu g/m^3$, and became ‘‘intolerable’’ (more than 4 per 1,000) beyond a Cr(VI) concentration of 1 $\mu g/m^3$. Occupational exposure limits for Cr(VI) based on excess absolute risks can be derived from published data identified by a systematic literature review. Lung cancer mortality is slightly lower for the German population compared to the European population. Therefore, the excess absolute risk for 1

		chromium. The ISI Web of Science database was also searched, with the search terms adapted accordingly. From 368 records identified, five studies of two cohorts of chromium production workers in Baltimore, Maryland, and Painesville, Ohio, were included	Studies eligible based on the above criteria were then examined independently by two reviewers that assessed their methodological quality.	µg/m^3 workplace air concentration of Cr(VI) reduces from 3.3 per 1,000 for the European population (Table 3) to 2.9 per 1,000 for the German population.
Occupational: Aromatic Hydrocarbons (aluminum production, iron and steel foundries, asphalt workers, carbon black production) 1 Review	Rota, 2014 (49) Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014	Literature search in MEDLINE, ISI Web of Science, SCOPUS and EMBASE of all cohort studies published as original articles, without any language restriction, from January 1, 2006, to January 31, 2014, on workers from selected industries characterized by exposure to polycyclic hydrocarbons (PAH). 13 articles out of 474 non-unique papers were included.	Articles must include data on the risk of lung cancer in least one of the mentioned occupations, and report the SIR or the SMR. Duplicate studies on the same cohort were excluded.	In the meta-analysis, an excess risk of respiratory tract cancers (mainly lung cancer) was found in iron and steel foundries [pooled relative risk (RR) 1.31, 95 % confidence interval (CI) 1.08–1.59 from 14 studies], while a weak excess risk (pooled RR 1.08, 95 % CI 0.95–1.23 from 11 studies) emerged for aluminum production. A borderline increase risk was also observed for cancer of the bladder in the aluminum production (pooled RR 1.28, 95 % CI 0.98– 1.68 from 10 studies) and in iron and steel foundries (pooled RR 1.38, 95 % CI 1.00–1.91 from 9 studies). This updated review and meta-analysis confirm the increased risk from respiratory tract and bladder cancers in selected PAH-related occupations. It cannot be ruled out whether such excesses are due, at least in part, to possible bias or residual confounding.

Occupational: Bricklayers (exposed to crystalline silica, asbestos and other carcinogens) 1 Review	Consonni, 2015 (50) Lung cancer risk among bricklayers in a pooled analysis of case–control studies	Selected relevant studies from the SYNERGY project, which pooled lung cancer case–control studies from 13 European countries, Canada, Hong Kong and New Zealand.	Relevant studies included in the SYNERGY project, pertaining to bricklaying and the associated risk of lung cancer.	In studies using population controls the OR was 1.55 (95% CI: 1.32– 1.81, 540/349 cases/controls), while it was 1.24 (95% CI: 0.93–1.64, 155/120 cases/controls) in hospital-based studies. There was a clear positive trend with length of employment ($p < 0.001$). The relative risk was higher for squamous (OR: 1.68, 95% CI: 1.42–1.98, 309 cases) and small cell carcinomas (OR: 1.78, 95% CI: 1.44–2.20, 140 cases), than for adenocarcinoma (OR: 1.17, 95% CI: 0.95–1.43, 150 cases) (p-homogeneity: 0.0007). ORs were still elevated after additional adjustment for education and in analyses using blue collar workers as referents. This study provided robust evidence of increased lung cancer risk in bricklayers. Although non-causal explanations cannot be completely ruled out, the association is plausible in view of the potential for exposure to several carcinogens, notably crystalline silica and to a lesser extent asbestos.
Occupational: Wood Dust 1 Review	Hancock, 2015 (51) Wood dust exposure and lung cancer risk: a meta-analysis	Databases CINAHL (from 1982), EMBASE (from 1974), Google Scholar (from ∼1980), JSTOR (from ∼1909), MEDLINE (from 1946), PubMed (from 1946), ScienceDirect from (from ∼1856), Web of Science (from 1990) and Wiley Online Library (from ∼1989) through to June 2014 were searched. The search terms used were combinations of Wood Dust, Wood-	1. Contained an estimate of relative risk for lung cancer or data allowing such estimates to be calculated. 2. Contained a risk estimate related to a dichotomous index of exposure (ever vs never) or data allowing such estimates to be calculated. 3a. Contained an explicit analysis of wood dust as an exposure category at an individual not occupational level OR	A significantly increased risk for developing lung cancer was observed among studies that directly assessed wood dust exposure (RR 1.21, 95% CI 1.05 to 1.39, n=33) and that assessed wood dust-related occupations (RR 1.15, 95% CI 1.07 to 1.23, n=59). In contrast, a reduced risk for lung cancer was observed among wood dust (RR 0.63, 95% CI 0.39 to 0.99, n=5) and occupation (RR 0.96, 95% CI 0.95 to 0.98, n=1) studies originating in Nordic countries, where softwood dust is the primary exposure. These results were independent of the presence of adjustment for smoking and exposure classification methods. However, the reduced risk for lung cancer was no longer significant among studies originating within the Nordic countries (predominantly softwood dust exposure) that controlled for smoking (RR 0.64, 95% CI 0.40 to 1.01, n=4, I^2 =62.2%). Only

		Related Occupations and Lung Cancer. Chinese literature from the CNKI database was also searched from 1915 to June 2014. A total of 85 articles were included in the final meta-analysis.	3b. Contained an analysis of a wood dust-related occupation (ie. woodworkers, carpenters and furniture/cabinet makers). 4. Were published in English or Chinese.	minor differences in risk between the histological subtypes were identified.
Occupational: Welding 1 Review	Kendzia, 2013 (52) Welding and Lung Cancer in a Pooled Analysis of Case-Control Studies	Data from the SYNERGY project, from 16 studies conducted in Europe, Canada, China, and New Zealand between 1985 and 2010. Most were population based case-control studies that included both women and men. Cases were recruited from hospitals or cancer registries and had a diagnosis of lung cancer that was confirmed by histology or cytology.	Population had to include men exposed to welding fumes: 1) men whose job title was "welder" for at least 1 year, and 2) men whose job title was 1 of several that we considered as potentially and occasionally involving welding activities. We refer to subjects in this category as "occasional welders." Occasional welding occupations were predominantly plumbers, fitters, and sheet-metal workers.	568 male lung cancer cases and 427 controls who worked as welders, and 1994 cases and 1930 controls who held occasional welding occupations were included in the study. Odds ratios and 95% confidence intervals between regular or occasional welding and lung cancer were estimated, with adjustment for smoking, age, study center, and employment in other occupations associated with lung cancer risk. Overall, 568 cases and 427 controls had ever worked as welders and had an odds ratio of developing lung cancer of 1.44 (95% confidence interval: 1.25, 1.67) with the odds ratio increasing for longer duration of welding. In never and light smokers, the odds ratio was 1.96 (95% confidence interval: 1.37, 2.79). The odds ratios were somewhat higher for squamous and small cell lung cancers than for adenocarcinoma. Another 1,994 cases and 1,930 controls had ever worked in occupations with occasional welding. Work in any of these occupations was associated with some elevation of risk, though not as much as observed in regular welders. Our findings lend further support to the hypothesis that welding is associated with an increased risk of lung cancer.
Household Use of Coal	Bruce, 2015 (53)	Carried out a systematic review and	Human studies that reported household	Fourteen eligible studies of biomass cooking or heating were identified: 13 had independent estimates (12

and Biomass Fuel 3 Reviews	Does household use of biomass fuel cause lung cancer? A systematic review and evaluation of the evidence for the GBD 2010 study	meta-analysis, following PRISMA reporting guidelines. Searches were conducted of 10 databases to July 2012 for studies of clinically diagnosed or pathologically confirmed lung cancer associated with household biomass use for cooking and/or heating. Fourteen eligible studies of biomass cooking or heating were identified:	biomass fuel use for cooking and/or heating; differentiated between risk of lung cancer associated with biomass fuels and coal; provided an effect estimate or sufficient data to calculate one with a 95% CI. Biomass fuel was defined as wood, straw, grass, crop waste or residue, animal dung and charcoal. Lung cancer had to be primary, any histology.	cooking only), all were case-control designs and provided 8221 cases and 11 342 controls. The ORs for lung cancer risk with biomass for cooking and/or heating were OR 1.17 (95% CI 1.01 to 1.37) overall, and 1.15 (95% CI 0.97 to 1.37) for cooking only. Publication bias was not detected, but more than half the studies did not explicitly describe a clean reference category. Sensitivity analyses restricted to studies with adequate adjustment and a clean reference category found ORs of 1.21 (95% CI 1.05 to 1.39) for men (two reports, compiling five studies) and 1.95 (95% CI 1.16 to 3.27) for women (five reports, compiling eight studies). Exposure–response evidence was seen for men, and higher risk for women in developing compared with developed countries, consistent with higher exposures in the former.
	Kurmi, 2012 (54) Lung cancer risk and solid fuel smoke exposure: a systematic review and meta-analysis	Papers published from January 1980 to October 2010 were identified through a systematic literature search in Ovid Medline, EMBASE and Google Scholar. References were also screened for any additional articles. There was no restriction on language in the original search but articles in English	(1) Written in English or Chinese; (2) Case–control, cross sectional or cohort study design that controlled for smoking; (3) Solid fuel used primarily for household cooking and/or heating in the study population; (4) Provided adjusted odds ratios or relative risks to measure the association between lung cancer and exposure to solid	The pooled effect estimate for coal smoke as a lung carcinogen (OR 1.82, 95% CI 1.60–2.06) was greater than that from biomass smoke (OR 1.50, 95% CI 1.17–1.94). The risk of lung cancer from solid fuel use was greater in females (OR 1.81, 95% CI 1.54–2.12) compared to males (OR 1.16, 95% CI 0.79–1.69). The pooled effect estimates were 2.33 (95% CI 1.72–3.17) for adenocarcinoma, 3.58 (1.58–8.12) for squamous cell carcinoma and 1.57 (1.38–1.80) for tumours of unspecified cell type. These findings suggest that in-home burning of both coal and biomass is consistently associated with an increased risk of lung cancer.

		and Chinese were retained for inclusion in the meta-analysis. 28 studies were included in the meta-analysis from 11398 papers identified.	fuels with corresponding 95% confidence intervals or p-values; (5) Specify the technique by which exposure and lung cancer were assessed and ascertained.	
	Hosgood, 2011 (55) Household coal use and lung cancer: systematic review and meta-analysis of case–control studies, with an emphasis on geographic variation	Studies examining the association between lung cancer risk and household coal use were identified by searching both English and Chinese databases. Studies in English published through June 2009 were identified by searches of the PubMed and Science Citation Index databases using keywords related to indoor air pollution. 25 case-control studies were analyzed.	Studies had to be case–control design; coal use exposures were primarily derived from household cooking and/or heating (not from other forms of urban/outdoor air pollution or occupational exposures); had an adjusted odds ratio and 95% confidence interval for the risk of household coal use; differentiated the risk associated with coal use from that of biomass fuels; results for the study population were not reported in another publication.	Household coal use was found to be associated with lung cancer risk among all studies throughout the world [odds ratio (OR) = 2.15; 95% confidence interval (CI) = 1.61–2.89, and particularly among those studies carried out in mainland China and Taiwan (OR = 2.27; 95% CI = 1.65–3.12). Stratification by regions of mainland China and Taiwan found a variation in effects across the regions, with south/southeastern (OR = 3.27; 95% CI = 1.27–8.42) and southwestern China (OR = 2.98; 95% CI =1.18–7.53) experiencing the highest risk. The elevated risk associated with coal use throughout Asia was also observed when stratifying studies by gender, smoking status, sample size, design (population vs hospital case–control) and publication language. No significant publication bias was found.
Diesel Motor Exhaust 2 Reviews	Pintos, J 2012 (56) Occupational exposure to	Studies the risk of lung cancer among men associated with exposure to diesel engine emissions	Studies included: -Patients with incident histologically confirmed cancers from any	Increased risks of lung cancer were found in both studies. The pooled analysis showed an OR of lung cancer associated with substantial exposure to diesel exhaust of 1.80 (95% CI 1.3 to 2.6). The risk associated with substantial exposure was higher for squamous cell

	diesel engine emissions and risk of lung cancer: evidence from two case–control studies in Montreal, Canada	incurred in a wide range of occupations and industries. 2 population-based lung cancer case-control studies which comprised of 857 cases and 533 population controls, and 736 cases and 894 population controls.	Montreal area hospitals. -Canadian citizens. -A series of randomly selected population controls -Controls were matched by age, sex and area of residence to all cancer cases for study I and to lung cancer cases for study II. -Detailed job history of study population was obtained. -Both were case-control.	carcinomas (OR 2.09; 95% CI 1.3 to 3.2) than other histological types. Joint effects between diesel exhaust exposure and tobacco smoking are compatible with a multiplicative synergistic effect.
	Olsson, 2011 (57) Exposure to Diesel Motor Exhaust and Lung Cancer Risk in a Pooled Analysis from Case-Control Studies in Europe and Canada	Data was pooled from 11 lung cancer case-control studies from Europe and Canada where the primary object is to the study the joint effects of exposure to concurrent occupational lung carcinogens and smoking. 11 case-control studies conducted in Europe and Asia.	-Well-designed population or hospital based case-control studies. -Risk of lung cancer associated with exposure to diesel motor exhaust.	Odds ratio of lung cancer and 95% confidence intervals were estimated by unconditional logistic regression, adjusted for age, sex, study, employment in an occupation with established lung cancer risk, cigarette-pack-years, and time since quitting smoking. Cumulative diesel exposure was associated with an increased lung cancer risk highest quartile versus unexposed (odds ratio 1.31; 95% confidence interval, 1.19–1.43), and a significant exposure-response relationship. Corresponding effect estimates were similar in workers never employed in occupations with established lung cancer risk, and in women and never smokers, although not statistically significant. Results show a consistent association between occupational exposure to diesel motor exhaust and increased risk of lung cancer.
Family history of lung cancer 1 Review	Cote, 2012 (58)	-Data was pooled from 24 case- control	Each study must have collected data regarding the lung cancer status,	Individuals with a first-degree relative with lung cancer had a 1.51-fold increase in risk of lung cancer, after adjustment for smoking and other potential

	Increased risk of lung cancer in individuals with a family history of the disease: a pooled analysis.	studies in the Lung Cancer Consortium. - Data from 24,380 lung cancer cases and 23,305 healthy controls were analyzed 24 case-control studies in the Lung Cancer Consortium.	age at diagnosis, smoking status and vital status (living/decease) for the mother, father and siblings of every case and control.	confounders (95% CI: 1.39, 1.63).The association was strongest for those with a family history in a sibling, after adjustment (OR=1.82, 95% CI: 1.62, 2.05). No modifying effect by histologic type was found. Never smokers showed a lower association with positive familial history of lung cancer (OR=1.25, 95% CI: 1.03, 1.52), slightly stronger for those with an affected sibling (OR=1.44, 95% CI: 1.07, 1.93), after adjustment.
Radon Exposure 3 Reviews	Garzillo, 2017 (59) Indoor radon exposure and lung cancer risk: a meta-analysis of case-control studies	Systematic literature search was carried out in PubMed, Web of Science, and Google Scholar to identify relevant studies published in English until January 2016. The key words used for the search were: “radon”, “lung cancer”, “radon epidemiology” and “radon case-control studies”. This search was supplemented by checking the reference lists of the identified manuscripts to verify if the database search was incomplete. Twenty-five lung cancer studies (case-	(I) full-text published article; (II) case-control study with a hospital-based or population-based design; (III) examined residential exposure to radon with passive alpha-track detectors by means of measurements of at least one month; (IV) lung cancer cases histologically confirmed; (V) relative risks (RR) with their corresponding 95% confidence intervals (CIs) reported; (VI) all authors independently selected eligible studies.	Indoor radon exposure was significantly associated with increased risk for lung cancer (RR, 1.19; 95% CI, 1.02–1.39). Study location analysis showed that radon exposure was associated with increased risk for lung cancer from 40 degrees absolute latitude (RR, 1.09; 95% CI, 0.92–1.31), to 50 degrees (RR 1.26; 95% CI, 1.08–1.48), to 60 degrees (RR, 1.46; 95% CI, 1.12–1.91). The correlation of latitude with radon may be due also to other determinants of lung cancer risk: although levels at equatorial latitudes should reflect higher ventilation rates because of higher average indoor temperatures, the general scatter in the results of concentrations of radon indoors in various countries in which measurements have been made in relation to latitude, indicated that many other factors are involved. Lagarde and Pershagen reported an increase of the county-mean radon levels (Bqm^{-3}) against latitude.

		control studies) with 13,569 cases and 22,701 controls were included.		
	Hassfjell, 2017 (60) Lung cancer prevalence associated with radon exposure in Norwegian homes	Estimates are based on the results from a dose-response model published by Darby and collaborators. 13 case-control studies were included.	13 European case-control studies, each with at least 150 individuals with lung cancer and 150 control persons, a detailed smoking history for each individual and the measured radon concentration in their homes over the last 15 years or longer.	Based on these estimates, we calculate that radon is a contributory factor in 12% of all cases of lung cancer annually, assuming an average radon concentration of 88 Bq/m^3 in Norwegian homes. For 2015, this accounted for 373 cases of lung cancer, with an approximate 95 % confidence interval of 145 – 682. Radon most likely contributes to a considerable number of cases of lung cancer.
	Zhang, 2012 (61) Residential Radon and lung Cancer Risk: An Updated Meta-analysis of case-control studies	-Performed a meta-analysis of relevant published case-control studies searched in the PubMed database through July 2011 to examine the association. -relevant information was extracted by two authors Zhang and Sun. -Search terms “radon” in combination of “lung cancer” were searched in the PubMed database in addition to a manual search using	(1) Case control studies; (2) the main exposure of interest was residential radon, which was determined by certain alpha-track radon detector and was expressed as time-weighted mean (Bq/m^3); (3) the outcome of interest was lung cancer incidence; (4) OR with 95% CI for the highest versus lowest category of residential radon exposure were reported or appropriate data	The combined OR of lung cancer for the highest with the lowest exposure was 1.29 (95% CI 1.10-1.51). Dose-response analysis showed that every 100 Bq/m^3 increment in residential radon exposure was associated with a significant 7% increase in lung cancer risk. Subgroup analysis displayed a more pronounced association in the studies conducted in Europe. Studies restricted to female or non-smokers demonstrated weakened associations between exposure and lung cancer.

		reference lists of original articles and recent reviews. 22 case-control studies of residential radon and lung cancer risk involving 13,380 cases and 21,102 controls.	were provided to calculate these values. If the same population was studied in more than one study, we included the study with the largest subjects.	
Air Pollution Exposure 4 Reviews	Yang, 2016 (62) An evidence-based assessment for the association between long-term exposure to outdoor air pollution and the risk of lung cancer	Searched PubMed and Web of Science databases through 31 May, 2014 for cohort studies that evaluated the long-term effects of $PM_{2.5}$, PM_{10}, NO_2, NO_x, SO_2, CO, and O_3 on the subsequent risk of lung cancer. No language restriction was applied. The search strategy included terms for outcome, exposure, and study design. Included 21 studies from 1023 citations	The authors reported data from an original, peer-reviewed study (no review articles or meeting abstracts); the study was a cohort or a nested case-control or case-cohort design; and the authors reported the RR or hazard ratio, and its 95% confidence interval or SE of lung cancer associated with long-term exposure to air pollutants including $PM_{2.5}$, PM_{10}, NO_2, NO_x, SO_2, CO, and ozone.	The risk of lung cancer mortality or morbidity increased 7.23 (95% CI: 1.48–13.31)%/ 10 μg/m^3 increase in fine particles ($PM_{2.5}$), 13.17 (95% CI: 5.57–21.30)%/10 parts per billion (ppb) increase in nitrogen dioxide (NO_2), 0.81 (95% CI: 0.14–1.49)%/10 ppb increase in nitrogen oxides (NO_x), and 14.76 (95% CI: 1.04–30.34)%/10 ppb increase in sulfur dioxide (SO_2). These positive associations remained when analysis was restricted to never-smokers or studies with high methodological quality, and showed no difference by sex. In addition, the association of fine particles with lung cancer was suggestively stronger among never-smokers (RR per each 10 μg/m^3=1.18, 95% CI: 1.06–1.32). There was a null association for carbon monoxide and ozone. Our study indicated that long-term exposure to $PM_{2.5}$, NO_2, NO_x, and SO_2 may be associated with an increased risk of lung cancer.
	Hamra, 2015 (63) Lung Cancer and Exposure to Nitrogen	Systematic review of the PubMed database using the following search terms: traffic OR nitrogen dioxide OR NO_2 OR nitrogen oxide	Studies were required to be human-based, case-control or cohort epidemiologic studies written in English. Studies were required to	The meta-estimate for the change in lung cancer associated with a 10-μg/m^3 increase in exposure to NO_2 was 4% (95% CI: 1%, 8%). The meta-estimate for change in lung cancer associated with a 10-μg/m^3 increase in NO_x was similar and slightly more precise, 3% (95% CI: 1%, 5%). The NO_2 meta-estimate was robust to

	Dioxide and Traffic: A Systematic Review and Meta-Analysis	AND lung cancer. This search was conducted in January 2014, and yielded 179 records. 20 studies were included	explicitly provide a quantitative value for change in lung cancer incidence or mortality associated with exposure to nitrogen oxides or of traffic-related air pollution.	different confounding adjustment sets as well as the exposure assessment techniques used. Trim-and-fill analyses suggest that if publication bias exists, the overall meta-estimate is biased away from the null. Forest plots for measures of traffic volume and distance to roadways largely suggest a modest increase in lung cancer risk.
	Hamra, 2014 (64) Outdoor Particulate Matter Exposure and Lung Cancer: A Systematic Review and Meta-Analysis	Systematic search of PubMed using the keywords "air pollution OR particulate matter OR traffic AND cancer" in the title or abstract, with the results restricted to studies of humans. An initial search was conducted in December 2012 and updated automatically through October 2013. Abstracts of the papers retrieved in the electronic search were screened manually for relevance to the topic. Reference lists were also searched. 18 studies were included from 604 initial studies	-Study provided quantitative estimates of residential exposure to $PM_{2.5}$ and/or PM_{10}. and quantitative estimates of the change in lung cancer incidence or mortality associated with exposure to either indicator of PM -Studies that reported results for the association of lung cancer with other air pollutants or exposure to traffic but did not provide quantitative estimates for PM were not included in the meta-analysis.	The meta-relative risk for lung cancer associated with $PM_{2.5}$ was 1.09 (95% CI: 1.04, 1.14). The meta-relative risk of lung cancer associated with PM_{10} was similar, but less precise: 1.08 (95% CI: 1.00, 1.17). Estimates were robust to restriction to studies that considered potential confounders, as well as subanalyses by exposure assessment method. Analyses by smoking status showed that lung cancer risk associated with $PM_{2.5}$ was greatest for former smokers [1.44 (95% CI: 1.04, 2.01)], followed by never-smokers [1.18 (95% CI: 1.00, 1.39)], and then current smokers [1.06 (95% CI: 0.97, 1.15)]. In addition, meta-estimates for adenocarcinoma associated with $PM_{2.5}$ and PM_{10} were 1.40 (95% CI: 1.07, 1.83) and 1.29 (95% CI: 1.02, 1.63), respectively.

	Raaschou-Nielsen, 2013 (65) Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE)	Prospective analysis of data obtained from ESCAPE, including 36 European areas in which air pollution was measured and cohort studies were located. The present study includes 17 cohort studies.	Cohorts from the ESCAPE study data, from which information about incident lung cancer cases and the most important potential confounders could be obtained, and where the resources needed for participation were available. Analysis of long-term exposure to air pollution and incidence of lung cancer.	The meta-analysis showed an association with risk for lung cancer that was statistically significant for PM_{10} concentration (hazard ratio [HR] 1·22 [95% CI 1·03–1·45] per 10 μg/m³) in confounder model 3. For $PM_{2·5}$ concentration, the HR was 1·18 (0·96–1·46) per 5 μg/m³, and for traffic load at major roads within 100 m the HR was 1·09 (0·99–1·21) per 4000 vehicle-km per day in confounder model 3 (table 2). The results from model 1, with adjustment only for age, sex, and calendar time, showed stronger associations; the effect of adjustment was due mainly to the smoking variables. Results of models 2 and 3 showed no association between risk for lung cancer and NO_2, NO_x, or traffic intensity at the nearest street. Squamous-cell carcinomas were not significantly associated with particulate matter air pollution. Restriction of participants to those exposed to air pollution below several predefined thresholds for particulate matter concentrations (including below European Union air quality limit values for PM_{10} [40 μg/m³] and $PM_{2·5}$ [25 μg/m³]) provided consistently raised HRs.
Asbestos 2 Reviews	Ngamwong, 2015 (66) Additive Synergism between Asbestos and Smoking in Lung Cancer Risk: A Systematic Review and Meta-Analysis	Titles and abstracts were searched in PubMed, Embase, Scopus, ISI Web of Knowledge, and TOXLINE databases from their inception to May 2015. Combinations of the following key words were used: asbestos, crocidolite, amosite, chrysotile, tremolite,	1) original articles published in peer-reviewed journals; 2) human studies; 3) observational studies; 4) studies investigating associations between asbestos exposure and smoking with lung cancer, and; 5) studies reporting sufficient data for	Lung cancer patients who were not exposed to asbestos and non-smoking (A-S-) were compared with; (i) asbestos-exposed and non-smoking (A+S-), (ii) non-exposure to asbestos and smoking (A-S+), and (iii) asbestos-exposed and smoking (A+S+). Case-control studies: the summary odds ratio of (A+S-) workers compared with (A-S-) workers was 1.70 (95% CI = 1.31–2.21). The summary odds ratio of (A-S+) workers compared with (A-S-) was 5.65 (95% CI = 3.38–9.42). Additionally, the summary odds ratio of (A+S +) workers compared with (A-S-) workers was 8.70 (95% CI = 5.78–13.10).

		actinolite, anthophyllite, cigarette, cigarette smoke, cigarette smoking, pipe, cigar, tobacco, tobacco smoking, lung cancer, mesothelioma, lung carcinoma, and lung adenocarcinoma.. Additional studies were also hand-searched from bibliographies of the selected studies. 10 case-control and 7 cohort studies were included from 2499 initial records.	calculating odds ratios and relative risks. Two reviewers (YN, WT) independently appraised titles and abstracts retrieved from the comprehensive searches. The controversial reviews were discussed and resolved by a third reviewer (OL) There was no language restriction	Cohort Studies: The summary relative risks for lung cancer in the cohort studies of (A+S-) workers was 2.72 (95% CI = 1.67–4.40), (A-S+) workers was 6.42 (95% CI = 4.23–9.75), and for (A+S+) workers was 8.90 (95% CI = 6.01–13.18) compared with (A-S-) workers. The results of the cohort studies are consistent with the analysis of the case-control studies. Results suggest that the interaction between asbestos exposure and smoking can be a positive interaction on the additive scale (an additive synergistic effect).
	Nielsen, 2014 (67) Occupational Asbestos Exposure and Lung Cancer—A Systematic Review of the Literature	Top-down searches were performed in PubMed MEDLINE and Embase using the terms asbestos and lung cancer (July 2–3, 2012). Hits from the 2 databases were merged and duplicates removed. The bottom-up searches consisted of 19 specific searches for each of the 19 predefined search	Studies were included if: (i) The main focus was on associations between lung cancer and asbestos exposure; (ii) they describe results from an original study; (iii) they were in English, Scandinavian, German, or French language. Exclusion criteria were (i) case reports, case series, or expert	The results show that histology and location are not helpful in differentiating asbestos-related lung cancer. Pleural plaques, asbestos bodies, or asbestos fibers are useful as markers of asbestos exposure. The interaction between asbestos and smoking regarding lung cancer risk is between additive and multiplicative. The findings indicate that the association between asbestos exposure and lung cancer risk is basically linear, but may level off at very high exposures. The relative risk for lung cancer increases between 1% and 4% per fiber-year (f-y)/mL, corresponding to a doubling of risk at 25–100 f-y/mL. However, one high-quality case-control study showed a doubling at 4 f-y/mL.

		questions and were restricted to PubMed MEDLINE (July 23–27, 2012). Additional studies were identified by reviewing the bibliographies of retrieved papers, and PubMed alerts that appeared after July 2012. 21 studies from 5864 citations.	opinions; (ii) very old publications and/or small study populations; (iii) high risk of bias; and (iv) older studies that were followed up with a more recent updated publication.	
Second Hand Smoke Exposure 1 Review	Hori, 2016 (68) Secondhand smoke exposure and risk of lung cancer in Japan: a systematic review and meta-analysis of epidemiologic studies	MEDLINE (PubMed) and Ichushi Web (Japanese) databases with a search strategy combining search terms and Medical Subject Headings (MeSH). A search using the same text words was conducted through J-STAGE (Japanese) and Medical Online (Japanese). Searches were limited to studies published through 31 July 2015. We did not specify an earliest date of publication in our searches. Citation	Must report on the relationship between SHS and lung cancer risk among Japanese people, be cohort study or case-control study, and report a risk estimate, i.e. relative risk or odds ratio of lung cancer incidence or mortality associated with SHS exposure. Experimental, mechanistic and ecological studies, as well as articles that presented no original data, were excluded.	Four cohort studies and five case-control studies were identified. Quantitative synthesis was conducted only for secondhand smoke exposure in the home during adulthood. Of the 12 populations included in meta-analysis, positive secondhand smoke exposure-lung cancer associations were observed in 11, whereas an inverse association was found in the remaining 1. The pooled relative risk of lung cancer associated with secondhand smoke exposure was 1.28 (95% confidence interval: 1.10–1.48). We found no evidence of publication bias, and a significant association remained even when potentially missing studies were included (pooled relative risk: 1.26; 95% confidence interval: 1.09–1.46). The results were stable across different subgroup analyses, including by study design, publication year, and when adjusting for confounding variables.

		tracking and manual searching of references were also carried out. 9 studies included from 426 identified.		
Marijuana Use 2 Reviews	Martinasek, 2016 (69) A Systematic Review of the Respiratory Effects of Inhalational Marijuana	Inhalational marijuana peer-reviewed articles published from 1967 to 2015 were identified from the PubMed, OVID and Web of Science databases using the search terms. 48 included articles from 281 initial search results.	Studies published in English from 1967-2015, pertaining to the effects of inhalational marijuana. Articles were removed if they did not contain burning marijuana; were animal studies; or were editorials, systematic reviews, commentaries, non-English language, or non-respiratory-related articles.	The research indicates that there is a risk of lung cancer from inhalational marijuana as well as an association between inhalational marijuana and spontaneous pneumothorax, bullous emphysema, or COPD. A variety of symptoms have been reported by inhalational marijuana smokers, including wheezing, shortness of breath, altered pulmonary function tests, cough, phlegm production, bronchodilation, and other symptoms.
	Zhang, 2015 (70) Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium	Data on 2,159 lung cancer cases and 2,985 controls were pooled from 6 case-control studies in the US, Canada, UK, and New Zealand within the International Lung Cancer Consortium. Two studies had previously reported effect estimates for cannabis smoking, and the remaining studies	Details of the International Lung Cancer Consortium and the requirements for inclusion of studies have been previously published and are available on the Consortium portal (http://ilcco.iarc.fr). All studies considered primary incident and histologically confirmed lung cancer cases.	The overall pooled OR for habitual versus nonhabitual or never users was 0.96 (95% CI: 0.66–1.38). Compared to nonhabitual or never users, the summary OR was 0.88 (95%CI: 0.63–1.24) for individuals who smoked 1 or more joint-equivalents of cannabis per day and 0.94 (95%CI: 0.67–1.32) for those consumed at least 10 joint-years. For adenocarcinoma cases the ORs were 1.73 (95%CI: 0.75– 4.00) and 1.74 (95%CI: 0.85–3.55), respectively. However, no association was found for the squamous cell carcinoma based on small numbers. Weak associations between cannabis smoking and lung cancer were observed in never tobacco smokers. Spline modeling indicated a weak positive monotonic association between cumulative cannabis use and lung

		represented unpublished data for the association of interest.		cancer, but precision was low at high exposure levels. Results from our pooled analyses provide little evidence for an increased risk of lung cancer among habitual or long-term cannabis smokers, although the possibility of potential adverse effect for heavy consumption cannot be excluded.
Smoking 1 Review	Ordonez-Mena, 2016 (71) Quantification of the smoking-associated cancer risk with rate advancement periods: meta-analysis of individual participant data from cohorts of the CHANCES consortium	Meta-analysis of 19 population-based prospective cohort studies with individual participant data for 897,021 European and American adults. 19 studies were included.	Studies from CHANCES: a multi-country including data from ongoing prospective cohort studies in Europe and the USA related to health and aging. From all available participating studies in CHANCES, a total of 897,021 participants from 19 cohorts with cancer incidence /mortality data and smoking characteristics were included.	Overall, 140,205 subjects had a first incident cancer, and 53,164 died from cancer, during an average follow-up of 12 years. Current smoking advanced the overall risk of developing and dying from cancer by eight and ten years, respectively, compared with never smokers. The greatest advancements in cancer risk and mortality were seen for lung cancer and the least for breast cancer. Smoking cessation was statistically significantly associated with delays in the risk of cancer development and mortality compared with continued smoking. This investigation shows that smoking, even among older adults, considerably advances, and cessation delays, the risk of developing and dying from cancer.
Tobacco Use 3 Reviews	Mamtani, 2017 (72) Cancer risk in waterpipe smokers: a meta-analysis	Systematic literature search using PubMed, Web of Science and Google Scholar, without language restrictions, for papers referring to the use of waterpipe, narghile, arghileh, hubble-bubble or hookah and cancer. References of	-Studies that contained the minimum information necessary to estimate the relative risk of any form of cancer associated with waterpipe smoking and a corresponding measure of uncertainty. - Case–control and cohort studies,	Considering only high quality studies, waterpipe smoking was associated with increased risk of head and neck cancer (SRR 2.97; 95 % CI 2.26–3.90), esophageal cancer (1.84; 1.42–2.38) and lung cancer (2.22; 1.24–3.97), with no evidence of heterogeneity or publication bias. Increased risk was also observed for stomach and bladder cancer but based mainly on poor-quality studies. The summary risk for the association between waterpipe smoking and lung cancer was 3.18 (95 % CI 1.87–5.42). The odds ratios reported in each individual

		relevant papers were searched. PubMed was searched for observational studies on the association between tobacco smoking and cancer conducted in Middle East countries, where waterpipe is a common form of smoking. Information was retrieved from 28 published reports.	published as original articles. - Independent studies. In case of multiple reports on the same population the estimates from the most recent or most informative report were considered.	study ranged from 1.78 (95 % CI 0.80–4.20) (Lubin et al. 1992) to 6.00 (95 % CI 1.78–20.3) (Aoun et al. 2013). Only one study provided risk estimates adjusted for cigarette use (Hsairi et al. 1993), and three studies reported lung cancer risk associated with exclusive waterpipe smoking (Qiao et al. 1989; Lubin et al. 1992; Koul et al. 2011). The summary risk of lung cancer considering the three high-quality studies (Qiao et al. 1989; Lubin et al. 1992; Hsairi et al. 1993) was 2.22 (95 % CI 1.24–3.97).
	Montazeri, 2017 (73) Waterpipe smoking and cancer: systematic review and meta-analysis	Systematic search of Pubmed, EmBase, Google Scholar and Web of Science, published between 1962 and September 2014. Search keywords were: waterpipe or hookah, sheesha, nargile, hubble-bubble, goza or gaylan, and cancer. 13 case–control studies met the inclusion criteria and were considered for meta-analysis.	Focus on observational studies (cohort, case–control, cross-sectional) that evaluated the association between waterpipe smoking and cancer. Studies with mixed exposures excluded.	The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS). Meta-analysis revealed a significant positive association between waterpipe smoking and the risk of developing lung cancer. The pooled OR is 4.58 with 95% CI (2.61 to 8.03), with low heterogeneity, I^2 =44.67%. The majority of studies had a NOS score of 5–6 or 7, indicating 'fair' or 'good' quality, respectively. Our findings support a positive association between waterpipe smoking and cancer risk.

	Boffetta, 2011 (74) Tobacco smoking as a risk factor of bronchioloalveolar carcinoma of the lung: pooled analysis of seven case–control studies in the International Lung Cancer Consortium (ILCCO)	Comprises data from seven case– control studies from the United States (Table 1). These studies represent a subset of studies included in the ILCCO collaboration.	The remaining studies participating in the ILCCO consortium either excluded by design rare histological types of lung cancer or enrolled less than 10 BAC cases. All BAC cases were diagnosed pathologically and validated through pathologic records. All studies collected information on lifetime history of tobacco smoking, including age of start smoking, duration, intensity, and time since quitting for the former smokers. All studies collected information on cigarette smoking.	Overall, 799 cases of BAC and 15,859 controls were included in the pooled analysis. A total of 514 cases (64.3%) and 5,779 controls (48.1%) were women. The median age of cases was 65 years (interquartile range 56–73 years) and that of controls was 56 years (interquartile range: 45–65 years). The odds ratio of BAC for ever smoking was 2.47 (95% confidence interval [CI] 2.08, 2.93); the risk increased linearly with duration, amount, and cumulative cigarette smoking and persisted long after smoking cessation. The proportion of BAC cases attributable to smoking was 0.47 (95% CI 0.39, 0.54).
Low socioeconomic status 1 Review	Hovanec, 2018 (75) Lung cancer and socioeconomic status in a pooled analysis of case-control studies	Studies were selected from the SYNERGY project, an international collaboration to study the role of occupational exposures on lung cancer risk. Studies were from Europe and North	All included studies solicited detailed information on the participants' occupational biography and smoking history.	The analysis dataset included 17,021 cases and 20,885 controls. There was a strong elevated OR between lung cancer and low SES, which was attenuated substantially after adjustment for smoking, however a social gradient persisted. SES differences in lung cancer risk were higher among men (lowest vs. highest SES category: ISEI OR 1.84 (95% CI 1.61– 2.09); ESeC OR 1.53 (95% CI 1.44–1.63)), than among women (lowest vs. highest SES category: ISEI OR 1.54 (95% CI 1.20–1.98); ESeC OR 1.34 (95% CI 1.19–1.52)).

		America and used data from 12 studies conducted in 18 study centers.		
Alcohol Consumption 2 Reviews	Garcia-Lavandeira, 2016 (76) Alcohol consumption and lung cancer risk in never smokers: a pooled analysis of case-control studies	Medline, EMBASE and CINAHL were searched using different combinations of MeSH terms and free text. 17 studies were included from 832 search results.	a) regarding the study design we included: meta-analysis, pooling studies, cohort studies and case-control studies; b) regarding the sample size we included only those studies with at least 25 lung cancer cases on persons who had never smoked. The overall sample size had to be higher than 100 individuals; c) regarding lung cancer diagnosis we included only studies where anatomopathological diagnosis was confirmed; d) regarding the follow-up period for cohort studies: it should be at least five years and; e) regarding smoking: studies that did not differentiate the results for smokers and for people who had never smoked were excluded.	Cohort-studies and pooling studies of cohort studies: no study in this category found a positive association between overall alcohol consumption and lung cancer risk in people who have never smoked. Case-control studies: in a population based case-control study most studies did not show a clear association between alcohol consumption and lung cancer risk in individuals who have never smoked.

	Bagnardi, 2011 (77) Alcohol consumption and lung cancer risk in never smokers: a meta-analysis	Medline search (from 1960 to January 2010) for studies investigating the association between alcohol consumption and lung cancer risk, published in English. In addition, the reference lists of retrieved articles and of reviews and meta-analyses published on the issue were hand-checked to identify additional relevant studies. 10 articles, including 1913 never smoker lung cancer cases.	(1) case–control or cohort studies (abstracts, letters, reviews and meta-analyses were excluded); (2) reported findings expressed as odds ratio, relative risk or hazard ratio (or reported sufficient data to compute them) in never smokers, with alcohol intake considered as an exposure and lung cancer incidence or mortality as an outcome; (3) reported standard errors or confidence intervals of the risk estimates or provided sufficient data to calculate them.	The random-effects pooled relative risk (RR) for drinkers versus nondrinkers was 1.21 [95% confidence interval (CI) 0.95–1.55]. Influence analysis showed that the heterogeneity was due in a large part to one study, reporting elevated ORs for lung cancer among never smoker women associated with very low levels of alcohol intake (ORs equal to 3.89, 8.76 and 12.06 for 1–4, 4–8 and ≥8 g/week, respectively). When omitting this study, the same figure was 1.05 (95% CI 0.89–1.23). At the dose–response analysis, RR for an increase in alcohol intake of 10 g/day was 1.01 (95% CI 0.92–1.10). We did not find evidence of heterogeneity in pooled estimates by design, gender, definition of 'never smokers' and area in which the study was carried out. When considering adjustment for potential confounders, we did not find a significant difference between estimates adjusted and those not adjusted for diet factors, body mass index and socioeconomic status and/or educational level.
Obesity 1 Review	Hidayat, 2016 (78) Abdominal Obesity and Lung Cancer Risk: Systematic Review and Meta-Analysis	PubMed and Web of Science databases were searched for studies assessing the association between abdominal obesity and lung cancer up to October 2016. The search strategy had no language, publication date, or publication	(a) The study had a prospective design (including cohort study, nested case-control study, and case-cohort study); (b) examined the association between measures of abdominal obesity (WC and/or WHR) and risk of lung cancer; and (c) relative	Each 10 cm increase in WC (waist circumference) and 0.1 unit increase in WHR (waist to hip ratio) were associated with 10% (RR 1.10; 95% CI 1.04, 1.17; I^2 = 27.7%, p-heterogeneity = 0.198) and 5% (RR 1.05; 95% CI 1.00, 1.11; I^2= 25.2%, p-heterogeneity = 0.211) greater risks of lung cancer, respectively. According to smoking status, greater WHR was only positively associated with lung cancer among former smokers (RR 1.11; 95% CI 1.00, 1.23). In contrast, greater WC was associated with increased lung cancer risk among never smokers (RR 1.11; 95% CI 1.00, 1.23), former smokers

	of Prospective Studies	type restriction. In addition, the reference lists of retrieved full publications were reviewed to identify relevant studies that were missed during the database search. 6 prospective cohort studies were included from 1414 publications initially identified.	risks or hazard ratios or odds ratios with 95% confidence intervals were available. Retrospective studies or studies on lung cancer mortality or recurrence were excluded.	(RR 1.12; 95% CI 1.03, 1.22) and current smokers (RR 1.16; 95% CI 1.08, 1.25). The summary RRs for highest versus lowest categories of WC and WHR were 1.32 (95% CI 1.13, 1.54; I^2= 18.2%, p-heterogeneity = 0.281) and 1.10 (95% CI 1.00, 1.23; I^2= 24.2%, p-heterogeneity = 0.211), respectively. In summary, abdominal obesity may play an important role in the development of lung cancer.
Coffee Consumption 1 Review	Xie, 2016 (79) Coffee consumption and the risk of lung cancer: an updated meta-analysis of epidemiological studies	Conducted a systematic search of the literature published on 1 March 2015 using the Cochrane, PubMed and Embase databases. The following search terms were used: 'coffee', 'beverages', and diet ', 'lifestyle 'and 'lung cancer'. Also performed a manual search via reference lists. Only full-length journal articles with a prospective cohort or case–control study design were considered.	(i) the study design was a population-based study, including cohort or case–control study; (ii) a relatively complete assessment of coffee intake was performed; (iii) the association of coffee intake with lung cancer risk was specifically evaluated; and (iv) the relative risk (RR), hazard ratio or odds ratio (OR) and the corresponding 95% confidence interval (95% CI) values were available. In cases in which duplicate reports from the same study were identified, we	The summary odds ratio (OR) of lung cancer was 1.17 (95% confidence interval (CI): 1.03–1.33) for coffee drinkers compared with nondrinkers and 1.31 (95% CI: 1.11–1.55) for the highest category of coffee consumption compared with the lowest category. Compared with nondrinkers, the pooled ORs for lung cancer were 1.10 (95% CI: 0.92–1.31) for ⩽1 cup per day, 1.10 (95% CI: 0.93–1.30) for 2–3 cups per day and 1.20 (95% CI: 1.02–1.39) for ⩾3 cups per day. Further analysis showed that the ORs for hospital-based case–control studies, population-based case–control studies and prospective cohort studies were 1.36 (95% CI: 1.10–1.69), 0.99 (95% CI: 0.77–1.28) and 1.59 (95% CI: 1.26–2.00), respectively. Significant associations for high coffee intake with increased risk of lung cancer were observed in men (OR = 1.41 95% CI: 1.21–1.63), but not in women (OR = 1.16, 95% CI: 0.86–1.56), in American (OR = 1.34 95% CI: 1.08–1.65) and Asian populations (OR = 1.49 95% CI: 1.28–1.74), but not in European populations (OR = 1.12, 95% CI: 0.74–1.67), and in smokers (OR = 1.24, 95% CI: 1.00–1.54), but not

		17 articles included from 2658 articles identified.	chose the most recent one.	in nonsmokers (OR = 0.85, 95% CI: 0.64–1.11). Particularly over the last 5 years, studies have consistently indicated that lung cancer risk is significantly increased by 47% in the population with the highest category intake of coffee compared with that with the lowest category intake (OR = 1.47, 95% CI: 1.21–1.79).
Depression 1 Review	Jia, 2017 (80) Depression and cancer risk: a systematic review and meta-analysis	Searched the Cochrane Library, Web of Science, MEDLINE, and PubMed databases for all studies published from January 1, 1990 to September 30, 2016 using search terms related to psychological depression and cancer. Selected journals and databases from germane published articles were also manually searched and reviewed to supplement the searches. 11 099 records were identified. In total, 1,469,179 participants and 89,716 incident cases of cancer from 25 studies were included.	(i) Observational designs and population-based sampling; (ii) depression defined by the DSM criteria, the ICD criteria, depression-related scales or physician-diagnosed; (iii) cancer defined by self-reported, physician-diagnosed or the ICD criteria; and (iv) participants without any subtype of cancer at the beginning of the study. Exclusion criteria: (i) reviews and case report studies; (ii) studies without usable data or of low quality; and (iii) animal studies.	Depression was significantly associated with overall cancer risk (RR = 1.15, 95% CI: 1.09-1.22) and with liver cancer (RR = 1.20, 95% CI: 1.01-1.43) and lung cancer (RR = 1.33, 95% CI: 1.04-1.72). Subgroup analysis of studies in North America resulted in a significant summary relative risk (RR = 1.30, 95% CI: 1.15-1.48). No significant associations were found for breast, prostate, or colorectal/colon cancer. The average Newcastle Ottawa score was 7.56 for all included studies. The findings showed a small and positive association between depression and the overall occurrence risk of cancer, as well as liver cancer and lung cancer risks. However, multinational and larger sample studies are required to further research and support these associations.

Menopausal Status 1 Review	Min, 2017 (81) Menopausal status and the risk of lung cancer in women A PRISMA-compliant meta-analysis	Conducted a literature search of the PubMed and Embase databases for studies published before October 2015. No language restrictions were applied. References of retrieved articles were also searched. Eight eligible studies, including 5 case–control studies and 3 cohort studies, provided data for meta-analysis.	Case-control or cohort study evaluating the relationship between menopausal status and lung cancer; outcome of interest was lung cancer incidence; odds ratio or relative risk estimates with 95% confidence interval were used.	Postmenopausal women had a statistically significant increased risk of lung cancer in all included studies (RR=1.44, 95% CI: 1.12–1.85) and cohort studies (RR=1.39, 95% CI: 1.05–1.86), but not in case–control studies (OR=1.46, 95% CI: 0.95–2.24). Overall, there was evidence that post-menopause is related to increased lung cancer risk. However, studies have produced slightly heterogeneous results (I^2=38.40%).
Tall Adult Height 1 Review	Wang, 2017 (82) Height and lung cancer risk: A meta-analysis of observational studies	A systematic literature search with no language restrictions was conducted in MEDLINE and EMBASE for studies on the association between height and lung cancer incidence in humans. All studies published before November 20, 2016 were searched. The reference lists of the retrieved papers were also searched.	(1) case–control or cohort study investigating the association between height and lung cancer; (2) the outcome was lung cancer incidence or mortality; (3) the exposure of interest was height; and (4) reported relative risk or odds ratio estimates with corresponding 95% confidence intervals (or sufficient data to calculate these).	Height was measured in eleven studies and was self-reported in 5 studies. Most studies additionally adjusted for a wide range of potential risk factors: 11 for smoking, six for alcohol use and seven for body mass index. Overall, per 10-cm height increases were associated with increased risk of lung cancer (RR 1.06; 95% CI 1.03–1.09, I^2 = 43.6%). In this meta-analysis, high adult height is related to increased lung cancer risk.

		16 studies (15 prospective studies and one case–control study) on adult height and lung cancer risk in the meta-analysis. The studies included a total 4,709,101 individuals, with 33,824 cases of lung cancer risk, and were published from 1981 to 2014.		

Non-RCT studies

Study	**Type of Study**	**Population**	**Outcomes of Interest**	**Results**
Topuzoglu, 2015 (83) Incidence of lung cancer in patients with systemic sclerosis treated with extracorporeal photopheresis	Retrospective	Seventy-one systemic sclerosis (SSc) patients treated with extracorporeal photopheresis (ECP) at the Photopheresis Unit of the Department of Dermatology at the Medical University of Vienna between 1991 and 2013.	Confirm the relationship between SSc and lung cancer, and evaluate the possible impact of ECP on lung cancer incidence in SSc patients.	A standardized incidence ratio (SIR) was calculated for lung cancer in ECP-treated SSc patients of 2.34 [95% confidence interval (CI) 1.63–2.49]. This is in accordance with recent meta-analyses demonstrating a significantly enhanced risk of lung carcinoma in SSc patients. Comparison of the lung cancer risks of these patients with our ECP-treated patients revealed that ECP has no influence. Each patient with lung carcinoma had previously been diagnosed with lung involvement of the non-specific interstitial pneumonitis (NSIP) type. SSc patients are at significantly increased risk for lung cancer. However, ECP does not influence this risk. NSIP may be a risk factor for lung cancer in SSc patients.
Vizcaya, 2013 (84)	Two case-control studies	2016 cases and 2001 population controls. Occupational	To determine whether exposure to various chlorinated	When the two studies were pooled, there was an increased risk of lung cancer associated with occupational exposure to perchloroethylene (OR $_{\text{any exposure}}$ 2.5, 95% CI 1.2 to 5.6; OR

Risk of lung cancer associated with six types of chlorinated solvents: results from two case–control studies in Montreal, Canada		exposure to a large number of agents was evaluated using a combination of subject-reported job history and expert assessment.	solvents is associated with lung cancer.	$_{\text{substantial exposure}}$ 2.4, 95% CI 0.8 to 7.7) and to carbon tetrachloride ($_{\text{OR any exposure}}$ 1.2, 95% CI 0.8 to 2.1; OR $_{\text{substantial exposure}}$ 2.5, 95% CI 1.1 to 5.7). No other chlorinated solvents showed both statistically significant associations and dose–response relationships. ORs appeared to be higher among non-smokers. When the lung cancer cases were separated by histological type, there was a suggestion of differential effects by tumor type, but statistical imprecision and multiple testing preclude strong inferences in this regard. There were suggestive indications that exposure to perchloroethylene and carbon tetrachloride may increase the risk of lung cancer.
Vallieres, 2012 (85) Exposure to welding fumes increases lung cancer risk among light smokers but not among heavy smokers: evidence from two case–control studies in Montreal	Two population-based case-control studies	Study I (1979–1986) included 857 cases and 1066 controls, and Study II (1996–2001) comprised 736 cases and 894 controls. Detailed job histories were obtained by interview and evaluated by an expert team of chemist–hygienists to estimate degree of exposure to approximately 300 substances.	Investigate the relationship between occupational exposure to gas and arc welding fumes and the risk of lung cancer.	The two studies provided similar results, so a pooled analysis was conducted. Among all subjects, no significant association was found between lung cancer and gas welding fumes (OR = 1.1; 95% CI = 0.9–1.4) or arc welding fumes (OR = 1.0; 95% CI = 0.8–1.2). However, when restricting attention to light smokers, there was an increased risk of lung cancer in relation to gas welding fumes (OR = 2.9; 95% CI = 1.7–4.8) and arc welding fumes (OR = 2.3; 95% CI = 1.3–3.8), with even higher OR estimates among workers with the highest cumulative exposures. In conclusion, there was no detectable excess risk of lung cancer due to welding fumes among moderate to heavy smokers; but among light smokers we found an excess risk related to both types of welding fumes.
Ramanakumar, 2011 (86) Exposures in painting-	Two population-based case-control studies	Study I: 1979-1986. 857 cases, 533 population controls, 1349 cancer controls. Study II:	Assess possible relationships between lung cancer and the occupation of painter as well as	In analyses pooling the two studies, painters had an OR of lung cancer of 1.3 (95% CI 0.9 to 2.2). Regarding exposures, ORs were: for wood varnishes and stains, 1.6 (95% CI 1.0 to 2.3); for wood and gypsum paints, 1.3 (95% CI 0.9 to 1.7); and for metal coatings, 1.1 (95% CI 0.8 to 1.6). Small

related occupations and risk of lung cancer among men: results from two case-control studies in Montreal		1996-2001. 765 cases and 899 controls. Detailed lifetime job histories were elicited; a team of hygienists and chemists evaluated the exposure to many occupational substances including paint-related substances.	exposure to paints, varnishes and stains.	numbers hampered evaluation of dose-response relationships. While our results cannot exclude chance or residual confounding by smoking or concomitant occupational exposures, they provide further evidence that some exposures in paint-related occupations, most notably wood varnishes and stains, increase the risk of lung cancer.

Table 5. Studies that examined factors associated with delayed referral

Systematic Review

Study	**Search Details**	**Inclusion Criteria**	**Intervention /Comparison**	**Results**
Chatwin, 2013 (87) The influence of social factors on help-seeking for people with lung cancer	Detailed topic-specific searches of relevant electronic resources [including MEDLINE, BIDS and AMED bibliographic databases, ISI WEB (PubMed) and Web of Science Social Science Citation Index]. Searches focused on identifying literature related to our main themes, published after 1995. Additional	*Lung cancer* and at least one of the other main themes appeared in the title or abstract (i.e. primarily, *help seeking; delays in presenting; understanding symptoms; social factors*). No other information regarding number included or excluded.	Determine the role and influence that social factors may play in determining when and how people decide to seek medical help. Delays in help seeking; patients' understanding of symptoms.	Simon et al. (2012) found that lower economic status was strongly associated with beliefs about cancer and lower levels of cancer symptom awareness. This finding has also been reported in recent work by Beeken et al (2011), who found that people with lower socio-economic status were more fatalistic about cancer, and this is partly why they saw it as less worthwhile to detect it and seek help early. -Molassiotis et al. (2010) outlined how older age, negative beliefs about cancer, fears about the consequences of having cancer and reluctance to engage with the process of receiving bad news can affect an individual's help seeking behaviour. -Some individuals who smoke have been reported to hold the belief that if they present with chest-related

	searches were also conducted using generic search engines and other conventional library resources. Fifty-eight relevant articles were initially located, and supplementary material was sourced using the reference lists from reviewed material.			symptoms, health professionals will view them as being at fault (Sant et al. 2003). -A study by De Nooijer et al. (2001) in the Netherlands similarly showed that shame and embarrassment about symptoms actively hindered early presentation and diagnosis, while associating symptoms with lung cancer and discussing symptoms with others stimulated the process of early detection. -Over half of all the patients studied in a study by Birring and Peake (2005) were found to have needed encouragement from family or friends before they decided to see their general practitioner. -Goodwin et al. (1987), noted significant connections between marital status and diagnostic delay in lung cancer, with those individuals who lived alone showing far more of a tendency to delay help seeking than those in long-term relationships. -Neal and Allgar (2005) reported it was single and separated/divorced people who had delayed longer than married people in seeking medical help.

RCTS, Cohort Studies and cross-sectional studies

Study	Type of study	Population	Outcomes of Interest	Brief results
Guldbrandt, 2015 (88) The effect of direct access to CT scan in early lung cancer detection: an unblended,	RCT	All incident lung cancer patients (in a 19-month period) listed with general practice in the municipality of Aarhus, Denmark. 266 GPs from 119 general practices.	Primary outcomes: primary care (referral) interval and diagnostic interval. Secondary outcome was the stage at diagnosis.	Direct low dose CT scans from primary care did not significantly influence stage at diagnosis or decrease time to diagnosis. However, when correcting for non-compliance, we found that the patients were at higher risk of experiencing a long diagnostic interval if their GPs were in the control group.

cluster-randomised trial		331 lung cancer patients.		
Smith, 2013 (89) Reducing the time before consulting with symptoms of lung cancer: a randomised controlled trial in primary care	RCT	Smokers and ex-smokers aged 55+ attending care in two general practices in north-east Scotland. 206 people completed the trial.	To evaluate whether a theory-based primary care intervention increased timely consulting of individuals with symptoms of lung cancer.	The consultation rate for new chest symptoms in the intervention group was 1.19 (95% confidence interval [CI] = 0.92 to 1.53; = 0.18) times higher than in the usual-care group and the proportion of consultations within the target time was 1.11(95% CI = 0.41 to 3.03; p= 0.83) times higher. One month after the intervention commenced, the intervention group reported intending to consult with chest symptoms 31 days (95% CI = 7 to 54; = 0.012) earlier than the usual care group, and at 6 months this was 25 days (95% CI = 1.5 to 48; = 0.037) earlier. Behavioural intervention in primary care shortened the time individuals at high risk of lung disease intended to take before consulting with new chest symptoms.
Stokstad, 2017 (90) Medical complexity and time to lung cancer treatment-a three-year retrospective chart review	Retrospective	All patients diagnosed with lung cancer at a university hospital during 2011-2013. “Non-complex” patients were defined as those who underwent 1 or 0 tissue diagnostic procedures and had no comorbidities or complications.	Quantify the proportion of patients who started treatment within the recommended timeframes and assess the proportion of non-complex patients for which there were no good reasons for delays.	Four hundred forty-nine cases were analyzed; 142 (32%) had >1 tissue diagnostic procedures; 67 (15%) had medical delays >3 days; 262 (58%) were non-complex and 363 (81%) received treatment for lung cancer. Median number of days until surgery or radiotherapy was 48 (overall) and 41 (non-complex patients). The proportions who started surgery or radiotherapy within 42 days were 41% (overall) and 56% (non-complex). Corresponding numbers for systemic therapy were 29 days (overall) and 25 days (non-complex), and 64% (overall) and 80% (non-complex).
Sirota, 2017 (91) Prevalence and	Prospective	300 GPs diagnosed and managed 2 patient cases where cancer was a possible diagnosis (one	The impact of two factors (cancer prevalence and alternative explanation for patient’s symptoms) on	The physicians did not refer for cancer at all 65.7% of the time, referred for cancer routinely 10.6% of the time, and urgently 23.7% of the time. Thus, although most responses included cancer as a diagnostic possibility, they did not always include a referral

alternative explanations influence cancer diagnosis: an experimental study with physicians		colorectal cancer, one lung). Experience in family medicine ranged from 0-40 years.	diagnosis and prompt management/referral	decision. More experienced family physicians diagnosed cancer slightly more often than less experienced physicians. A second consultation increased the odds of referral and urgent referral (vs. delayed or no referral) on average by a factor of 5. Having cancer as the main diagnosis led to a higher rate of referrals. Both higher prevalence (OR = 1.92, [95% CI 1.27, 2.92]) and absence of an alternative explanation (OR = 1.70, 95% CI [1.11, 2.59]) increased the likelihood of a cancer diagnosis, which increased the likelihood of prompt referral (OR = 22.84, 95% CI [16.14, 32.32]). Listing cancer as a diagnostic possibility would likely reduce referral delays.
Largey, 2016 (92) Lung cancer interval times from point of referral to the acute health sector to the start of first treatment	Retrospective medical record audit	78 patients admitted with a new diagnosis of lung cancer at one of the three principal referral hospitals in Victoria, Australia between 1 January and 30 June 2013	Interval times from referral to diagnosis, diagnosis to first treatment and referral to first treatment; Factors that influence diagnostic delays	There was a significant difference in the mean number of days from referral to diagnosis across treatment type. Patients who underwent surgery waited significantly longer (mean (+/- s.d.) 41.6 +/- 38.4 days) to obtain a diagnosis than those who received radiotherapy (15.1 +/-18.6 days). Only 47% of surgical patients obtained a diagnosis within the recommended 28 days. Missed opportunities, such as failure to recognise abnormal imaging and the ineffective coordination of key tests, have been identified as causative factors for delays in the diagnosis of lung cancer in 37.8% of cancer cases. Ineffective referral and triage processes and/or prolonging waiting times to tests may cause further diagnostic delays.
Ramachandran, 2016 (93) Physician related delays in the diagnosis of	Prospective	96 consecutive patients diagnosed with lung cancer	Assess physician related delays in the diagnosis of lung cancer and the treatments given before presenting to the centre.	Patients, on an average consulted two physicians before presenting to our center. Less than half of the physicians (45%) suspected lung cancer during their evaluation. Around 18% of physicians made an incorrect diagnosis of tuberculosis, out of whom, 88.6% had prescribed anti-tuberculous therapy. Only 27% of physicians referred the patients to higher medical

lung cancer in India				centres for evaluation. Pulmonology Specialists were the most likely to diagnose lung cancer p<.0001.
Fernandez, 2015 (94) Lung cancer diagnostic delay in a Havana hospital	Retrospective	Lung cancer patients who were diagnosed at Joaquín Albarrán Clinical-Surgical Teaching Hospital, Havana, Cuba, from 2007 to 2010 (54 pts.). 74.1% were men; largest age group was 51-60 years.	Diagnostic delay and the link to survival and prognosis	Of the total, 61.1% sought care first at the primary level. Total diagnostic delay for these patients was 67.4 days: 24.3 days due to patient delay (SD 32.8), 16.2 days due to primary care delay (SD 5.2), and 26.9 days due to secondary care delay (SD 20.1). The total delay for patients first seen at the secondary care level was 79.1 days (SD 81.8): 47.8 days due to patient delay (SD 25.6), and 31.3 days due to secondary level delay (SD 14.4). Patients who went directly to hospital did not benefit from shorter delay in diagnosis.
Guldbrandt, 2015 (95) The role of general practice in routes to diagnosis of lung cancer in Denmark: a population-based study of general practice involvement, diagnostic activity and diagnostic intervals	Prospective cohort study (using some retrospective data)	971 first time lung cancer patients in Denmark.	Describe the routes to diagnosis, the diagnostic activity preceding diagnosis and the primary care and diagnostic intervals for lung cancer in Denmark.	The overall median primary care interval was 7 days; the median diagnostic interval was 29 days. The median primary care and diagnostic intervals were longer among patients with the lowest educational level than among better educated patients. Older age was statistically significantly associated with longer intervals of both primary care interval of >30 days and diagnostic interval of ≥69 days. The median primary care and diagnostic intervals were statistically significantly shorter if the GP suspected cancer or a serious disease. Patients referred to a fast-track route experienced a significantly shorter diagnostic interval. A long primary care and/or diagnostic interval were more likely if the GP interpreted the symptoms as “vague” than if the GP interpreted them as “alarm” symptoms.
Jiwa, 2015 (96)	Prospective video-	102 practicing GPs reviewed 24 video-vignettes and case	Determine how GPs manage patients with cancer symptoms and	In more than one-in-eight cases, the patient was not investigated or referred, despite symptoms that were highly suggestive of cancer. Compared with vignettes

How do general practitioners manage patients with cancer symptoms?	vignette study	notes on patients with cancer symptoms. According to guidelines all cases warranted referral to a specialist.	how often they are properly referred.	featuring colorectal cancer participants were less likely to manage breast, bladder, endometrial, and lung cancers with a 'prescription only' or 'referral only' option. Compared with those who practiced in a major city, participants who practiced in a remote or very remote practice were significantly less likely to opt for a 'prescription' or a 'referral only', yet more likely to manage the patient with an 'investigation only'. In the case of lung cancer, a suspicious lesion on a chest X-ray did not appear to warrant immediate referral in most cases.
Yurdakul, 2015 (97) Patient and physician delay in the diagnosis and treatment of non-small cell lung cancer in Turkey	Prospective	A total of 1016 patients, including 926 (91.1%) males and 90 (8.9%) females with a mean age of 61.5±10.1 years, were enrolled between May 2010 and May 2011 from 17 sites in various Turkish provinces.	Investigate patient and doctor related delays in the diagnosis and treatment of non-small cell lung cancer (NSCLC).	The average patient delay was found to be 49.9 days, doctor delay was found to be 87.7 days, and total delay was found to be 131.3. The referral delay was found to be 61.6 days, diagnostic delay was found to be 20.4 days, and treatment delay was found to be 24.4 days. When the major factors responsible for these delays were examined, patient delay was found to be more frequent in workers, while referral delay was found to be more frequent in patients living in villages. We determined that referral delay, doctor delay, and total delay increased as the number of doctors who were consulted by patients increased. Additionally, we determined that diagnostic and treatment delays were more frequent at the early tumour stages in NSCLC patients.
Gonzalez-Barcala, 2014 (98) Timeliness of Care and Prognosis in	Retrospective	Patients with cytohistologically confirmed diagnosis of lung cancer between 1 June 2005 and 31 May 2008.	Time delays for consultation (specialist delay), diagnosis delay and treatment delay.	Mean specialist delay was 53.6 days (median 35 days), diagnosis delay 31.5 days (median 18 days), treatment delay 23.5 days (median 14 days). Older patient age and advanced stage were associated with a shorter specialist delay. Male sex, a more advanced stage, and poor general status were associated with a shorter treatment delay. The survival is longer in patients with a

Patients with Lung Cancer				longer treatment delay. Specialist delay and diagnostic delay did not influence survival.
Hsieh, 2012 (99) Referral-free health care and delay in diagnosis for lung cancer patients	Prospective Questionnaire answered on a recall basis	840 patients diagnosed with lung cancer who had completed or were undergoing cancer treatments at a medical centre in central Taiwan from July 2007 to January 2011.	Identify factors associated with the delay in the diagnosis of lung cancer under the healthcare system in Taiwan.	52.16 days to diagnosis on average. Number of hospital visits before confirmation of diagnosis differed significantly with the level of healthcare institution initially visited. Compared with patients who had three or more hospital visits, patients who only visited two and one hospital(s) had a significant 34.91-day (95% confidence interval: 16.29–53.53) and 42.25-day (95% confidence interval: 20.76–63.76) reduction in their time to diagnosis. Women generally experienced a longer delay in diagnosis (56 days) compared with men (49 days). Patients of 51–60 years of age experienced the longest time to diagnosis (55 days) among all age groups. Patients whose highest level of education was elementary school experienced longest delay in diagnosis (58 days) among all education groups. **In Taiwan patients can access any level of healthcare institution without requiring referral from a primary physician. For the purpose of this study, 'delay in diagnosis' has been defined as the period from a patient's initial medical visit to any hospital to his/her confirmed diagnosis of lung cancer, and has been compared in relative terms with a reference group in our analyses.
Athey, 2012 (100) Early diagnosis of lung cancer: evaluation of a community-	Prospective (results were compared against retrospective data)	Six localities with high lung cancer incidence	Self-reported awareness of lung cancer symptoms, intention to seek healthcare, chest x-ray referral rates in primary care and stage at diagnosis	A public awareness campaign was launched in conjunction with brief intervention training in general practices. 21% (95% CI 18% to 25% of the targeted population recalled something about the campaign. Compared with a responder in the control area, the odds of a responder in the intervention area saying that they would visit their general practitioner and request a chest x-ray for a cough was 1.97 times (95% CI 1.18 to

based social marketing intervention				3.31, p=0.01). Primary care chest x-ray referral rates increased by 20% in the targeted practices in the year following the intervention compared with a 2% fall in the control practices. The difference was highly significant, with an incidence rate ratio of 1.22 (95% CI 1.12 to 1.33, p=0.001). There was a 27% increase in lung cancer diagnoses in the intervention area compared with a fall in the control area. The incidence rate ratio was 1.42 (95% CI 0.83 to 2.44 p=0.199).
Giroux Leprieur, 2012 (101) Delay between the initial symptoms, the diagnosis and the onset of specific treatment in elderly patients with lung cancer	Retrospective	193 lung cancer patients (26 small-cell cancers and 167 non–small-cell lung cancers) were separated by age. Ninety-two patients (47.7%) were 70+ years old.	Initial symptoms in elderly patients, diagnostic delay, treatment delay	No statistical differences were identified between the 2 groups concerning initial symptoms. In elderly patients, the delay between the initial symptoms and the first visit with a thoracic oncologist (median 1.6 months [IQR 23 days-3.3 months]), the delay between the first visit and the specific treatment (median 1.1 months [IQR 18 days-1.8 months]), and the delay between initial symptoms and the specific treatment (median 3 months [IQR 2-5.7 months]) were similar to those in the younger patients (P = .101, P = .084, and P = .671, respectively). Eighty-four percent of the elderly patients were actively treated vs. 98% of the younger patients (P = .001).
Lyratzopoulos, 2012 (102) Variation in number of general practitioner consultations before hospital referral for	Retrospective (survey-based)	41 299 patients with 24 different types of cancers who took part in the 2010 National Cancer Patient Experience Survey in England	Number of general practitioner consultations with cancer symptoms before hospital referral to diagnose cancer. Identify predictors of three or more pre-referral consultations adjusting for cancer type, age, sex,	In multivariable analysis, with patients with rectal cancer as the reference group, those with subsequent diagnosis of lung cancer were more likely to have had three or more pre-referral GP consultations. The probability of three or more pre-referral consultations was higher in young patients (OR for patients aged 16–24 years vs 65–74 years 2·12, 95% CI 1·63–2·75; p <0·0001), those from ethnic minorities (OR for Asian vs white 1·73, 1·45–2·08; p<0·0001; OR for black vs white

cancer: findings from the 2010 National Cancer Patient Experience Survey in England			deprivation quintile and ethnic group.	1·83, 1·51–2·23; p<0·0001) and women (OR women vs men 1·28, 1·21–1·36; p<0·0001).
Brocken, 2012 (103) Timeliness of lung cancer diagnosis and treatment in a rapid outpatient diagnostic program combined with FDG-PET and contrast-enhanced CT scanning	Retrospective	Patients with suspected lung cancer who were referred to the rapid outpatient diagnostic program (RODP) of the tertiary care university clinic between 1999 and 2009 (565 pts.)	Effects of referral route and symptoms on delays, and whether delays were related to disease stage and outcome	Medical charts of 565 patients were retrieved. 290 patients (51.3%) were diagnosed with lung cancer, 48 (8.5%) with another type of malignancy, and in 111 patients (19.6%) the radiological anomaly was diagnosed as non-malignant. In 112 (19.8%) no immediate definite diagnosis was obtained, however in 82 of these cases (73.2%) the proposed follow-up strategy confirmed a benign outcome. The median first line delay was 54 days, IQR (interquartile range) 20–104 days, median patient delay 19 days (IQR 4–52 days), median referral delay was 7 days (IQR 5–9 days), median diagnostic delay 2 days (IQR 1–19 days). In 87% a diagnosis was obtained within 3 weeks after visiting a chest physician and 52.5% started curative therapy within 2 weeks after diagnosis. Patients presenting with hemoptysis had shorter first line delays. The RODP care was generally far more timely compared to literature and published guidelines, except for both referral and palliative therapeutic delay. No specific delay was significantly related to disease stage or survival.
Radzikowska, 2012 (104) The impact of timeliness of care on	Retrospective	8705 squamous cell lung cancer patients and 1881 adenocarcinoma patients; 1064 (12%) women and 9322	Patient and doctor related delays and the impact on survival	The median waiting time between first symptom(s) and first visit to a doctor's was 30 days (mean 57 days). The mean time from first contact with a doctor until the date of first appointment to chest physician (specialist) was 41 days (median 17 days). Chest physicians diagnosed fifty per cent of patients during 28 days, but

survival in non-small cell lung cancer patients		(88%) men; 1392 (13.2%) patients below 50 years old and 9194 (86.8%) patients were over 50 years old		the mean specialist's delay was 51 days. Delays may be due to technical difficulties, additional diseases, problems with cooperation, low suspicion of cancer - particularly in younger patients (more than 13 % were below 50 years of age), and errors in interpretation of chest X-rays. Lack of patient's delay had a positive (HR = 0.81) impact on survival, but lack of doctor's delay had a negative (HR = 1.18) impact on survival.
Carter-Harris, 2014 (105) Lung cancer stigma predicts timing of medical help-seeking behaviour	Cross-sectional correlational study (survey and interview)	94 patients diagnosed with all stages of lung cancer; majority were female, Caucasian and married, mean age was 62.	Timing of medical help-seeking behaviour (from symptom onset to medical help), healthcare system distrust, lung cancer stigma, smoking status	Lung cancer stigma was a significant predictor of increased time from symptom onset to medical help-seeking behaviour. Healthcare system distrust and smoking status were not independently associated with timing of medical help-seeking behavior. The median number of days from symptom onset to medical help-seeking behaviour for symptoms suggestive of lung cancer was 41 days (range = 0-366 days).

References

1. Small Cell Lung Cancer – Version 2.2018 Developer organization: National Comprehensive Cancer Network https://www.nccn.org/professionals/physician_gls/default.aspx#site
2. Suspected Cancer: Recognition and Referral, 2015 Developer organization: National Institute for Health and Care Excellence https://www.nice.org.uk/guidance/ng12
3. Combined Endobronchial and Esophageal Endosonography for the Diagnosis and Staging of Lung Cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in Cooperation With the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS), 2015 Developer organization: European Society of Gastrointestinal Endoscopy (ESGE) https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0034-1392040
4. Management of Lung Cancer: A National Clinical Guideline, 2014 Developer organization: Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/assets/sign137.pdf
5. Establishing the Diagnosis of Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 2013 Developer organization: American College of Chest Physicians https://journal.chestnet.org/article/S0012-3692(13)60293-7/fulltext?code=chest-site
6. Non-Small Cell Lung Cancer – Version 5.2018 Developer organization: National Comprehensive Cancer Network https://www.nccn.org/professionals/physician_gls/default.aspx#site
7. Latimer KM, Mott TF. Lung cancer: diagnosis, treatment principles, and screening. American Family Physician. 2015 Feb 15;91(4):250-6. PubMed PMID: 25955626. English.
8. Mitchell ED, Pickwell-Smith B, Macleod U. Risk factors for emergency presentation with lung and colorectal cancers: a systematic review. BMJ Open. 2015 Apr 02;5(4):e006965. PubMed PMID: 25838506. English.
9. Shim J, Brindle L, Simon M, George S. A systematic review of symptomatic diagnosis of lung cancer. Family Practice. 2014 Apr;31(2):137-48. PubMed PMID: 24347594. English.
10. Baburao A, Narayanswamy H. Clinico-Pathological Profile and Haematological Abnormalities Associated with Lung Cancer in Bangalore, India. Asian Pacific Journal of Cancer Prevention: Apjcp. 2015;16(18):8235-8. PubMed PMID: 26745066. English.
11. Walter FM, Rubin G, Bankhead C, Morris HC, Hall N, Mills K, et al. Symptoms and other factors associated with time to diagnosis and stage of lung cancer: a prospective cohort study. British Journal of Cancer. 2015 Mar 31;112 Suppl 1:S6-13. PubMed PMID: 25734397. English.
12. Ades AE, Biswas M, Welton NJ, Hamilton W. Symptom lead time distribution in lung cancer: natural history and prospects for early diagnosis. International Journal of Epidemiology. 2014 Dec;43(6):1865-73. PubMed PMID: 25172138. English.
13. Gonzalez-Barcala FJ, Falagan JA, Garcia-Prim JM, Valdes L, Carreira JM, Pose A, et al. Symptoms and reason for a medical visit in lung cancer patients. Acta Medica Portuguesa. 2014 May-Jun;27(3):318-24. PubMed PMID: 25017343. English.
14. Iyen-Omofoman B, Tata LJ, Baldwin DR, Smith CJ, Hubbard RB. Using socio-demographic and early clinical features in general practice to identify people with lung cancer earlier. Thorax. 2013 May;68(5):451-9. PubMed PMID: 23321602. English.
15. Cakar B, Karaoglanoglu M, Sayici Y, Gonullu Demirag G, Yucel I. The prognostic value of thrombocytosis in newly diagnosed lung cancer patients: a retrospective analysis. Journal of BUOn. 2011 Oct-Dec;16(4):677-81. PubMed PMID: 22331721. English.

16. Madsen PH, Holdgaard PC, Christensen JB, Hoilund-Carlsen PF. Clinical utility of F-18 FDG PET-CT in the initial evaluation of lung cancer. European Journal of Nuclear Medicine & Molecular Imaging. 2016 Oct;43(11):2084-97. PubMed PMID: 27164899. English.
17. Feng M, Yang X, Ma Q, He Y. Retrospective analysis for the false positive diagnosis of PET-CT scan in lung cancer patients. Medicine. 2017 Oct;96(42):e7415. PubMed PMID: 29049175. English.
18. Zheng K, Liang N, Zhang J, Lang L, Zhang W, Li S, et al. 68Ga-NOTA-PRGD2 PET/CT for Integrin Imaging in Patients with Lung Cancer. Journal of Nuclear Medicine. 2015 Dec;56(12):1823-7. PubMed PMID: 26429958. English.
19. de Vries R, Brinkman P, van der Schee MP, Fens N, Dijkers E, Bootsma SK, et al. Integration of electronic nose technology with spirometry: validation of a new approach for exhaled breath analysis. Journal of Breath Research. 2015 Oct 15;9(4):046001. PubMed PMID: 26469298. English.
20. Hubers AJ, Heideman DA, Herder GJ, Burgers SA, Sterk PJ, Kunst PW, et al. Prolonged sampling of spontaneous sputum improves sensitivity of hypermethylation analysis for lung cancer. Journal of Clinical Pathology. 2012 Jun;65(6):541-5. PubMed PMID: 22461647. English.
21. Harders SW, Madsen HH, Hjorthaug K, Rehling M, Rasmussen TR, Pedersen U, et al. Limited value of 99mTc depreotide single photon emission CT compared with CT for the evaluation of pulmonary lesions. British Journal of Radiology. 2012 Jul;85(1015):e307-13. PubMed PMID: 22745210. English.
22. Guerra L, De Ponti E, Elisei F, Bettinardi V, Landoni C, Picchio M, et al. Respiratory gated PET/CT in a European multicentre retrospective study: added diagnostic value in detection and characterization of lung lesions. European Journal of Nuclear Medicine & Molecular Imaging. 2012 Sep;39(9):1381-90. PubMed PMID: 22588628. English.
23. Qu YL, Liu J, Zhang LX, Wu CM, Chu AJ, Wen BL, et al. Asthma and the risk of lung cancer: a meta-analysis.[Erratum appears in Oncotarget. 2017 Jul 18;8(29):48525; PMID: 28753908]. Oncotarget. 2017 Feb 14;8(7):11614-20. PubMed PMID: 28086224. English.
24. Mouronte-Roibas C, Leiro-Fernandez V, Fernandez-Villar A, Botana-Rial M, Ramos-Hernandez C, Ruano-Ravina A. COPD, emphysema and the onset of lung cancer. A systematic review. Cancer Letters. 2016 11 28;382(2):240-4. PubMed PMID: 27666776. English.
25. Zhai K, Ding J, Shi HZ. HPV and lung cancer risk: a meta-analysis. Journal of Clinical Virology. 2015 Feb;63:84-90. PubMed PMID: 25315992. English.
26. Hua-Feng X, Yue-Ming W, Hong L, Junyi D. A meta-analysis of the association between Chlamydia pneumoniae infection and lung cancer risk. Indian Journal of Cancer. 2015 Dec;52 Suppl 2:e112-5. PubMed PMID: 26728667. English.
27. Huang R, Wei Y, Hung RJ, Liu G, Su L, Zhang R, et al. Associated Links Among Smoking, Chronic Obstructive Pulmonary Disease, and Small Cell Lung Cancer: A Pooled Analysis in the International Lung Cancer Consortium. EBioMedicine. 2015 Nov;2(11):1677-85. PubMed PMID: 26870794. English.
28. Rosenberger A, Bickeboller H, McCormack V, Brenner DR, Duell EJ, Tjonneland A, et al. Asthma and lung cancer risk: a systematic investigation by the International Lung Cancer Consortium. Carcinogenesis. 2012 Mar;33(3):587-97. PubMed PMID: 22198214. English.
29. Brenner DR, Boffetta P, Duell EJ, Bickeboller H, Rosenberger A, McCormack V, et al. Previous lung diseases and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium. American Journal of Epidemiology. 2012 Oct 01;176(7):573-85. PubMed PMID: 22986146. English.
30. Brenner, 2011 (30) Previous Lung Diseases and Lung Cancer Risk: A Systematic Review and Meta-Analysis

31. Zhan P, Suo LJ, Qian Q, Shen XK, Qiu LX, Yu LK, et al. Chlamydia pneumoniae infection and lung cancer risk: a meta-analysis. European Journal of Cancer. 2011 Mar;47(5):742-7. PubMed PMID: 21194924. English.
32. Lin X, Lu L, Liu L, Wei S, He Y, Chang J, et al. Blood lipids profile and lung cancer risk in a meta-analysis of prospective cohort studies. Journal of Clinical Lipidology. 2017 Jul - Aug;11(4):1073-81. PubMed PMID: 28669687. English.
33. Wu Y, Hou Q. Systemic lupus erythematous increased lung cancer risk: Evidence from a meta-analysis. Journal of Cancer Research & Therapeutics. 2016 Apr-Jun;12(2):721-4. PubMed PMID: 27461640. English.
34. Zeng XT, Xia LY, Zhang YG, Li S, Leng WD, Kwong JS. Periodontal Disease and Incident Lung Cancer Risk: A Meta-Analysis of Cohort Studies. Journal of Periodontology. 2016 Oct;87(10):1158-64. PubMed PMID: 27294431. English.
35. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Research & Therapy. 2015 Aug 15;17:212. PubMed PMID: 26271620. English.
36. Hasegawa Y, Ando M, Kubo A, Isa S, Yamamoto S, Tsujino K, et al. Human papilloma virus in non-small cell lung cancer in never smokers: a systematic review of the literature. Lung Cancer. 2014 Jan;83(1):8-13. PubMed PMID: 24252423. English.
37. Hou W, Fu J, Ge Y, Du J, Hua S. Incidence and risk of lung cancer in HIV-infected patients. Journal of Cancer Research & Clinical Oncology. 2013 Nov;139(11):1781-94. PubMed PMID: 23892408. English.
38. Onishi A, Sugiyama D, Kumagai S, Morinobu A. Cancer incidence in systemic sclerosis: meta-analysis of population-based cohort studies. Arthritis & Rheumatism. 2013 Jul;65(7):1913-21. PubMed PMID: 23576072. English.
39. Lee JY, Jeon I, Lee JM, Yoon JM, Park SM. Diabetes mellitus as an independent risk factor for lung cancer: a meta-analysis of observational studies. European Journal of Cancer. 2013 Jul;49(10):2411-23. PubMed PMID: 23562551. English.
40. Bonifazi M, Tramacere I, Pomponio G, Gabrielli B, Avvedimento EV, La Vecchia C, et al. Systemic sclerosis (scleroderma) and cancer risk: systematic review and meta-analysis of observational studies. Rheumatology. 2013 Jan;52(1):143-54. PubMed PMID: 23175568. English.
41. Boffetta P, Hashim D. Exposure to silicon carbide and cancer risk: a systematic review. International Archives of Occupational & Environmental Health. 2017 Jan;90(1):1-12. PubMed PMID: 27628329. English.
42. Poinen-Rughooputh S, Rughooputh MS, Guo Y, Rong Y, Chen W. Occupational exposure to silica dust and risk of lung cancer: an updated meta-analysis of epidemiological studies. BMC Public Health. 2016 11 04;16(1):1137. PubMed PMID: 27814719. English.
43. Gamble JF. Crystalline silica and lung cancer: a critical review of the occupational epidemiology literature of exposure-response studies testing this hypothesis. Critical Reviews in Toxicology. 2011 May;41(5):404-65. PubMed PMID: 21548755. English.
44. Erren TC, Morfeld P, Glende CB, Piekarski C, Cocco P. Meta-analyses of published epidemiological studies, 1979-2006, point to open causal questions in silica-silicosis-lung cancer research. Medicina del Lavoro. 2011 Jul-Aug;102(4):321-35. PubMed PMID: 21834269. English.
45. Taeger D, Pesch B, Kendzia B, Behrens T, Jockel KH, Dahmann D, et al. Lung cancer among coal miners, ore miners and quarrymen: smoking-adjusted risk estimates from the synergy pooled analysis of case-control studies. Scandinavian Journal of Work, Environment & Health. 2015 Sep 01;41(5):467-77. PubMed PMID: 26153779. English.

46. Guha N, Merletti F, Steenland NK, Altieri A, Cogliano V, Straif K. Lung cancer risk in painters: a meta-analysis.[Erratum appears in Cien Saude Colet. 2012 Mar;17(3):809]. Ciencia & Saude Coletiva. 2011 Aug;16(8):3613-32. PubMed PMID: 21860961. English.
47. Peters S, Kromhout H, Olsson AC, Wichmann HE, Bruske I, Consonni D, et al. Occupational exposure to organic dust increases lung cancer risk in the general population. Thorax. 2012 Feb;67(2):111-6. PubMed PMID: 21856697. English.
48. Seidler A, Jahnichen S, Hegewald J, Fishta A, Krug O, Ruter L, et al. Systematic review and quantification of respiratory cancer risk for occupational exposure to hexavalent chromium. International Archives of Occupational & Environmental Health. 2013 Nov;86(8):943-55. PubMed PMID: 23079792. English.
49. Rota M, Bosetti C, Boccia S, Boffetta P, La Vecchia C. Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014. Archives of Toxicology. 2014 Aug;88(8):1479-90. PubMed PMID: 24935254. English.
50. Consonni D, De Matteis S, Pesatori AC, Bertazzi PA, Olsson AC, Kromhout H, et al. Lung cancer risk among bricklayers in a pooled analysis of case-control studies. International Journal of Cancer. 2015 Jan 15;136(2):360-71. PubMed PMID: 24861979. English.
51. Hancock DG, Langley ME, Chia KL, Woodman RJ, Shanahan EM. Wood dust exposure and lung cancer risk: a meta-analysis. Occupational & Environmental Medicine. 2015 Dec;72(12):889-98. PubMed PMID: 26403531. English.
52. Kendzia B, Behrens T, Jockel KH, Siemiatycki J, Kromhout H, Vermeulen R, et al. Welding and lung cancer in a pooled analysis of case-control studies. American Journal of Epidemiology. 2013 Nov 15;178(10):1513-25. PubMed PMID: 24052544. English.
53. Bruce N, Dherani M, Liu R, Hosgood HD, 3rd, Sapkota A, Smith KR, et al. Does household use of biomass fuel cause lung cancer? A systematic review and evaluation of the evidence for the GBD 2010 study. Thorax. 2015 May;70(5):433-41. PubMed PMID: 25758120. English.
54. Kurmi OP, Arya PH, Lam KB, Sorahan T, Ayres JG. Lung cancer risk and solid fuel smoke exposure: a systematic review and meta-analysis. European Respiratory Journal. 2012 Nov;40(5):1228-37. PubMed PMID: 22653775. English.
55. Hosgood HD, 3rd, Wei H, Sapkota A, Choudhury I, Bruce N, Smith KR, et al. Household coal use and lung cancer: systematic review and meta-analysis of case-control studies, with an emphasis on geographic variation. International Journal of Epidemiology. 2011 Jun;40(3):719-28. PubMed PMID: 21278196. English.
56. Pintos J, Parent ME, Richardson L, Siemiatycki J. Occupational exposure to diesel engine emissions and risk of lung cancer: evidence from two case-control studies in Montreal, Canada. Occupational & Environmental Medicine. 2012 Nov;69(11):787-92. PubMed PMID: 22843434. English.
57. Olsson AC, Gustavsson P, Kromhout H, Peters S, Vermeulen R, Bruske I, et al. Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from case-control studies in Europe and Canada. American Journal of Respiratory & Critical Care Medicine. 2011 Apr 01;183(7):941-8. PubMed PMID: 21037020. English.
58. Cote ML, Liu M, Bonassi S, Neri M, Schwartz AG, Christiani DC, et al. Increased risk of lung cancer in individuals with a family history of the disease: a pooled analysis from the International Lung Cancer Consortium. European Journal of Cancer. 2012 Sep;48(13):1957-68. PubMed PMID: 22436981. Pubmed Central PMCID: NIHMS365912. English.
59. Garzillo C, Pugliese M, Loffredo F, Quarto M. Indoor radon exposure and lung cancer risk: A meta-analysis of case-control studies. Translational Cancer Research. 2017 01 Jul;6(Supplement5):S934-S43. PubMed PMID: 617513157. English.

60. Hassfjell CS, Grimsrud TK, Standring WJF, Tretli S. Lung cancer prevalence associated with radon exposure in Norwegian homes. Tidsskrift for Den Norske Laegeforening. 2017 08 22;137(14-15):22. PubMed PMID: 28828814. Lungekreftforekomst knyttet til radoneksponering i norske boliger. English Norwegian.
61. Zhang ZL, Sun J, Dong JY, Tian HL, Xue L, Qin LQ, et al. Residential radon and lung cancer risk: an updated meta- analysis of case-control studies. Asian Pacific Journal of Cancer Prevention: Apjcp. 2012;13(6):2459-65. PubMed PMID: 22938404. English.
62. Yang WS, Zhao H, Wang X, Deng Q, Fan WY, Wang L. An evidence-based assessment for the association between long-term exposure to outdoor air pollution and the risk of lung cancer. European Journal of Cancer Prevention. 2016 May;25(3):163-72. PubMed PMID: 25757194. English.
63. Hamra GB, Laden F, Cohen AJ, Raaschou-Nielsen O, Brauer M, Loomis D. Lung Cancer and Exposure to Nitrogen Dioxide and Traffic: A Systematic Review and Meta-Analysis. Environmental Health Perspectives. 2015 Nov;123(11):1107-12. PubMed PMID: 25870974. English.
64. Hamra GB, Guha N, Cohen A, Laden F, Raaschou-Nielsen O, Samet JM, et al. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environmental Health Perspectives. 2014 Sep;122(9):906-11. PubMed PMID: 24911630. English.
65. Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). Lancet Oncology. 2013 Aug;14(9):813-22. PubMed PMID: 23849838. English.
66. Nawrot TS, Martens DS, Hara A, Plusquin M, Vangronsveld J, Roels HA, et al. Association of total cancer and lung cancer with environmental exposure to cadmium: the meta-analytical evidence. Cancer Causes & Control. 2015 Sep;26(9):1281-8. PubMed PMID: 26109463. English.
67. Nielsen LS, Baelum J, Rasmussen J, Dahl S, Olsen KE, Albin M, et al. Occupational asbestos exposure and lung cancer--a systematic review of the literature. Archives of Environmental & Occupational Health. 2014;69(4):191-206. PubMed PMID: 24410115. English.
68. Hori M, Tanaka H, Wakai K, Sasazuki S, Katanoda K. Secondhand smoke exposure and risk of lung cancer in Japan: a systematic review and meta-analysis of epidemiologic studies. Japanese Journal of Clinical Oncology. 2016 Oct;46(10):942-51. PubMed PMID: 27511987. English.
69. Martinasek MP, McGrogan JB, Maysonet A. A Systematic Review of the Respiratory Effects of Inhalational Marijuana. Respiratory Care. 2016 Nov;61(11):1543-51. PubMed PMID: 27507173. English.
70. Zhang LR, Morgenstern H, Greenland S, Chang SC, Lazarus P, Teare MD, et al. Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. International Journal of Cancer. 2015 Feb 15;136(4):894-903. PubMed PMID: 24947688. Pubmed Central PMCID: NIHMS607200. English.
71. Ordonez-Mena JM, Schottker B, Mons U, Jenab M, Freisling H, Bueno-de-Mesquita B, et al. Quantification of the smoking-associated cancer risk with rate advancement periods: meta-analysis of individual participant data from cohorts of the CHANCES consortium. BMC Medicine. 2016 Apr 05;14:62. PubMed PMID: 27044418. English.
72. Mamtani R, Cheema S, Sheikh J, Al Mulla A, Lowenfels A, Maisonneuve P. Cancer risk in waterpipe smokers: a meta-analysis. International Journal of Public Health. 2017 Jan;62(1):73-83. PubMed PMID: 27421466. English.

73. Montazeri Z, Nyiraneza C, El-Katerji H, Little J. Waterpipe smoking and cancer: systematic review and meta-analysis. Tobacco Control. 2017 01;26(1):92-7. PubMed PMID: 27165994. English.
74. Boffetta P, Jayaprakash V, Yang P, Asomaning K, Muscat JE, Schwartz AG, et al. Tobacco smoking as a risk factor of bronchioloalveolar carcinoma of the lung: pooled analysis of seven case-control studies in the International Lung Cancer Consortium (ILCCO). Cancer Causes & Control. 2011 Jan;22(1):73-9. PubMed PMID: 21072579. English.
75. Hovanec J, Siemiatycki J, Conway DI, Olsson A, Stucker I, Guida F, et al. Lung cancer and socioeconomic status in a pooled analysis of case-control studies. PLoS ONE [Electronic Resource]. 2018;13(2):e0192999. PubMed PMID: 29462211. English.
76. Garcia-Lavandeira JA, Ruano-Ravina A, Barros-Dios JM. Alcohol consumption and lung cancer risk in never smokers. Gaceta Sanitaria. 2016 Jul-Aug;30(4):311-7. PubMed PMID: 27266513. English.
77. Bagnardi V, Rota M, Botteri E, Scotti L, Jenab M, Bellocco R, et al. Alcohol consumption and lung cancer risk in never smokers: a meta-analysis. Annals of Oncology. 2011 Dec;22(12):2631-9. PubMed PMID: 21427064. English.
78. Hidayat K, Du X, Chen G, Shi M, Shi B. Abdominal Obesity and Lung Cancer Risk: Systematic Review and Meta-Analysis of Prospective Studies. Nutrients. 2016 Dec 15;8(12):15. PubMed PMID: 27983672. English.
79. Xie Y, Qin J, Nan G, Huang S, Wang Z, Su Y. Coffee consumption and the risk of lung cancer: an updated meta-analysis of epidemiological studies. European Journal of Clinical Nutrition. 2016 Feb;70(2):199-206. PubMed PMID: 26081490. English.
80. Jia Y, Li F, Liu YF, Zhao JP, Leng MM, Chen L. Depression and cancer risk: a systematic review and meta-analysis. Public Health. 2017 Aug;149:138-48. PubMed PMID: 28641155. English.
81. Min L, Wang F, Liang S, Yang J, Xu X. Menopausal status and the risk of lung cancer in women: A PRISMA-compliant meta-analysis. Medicine. 2017 Jun;96(26):e7065. PubMed PMID: 28658099. English.
82. Wang F, Xu X, Yang J, Min L, Liang S, Chen Y. Height and lung cancer risk: A meta-analysis of observational studies. PLoS ONE [Electronic Resource]. 2017;12(9):e0185316. PubMed PMID: 28949980. English.
83. Topuzoglu S, Knobler R, Movadat O, Petkov V, Foedinger D, Just U, et al. Incidence of lung cancer in patients with systemic sclerosis treated with extracorporeal photopheresis. Photodermatology, Photoimmunology & Photomedicine. 2015 Jul;31(4):175-83. PubMed PMID: 25495608. English.
84. Vizcaya D, Christensen KY, Lavoue J, Siemiatycki J. Risk of lung cancer associated with six types of chlorinated solvents: results from two case-control studies in Montreal, Canada. Occupational & Environmental Medicine. 2013 Feb;70(2):81-5. PubMed PMID: 23104733. English.
85. Vallieres E, Pintos J, Lavoue J, Parent ME, Rachet B, Siemiatycki J. Exposure to welding fumes increases lung cancer risk among light smokers but not among heavy smokers: evidence from two case-control studies in Montreal. Cancer Medicine. 2012 Aug;1(1):47-58. PubMed PMID: 23342253. English.
86. Ramanakumar AV, Parent ME, Richardson L, Siemiatycki J. Exposures in painting-related occupations and risk of lung cancer among men: results from two case-control studies in Montreal. Occupational & Environmental Medicine. 2011 Jan;68(1):44-51. PubMed PMID: 20817942. English.
87. Chatwin J, Sanders C. The influence of social factors on help-seeking for people with lung cancer. European Journal of Cancer Care. 2013 Nov;22(6):709-13. PubMed PMID: 23731280. English.

88. Guldbrandt LM, Fenger-Gron M, Rasmussen TR, Rasmussen F, Meldgaard P, Vedsted P. The effect of direct access to CT scan in early lung cancer detection: an unblinded, cluster-randomised trial. BMC Cancer. 2015 Nov 25;15:934. PubMed PMID: 26608727. English.
89. Smith S, Fielding S, Murchie P, Johnston M, Wyke S, Powell R, et al. Reducing the time before consulting with symptoms of lung cancer: a randomised controlled trial in primary care. British Journal of General Practice. 2013 Jan;63(606):e47-54. PubMed PMID: 23336469. English.
90. Stokstad T, Sorhaug S, Amundsen T, Gronberg BH. Medical complexity and time to lung cancer treatment - a three-year retrospective chart review. BMC Health Services Research. 2017 Jan 17;17(1):45. PubMed PMID: 28095840. English.
91. Sirota M, Kostopoulou O, Round T, Samaranayaka S. Prevalence and alternative explanations influence cancer diagnosis: An experimental study with physicians. Health Psychology. 2017 05;36(5):477-85. PubMed PMID: 28240921. English.
92. Largey G, Ristevski E, Chambers H, Davis H, Briggs P. Lung cancer interval times from point of referral to the acute health sector to the start of first treatment. Australian Health Review. 2016 Jan;40(6):649-54. PubMed PMID: 26909516. English.
93. Ramachandran K, Thankagunam B, Karuppusami R, Christopher DJ. Physician related delays in the diagnosis of lung cancer in India. Journal of Clinical and Diagnostic Research. 2016 01 Nov;10(11):OC05-OC8. PubMed PMID: 613086893. English.
94. Fernandez de la Vega JF, Perez H, Samper JA. Lung cancer diagnostic delay in a Havana hospital. MEDICC review. 2015 Jan;17(1):55-8. PubMed PMID: 25725770. English.
95. Guldbrandt LM, Fenger-Gron M, Rasmussen TR, Jensen H, Vedsted P. The role of general practice in routes to diagnosis of lung cancer in Denmark: a population-based study of general practice involvement, diagnostic activity and diagnostic intervals. BMC Health Services Research. 2015 Jan 22;15:21. PubMed PMID: 25608462. English.
96. Jiwa M, Meng X, O'Shea C, Magin P, Dadich A, Pillai V. How do general practitioners manage patients with cancer symptoms? A video-vignette study. BMJ Open. 2015 Sep 14;5(9):e008525. PubMed PMID: 26369800. English.
97. Yurdakul AS, Kocaturk C, Bayiz H, Gursoy S, Bircan A, Ozcan A, et al. Patient and physician delay in the diagnosis and treatment of non-small cell lung cancer in Turkey. Cancer Epidemiology. 2015 Apr;39(2):216-21. PubMed PMID: 25670053. English.
98. Gonzalez-Barcala FJ, Falagan JA, Garcia-Prim JM, Valdes L, Carreira JM, Puga A, et al. Timeliness of care and prognosis in patients with lung cancer. Irish Journal of Medical Science. 2014 Sep;183(3):383-90. PubMed PMID: 24091615. English.
99. Hsieh VC, Wu TN, Liu SH, Shieh SH. Referral-free health care and delay in diagnosis for lung cancer patients. Japanese Journal of Clinical Oncology. 2012 Oct;42(10):934-9. PubMed PMID: 22826351. English.
100. Athey VL, Suckling RJ, Tod AM, Walters SJ, Rogers TK. Early diagnosis of lung cancer: evaluation of a community-based social marketing intervention. Thorax. 2012 May;67(5):412-7. PubMed PMID: 22052579. English.
101. Giroux Leprieur E, Labrune S, Giraud V, Gendry T, Cobarzan D, Chinet T. Delay between the initial symptoms, the diagnosis and the onset of specific treatment in elderly patients with lung cancer. Clinical Lung Cancer. 2012 Sep;13(5):363-8. PubMed PMID: 22264658. English.
102. Lyratzopoulos G, Neal RD, Barbiere JM, Rubin GP, Abel GA. Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England. Lancet Oncology. 2012 Apr;13(4):353-65. PubMed PMID: 22365494. English.
103. Brocken P, Kiers BA, Looijen-Salamon MG, Dekhuijzen PN, Smits-van der Graaf C, Peters-Bax L, et al. Timeliness of lung cancer diagnosis and treatment in a rapid outpatient

diagnostic program with combined 18FDG-PET and contrast enhanced CT scanning. Lung Cancer. 2012 Mar;75(3):336-41. PubMed PMID: 21943652. English.
104. Radzikowska E, Roszkowski-Sliz K, Glaz P. The impact of timeliness of care on survival in non-small cell lung cancer patients. Pneumonologia i Alergologia Polska. 2012;80(5):422-9. PubMed PMID: 22926903. English.
105. Carter-Harris L, Hermann CP, Schreiber J, Weaver MT, Rawl SM. Lung cancer stigma predicts timing of medical help-seeking behavior. Oncology Nursing Forum. 2014 May;41(3):E203-10. PubMed PMID: 24769603. Pubmed Central PMCID: NIHMS624280. English.

Appendix 1. Members of the Expert Panel

Name	Affiliation	Conflict of Interest
Marla Ash Primary Care	Southlake Regional Health Centre	No conflict of interest declared
Lee Donohue Primary Care	The Ottawa Hospital	No conflict of interest declared
Anthony D'Urzo Primary Care	University of Toronto	No conflict of interest declared
Conrad Falkson Lung cancer – radiation oncology	Southeast Regional Cancer Centre	No conflict of interest declared
Amanda Hey Primary Care	Health Sciences North	No conflict of interest declared
Hugh Langley Primary Care	Southeast Regional Cancer Centre	No conflict of interest declared
Aisha Lofters Primary Care	Primary Care Lead Cancer Care Ontario	Currently hold a grant from CIHR and the Canadian Cancer Society to explore implementation of lung cancer screening for patients living with low income
Donna Maziak Lung cancer - surgery	Ottawa General Hospital	No conflict of interest declared
Roland Skrastins Respirology	Toronto East General Hospital	No conflict of interest declared
Yee Ung Lung cancer – radiation oncology	Odette Cancer Centre	No conflict of interest declared
Robert Zeldin Lung cancer - surgery	Toronto East General Hospital	Advisory board member for Boeringer-Ingelheim

Appendix 2. Search Strategies

MEDLINE signs/symptoms

Database: Ovid MEDLINE(R) <2011 to May Week 2 2018> Search Strategy:

---

1 exp "Sensitivity and Specificity"/
2 false negative reactions/ or false positive reactions/
3 (sensitivity or specificity or accura$).ab,ti.
4 diagnos$.ab,ti.
5 predictive value$.ab,ti.
6 reference value$.ab,ti.
7 ROC.ab,ti.
8 (likelihood adj ratio$1).ab,ti.
9 monitoring.tw.
10 (false adj (negative$1 or positive$1)).ab,ti.
11 (randomized controlled trial or controlled clinical trial).pt.
12 double-blind method/ or single-blind method/
13 practice guideline.pt.
14 consensus development conference$.pt.
15 review.pt.
16 review.ab.
17 (meta-analysis or metaanalysis).ab.
18 meta-analysis.pt.
19 meta-analysis.ti.
20 (cohort adj stud$).ab,ti.
21 exp cohort studies/
22 (single blind$3 or double blind$3 or triple blind$3).ab,ti.
23 or/1-22
24 letter.pt.
25 comment.pt.
26 editorial.pt.
27 or/24-26
28 23 not 27
29 exp Respiratory Tract Neoplasms/
30 Adenocarcinoma, Bronchiolo-Alveolar/
31 ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis)).tw.
32 or/29-31
33 Cough/
34 cough$.tw.
35 Dyspnea/
36 dyspn$.tw.
37 short$ of breath.tw.
38 breathless$.tw.
39 Hemoptysis/
40 (hemoptysis or haemoptysis).tw.
41 (blood$ adj2 (sputum or spit or spittle or phlegm)).ab,ti.
42 Hoarseness/
43 hoarse$.tw.
44 chest pain/ or shoulder pain/
45 ((chest or shoulder) adj3 pain$).tw.
46 Respiratory Sounds/
47 wheez$.tw.

48 exp body weight changes/
49 (weight adj1 (loss or gain or chang$)).tw.
50 Flushing/
51 ((face or facial) adj flushing).tw.
52 Diarrhea/
53 (diarrhea or diarrhoea).tw.
54 (Bronchitis/ or exp Pneumonia/) and Recurrence/
55 ((bronchitis or pneumonia) adj recur$).tw.
56 "signs and symptoms"/
57 or/33-56
58 28 and 32 and 57
59 limit 58 to (english language and humans)
60 (2011: or 2012: or 2013: or 2014: or 2015: or 2016: or 2017: or 2018:).ed.
61 59 and 60

EMBASE signs/symptoms
Database: EMBASE <2011 to 2018 Week 20>
Search Strategy:
---
1 "sensitivity and specificity"/
2 false negative result/ or false positive result/
3 (sensitivity or specificity or accura$).ab,ti.
4 diagnos$.ab,ti.
5 predictive value$.ab,ti.
6 reference value$.ab,ti.
7 ROC.ab,ti.
8 (likelihood adj ratio$1).ab,ti.
9 monitoring.tw.
10 (false adj (negative$1 or positive$1)).ab,ti.
11 double blind procedure/ or single blind procedure/ or triple blind procedure/
12 exp controlled clinical trial/
13 double blind procedure/ or single blind procedure/ or triple blind procedure/
14 exp practice guideline/
15 review.pt.
16 review.ab.
17 (meta-analysis or metaanalysis).ab.
18 Meta Analysis/
19 meta-analysis.ti.
20 (cohort adj stud$).ab,ti.
21 cohort analysis/
22 (single blind$3 or double blind$3 or triple blind$3).ab,ti.
23 or/1-22
24 letter.pt.
25 editorial.pt.
26 or/24-25
27 23 not 26
28 exp Respiratory Tract Cancer/
29 exp Respiratory Tract Tumor/
30 ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis)).tw.
31 or/28-30
32 coughing/ or irritative coughing/
33 cough$.tw.

34 Dyspnea/
35 dyspn$.tw.
36 short$ of breath.tw.
37 breathless$.tw.
38 Hemoptysis/
39 (hemoptysis or haemoptysis).tw.
40 (blood$ adj2 (sputum or spit or spittle or phlegm)).ab,ti.
41 Hoarseness/
42 hoarse$.tw.
43 exp Pain/ and (chest or shoulder$).tw.
44 ((chest or shoulder) adj3 pain$).tw.
45 Wheezing/
46 weight change/ or weight gain/ or weight reduction/
47 (weight adj1 (loss or gain or chang$)).tw.
48 Flushing/ and (face or facial).tw.
49 ((face or facial) adj flushing).tw.
50 Diarrhea/
51 (diarrhea or diarrhoea).tw.
52 (Bronchitis/ or exp Pneumonia/) and Recurrent Disease/
53 ((bronchitis or pneumonia) adj recur$).tw.
54 clinical feature/ or symptom/
55 or/32-54
56 and/27,31,55
57 limit 56 to (human and english language)
58 (2011: or 2012: or 2013: or 2014: or 2015: or 2016: or 2017: or 2018:).dd.
59 57 and 58

MEDLINE tests

Database: Ovid MEDLINE(R) <2011 to May Week 2 2018> Search Strategy:

---

1 Primary health care/
2 Family physician/
3 ((family or general) adj practitioner$).mp.
4 gp.mp.
5 family physician$.mp.
6 family doctor$.mp.
7 Family practice/
8 ((family or general) adj practice$).mp.
9 primary care.mp.
10 primary health care.mp.
11 or/1-10
12 meta-analysis/
13 "review literature"/
14 meta-analy$.mp.
15 metaanal$.mp.
16 (systematic$ adj (review$ or overview$)).mp.
17 meta-analysis.pt.
18 review.pt.
19 review.ti.
20 or/12-19
21 "case reports [publication type]"/
22 letter.pt.
23 historical article.pt.
24 comment.pt.
25 editorial.pt.

26 or/21-25
27 20 not 26
28 exp "sensitivity and specificity"/
29 (sensitivity or specificity).tw.
30 exp Diagnostic Errors/
31 predictive value$.tw.
32 predictive value$ of test$.tw.
33 ROC.tw.
34 (ROC adj (analys$ or area or auc or characteristic$ or curve$)).tw.
35 (false adj (negative or positive)).tw.
36 accuracy.tw.
37 reference value$.tw.
38 likelihood ratio$.tw.
39 ((pre-test or pretest) adj probability).tw.
40 post-test probability.tw.
41 Diagnosis, differential/
42 Diagnostic tests, routine/
43 or/28-42
44 exp Lung Neoplasms/
45 exp Lung neoplasms/di
46 exp Lung Neoplasms/bl, pa, di, ra, ri, us, ul [Blood, Pathology, Diagnosis, Radiography, Radionuclide Imaging, Ultrasonography, Ultrastructure]
47 exp Spirometry/
48 exp Radiography, Thoracic/
49 Sputum/cy
50 Tomography, X-ray Computed/
51 cxr.mp.
52 (chest adj X-ray$).mp.
53 (sputum adj cytolog$).mp.
54 (cytolog$ adj sputum).mp.
55 (CT adj scan$).mp.
56 exp Blood Cell Count/
57 (CBC or FBC).mp.
58 exp thrombocytosis/
59 thrombocytosis.mp.
60 C-reactive protein/
61 c-reactive protein$.mp.
62 Blood sedimentation/
63 erythrocyte sedimentation rate.mp.
64 or/47-63
65 43 and 44 and 64
66 limit 65 to (english language and humans)
67 (2011: or 2012: or 2013: or 2014: or 2015: or 2016: or 2017: or 2018:).ed.
68 66 and 67

EMBASE tests

Database: EMBASE <2011 to 2018 Week 20>
Search Strategy:

---

1 exp Primary health care/
2 general practitioner/
3 ((family or general) adj practitioner$).mp.
4 gp.mp.
5 Family physician/
6 family physician$.mp.

7 family doctor$.mp.
8 general practice/
9 ((family or general) adj practice$).mp.
10 primary care.mp.
11 primary health care.mp.
12 or/1-11
13 Meta Analysis/
14 "systematic review"/
15 (meta-analy$ or metaanaly$).mp.
16 (systematic adj (review$ or overview$)).mp.
17 review.pt.
18 review.ti.
19 or/13-18
20 letter.pt.
21 editorial.pt.
22 or/20-21
23 19 not 22
24 "sensitivity and specificity"/
25 sensitivity.tw.
26 specificity.tw.
27 exp "prediction and forecasting"/
28 predictive value$.tw.
29 predictive value$ of test$.tw.
30 roc curve/
31 (ROC adj (analys$ or area or auc or characteristic$ or curve$)).tw.
32 exp diagnostic error/
33 (false adj (positive or negative)).tw.
34 diagnostic accuracy/
35 accuracy.tw.
36 reference value/
37 reference value$.tw.
38 likelihood ratio$.tw.
39 ((pre-test or pretest) adj probability).tw.
40 post-test probability.tw.
41 differential diagnosis/
42 or/24-41
43 exp thorax radiography/
44 (chest adj X-ray$).mp.
45 cxr.mp.
46 sputum cytodiagnosis/
47 (sputum adj cytolog$).mp.
48 (cytolog$ adj sputum).mp.
49 spirometry/
50 spirometry.mp.
51 exp computer assisted tomography/
52 (ct adj scan$).mp.
53 exp blood cell count/
54 (CBC or FBC).mp.
55 thrombocytosis.mp. or THROMBOCYTOSIS/
56 c-reactive protein.mp. or C Reactive Protein/
57 erythrocyte sedimentation rate/
58 erythrocyte sedimentation rate.mp.
59 or/43-58
60 exp Respiratory Tract Tumor/
61 42 and 59 and 60

62 limit 61 to (human and english language)
63 (2011: or 2012: or 2013: or 2014: or 2015: or 2016: or 2017: or 2018:).dd.
64 62 and 63

MEDLINE risk factors

Database: Ovid MEDLINE(R) <2011 to May Week 2 2018> Search Strategy:

---

1 meta-Analysis as topic/
2 meta analysis.pt.
3 (meta analy$ or metaanaly$).tw.
4 (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
5 (systematic adj (review$ or overview?)).tw.
6 (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7 or/1-6
8 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9 (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10 (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11 (study adj selection).ab.
12 10 or 11
13 review.pt.
14 12 and 13
15 7 or 8 or 9 or 14
16 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
17 15 not 16
18 limit 17 to (english language and humans)
19 exp Respiratory Tract Neoplasms/
20 Adenocarcinoma, Bronchiolo-Alveolar/
21 ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis)).tw.
22 exp Lung Neoplasms/
23 exp Bronchial Neoplasms/
24 exp Carcinoma, Bronchogenic/ or exp Carcinoma, Small Cell/
25 exp Carcinoma, Non-Small-Cell Lung/ or exp Carcinoma, Bronchogenic/ or exp Carcinoma, Small Cell/
26 or/19-25
27 18 and 26
28 (2011: or 2012: or 2013: or 2014: or 2015: or 2016: or 2017: or 2018:).ed.
29 27 and 28

EMBASE risk factors

Database: EMBASE <2011 to 2018 Week 20>
Search Strategy:

---

1 exp Meta Analysis/ or exp "Systematic Review"/
2 (meta analy$ or metaanaly$).tw.
3 (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4 (systematic adj (review$ or overview?)).tw.

5 exp "Review"/ or review.pt.
6 (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7 (study adj selection).ab.
8 5 and (6 or 7) (
9 or/1-4,8
10 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11 (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12 9 or 10 or 11
13 (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
14 12 not 13
15 limit 14 to (human and english language)
16 exp Respiratory Tract Cancer/
17 exp Respiratory Tract Tumor/
18 ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis)).tw.
19 exp lung tumor/
20 exp bronchus tumor/
21 exp lung carcinoma/
22 exp lung non small cell cancer/
23 exp small cell carcinoma/
24 or/16-23
25 15 and 24
26 (2011: or 2012: or 2013: or 2014: or 2015: or 2016: or 2017: or 2018:).dd.
27 25 and 26

MEDLINE delay

Database: Ovid MEDLINE(R) <2011 to May Week 2 2018> Search Strategy:

---

1 (lung adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$)).mp.
2 exp respiratory tract neoplasms/
3 1 or 2
4 (delay$ adj3 practitioner$).mp.
5 (delay$ adj3 diagnos$).mp.
6 diagnos$ delay$.mp.
7 diagnos$ early.mp.
8 early diagnosis/
9 earl$ diagnosis.mp.
10 earl$ detection.mp.
11 earl$ presentation.mp.
12 earl$ symptom$.mp.
13 exp health behavior/
14 exp attitude to health/
15 (delay$ adj3 patient$).mp.
16 or/4-15
17 "referral and consultation"/
18 referral$.mp.
19 late$ referral$.mp.
20 earl$ referral$.mp.
21 or/17-20
22 Disease progression/
23 Time factors/

24 Physician's practice patterns/
25 or/17-24
26 3 and 16 and 25
27 limit 26 to (english language and humans)
28 (2011: or 2012: or 2013: or 2014: or 2015: or 2016: or 2017: or 2018:).ed.
29 27 and 28

EMBASE delay
Database: EMBASE <2011 to 2018 Week 20>
Search Strategy:
---
1 exp Lung Cancer/di [Diagnosis]
2 exp lung cancer/
3 (lung adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$)).tw.
4 or/1-3
5 Cancer diagnosis/
6 early diagnosis/
7 earl$ diagnosis.tw.
8 diagnos$ earl$.tw.
9 Delayed Diagnosis/
10 (delay$ adj3 diagnos$).tw.
11 diagnos$ delay$.tw.
12 (delay$ adj3 practitioner$).tw.
13 exp Patient attitude/
14 Attitude to health/ or Attitude to illness/
15 earl$ detection.tw.
16 detect$ earl$.tw.
17 earl$ presentation.tw.
18 earl$ symptom$.tw.
19 or/5-18
20 patient referral/
21 referral$.tw.
22 earl$ referral$.tw.
23 late$ referral$.tw.
24 or/20-23
25 Time factors/
26 exp disease course/
27 clinical practice/
28 or/20-27
29 4 and 19 and 28
30 limit 29 to (human and english language)
31 (2011: or 2012: or 2013: or 2014: or 2015: or 2016: or 2017: or 2018:).dd.
32 30 and 31
33 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
34 32 not 33

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "ARCHIVE."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.