Non-small Cell Lung Cancer T114774 (Lung cancer broad)

[**Overview and Recommendations** 1](#_Toc166358244)

[**Background** 1](#_Toc166358245)

[**Evaluation** 1](#_Toc166358246)

[**Management** 2](#_Toc166358247)

[**Background Information** 4](#_Toc166358248)

[**Description** 4](#_Toc166358249)

[**Also Called** 4](#_Toc166358250)

[**Definitions** 4](#_Toc166358251)

[**Types** 5](#_Toc166358252)

[**Epidemiology** 5](#_Toc166358253)

[**Who is Most Affected** 5](#_Toc166358254)

[**Incidence/Prevalence** 5](#_Toc166358255)

[**Risk Factors** 9](#_Toc166358256)

[**Factors Associated with Decreased Risk** 20](#_Toc166358257)

[**Associated Conditions** 22](#_Toc166358258)

[**Etiology and Pathogenesis** 23](#_Toc166358259)

[**Causes** 23](#_Toc166358260)

[**Pathogenesis** 23](#_Toc166358261)

[**History and Physical** 23](#_Toc166358262)

[**Clinical Presentation** 23](#_Toc166358263)

[**History** 24](#_Toc166358264)

[**Physical** 25](#_Toc166358265)

[**Diagnosis and Staging** 25](#_Toc166358266)

[**Management** 29](#_Toc166358267)

[**Management of Resectable Disease** 29](#_Toc166358268)

[**Management of Unresectable Nonmetastatic Disease** 31](#_Toc166358269)

[**Management of Advanced Disease** 31](#_Toc166358270)

[**Prevention and Management of Complications** 34](#_Toc166358271)

[**Complications** 36](#_Toc166358272)

[**Prognosis** 37](#_Toc166358273)

[**Prevention and Screening** 38](#_Toc166358274)

[**Prevention** 38](#_Toc166358275)

[**Screening** 49](#_Toc166358276)

[**Lung Cancer in Female Persons** 51](#_Toc166358277)

[**General Information** 51](#_Toc166358278)

[**Comparative Lung Cancer Risk in Female Persons vs. Male Persons** 51](#_Toc166358279)

[**Treatment Outcomes** 52](#_Toc166358280)

[**Guidelines and Resources** 54](#_Toc166358281)

[**Guidelines** 54](#_Toc166358282)

[**Review Articles** 64](#_Toc166358283)

[**MEDLINE Search** 65](#_Toc166358284)

[**References** 65](#_Toc166358285)

[**General References Used** 65](#_Toc166358286)

[**Recommendation Grading Systems Used** 66](#_Toc166358287)

[**Synthesized Recommendation Grading System for DynaMed Content** 69](#_Toc166358288)

[**DynaMed Editorial Process** 69](#_Toc166358289)

## **Overview and Recommendations**

Overview and RecommendationsOverview and Recommendations

### **Background**

* Non-small cell lung cancers are the most frequent (85%-90%) cause of malignant lung tumors, usually affecting adults who smoke and who are ≥ 65 years old.
* In 2018, there were 2,093,876 new cases of lung cancer worldwide, with annual age-standardized incidence 31.5 per 100,000 male persons and 14.6 per 100,000 female persons. Lung cancer was also the most common cause of cancer death, with annual age-standardized mortality 27.1 per 100,000 male persons and 11.2 per 100,000 female persons.
* Tobacco use is the main risk factor. Other risk factors include environmental exposures and genetic predisposition.
* Screening for lung cancer, with shared decision-making, is recommended for at-risk population persons.
  + Engage screening in persons aged 55-74 years with ≥ 30 pack-year history of smoking and smoking cessation < 15 years (Strong recommendation).
  + Consider engaging screening in persons aged ≥ 50 years with ≥ 20 pack-year history of smoking and additional risk factors (personal history of cancer or lung disease, family history of lung cancer, radon exposure, or relevant occupational exposure) that increases risk of lung cancer to ≥ 1.3% (not including second-hand smoke exposure) (Conditional recommendation).
  + See Lung Cancer Screening for details.
* Strategies for prevention of lung cancer include smoking cessation and dietary intervention.

### **Evaluation**

* Some common presenting symptoms include coughing, dyspnea, chest pain and hemoptysis. Up to 25% of lung cancers may be asymptomatic.
* Assessment for lung cancer should be performed by a multidisciplinary team, including thoracic surgeons, thoracic radiologists, and pulmonologists.
* For patients with suspected lung cancer based on history and physical examination, diagnosis is based on computed tomography (CT) with contrast of chest and upper abdomen, biopsy and pathology review, and blood tests (Strong recommendation).
* The first staging tests used should be the least invasive and safest method that will give the highest diagnostic yield. Options include:
  + Bronchoscopy with transbronchial needle aspiration (TBNA)
  + Endobronchial ultrasound-guided (EBUS) needle aspiration
  + Endoscopic ultrasound-guided (EUS) needle aspiration
  + Transthoracic needle aspiration
  + Mediastinoscopy.
* See Non-small Cell Lung Cancer Diagnosis and Staging for details.

### **Management**

#### **Management of Resectable Disease**

* For patients with stage I and II resectable disease, if mediastinal nodes are negative on pretreatment evaluation (including minimally invasive nodal sampling) and the patient can tolerate surgery, consider surgical resection plus mediastinal systematic sampling of lymph nodes or mediastinal lymph node dissection (Strong recommendation).
* Follow-up treatment options after resection depend on postsurgical stage and resection margins.
* For patients with clinical stage IIIA resectable disease:
  + For patients with clinical stage IIIA (T3, N1) and negative mediastinal nodes on pretreatment evaluation (including minimally invasive nodal sampling), offer surgical exploration and resection plus systematic sampling of lymph nodes or mediastinal lymph node dissection (Strong recommendation).
  + Follow-up treatment options after resection depend on postsurgical stage and resection margins.
  + For patients with clinical stage IIIA disease and T3 (invasion), N1, or T4 (extension), N0-N1:
    - For superior sulcus tumor (T3 invasion, N1), consider neoadjuvant concurrent chemoradiation, followed by surgery and adjuvant chemotherapy (Conditional recommendation).
    - For superior sulcus tumor (T4 extension, N0-N1) and tumor deemed possibly resectable, consider neoadjuvant concurrent chemoradiation followed by resection plus adjuvant chemotherapy if disease becomes resectable (Conditional recommendation).
    - For disease in the chest wall, proximal airway, or mediastinum (T3 invasion, N1, or resectable T4 extension, N0-N1), consider surgery alone as the preferred initial treatment (Conditional recommendation). Another option is surgery preceded by neoadjuvant concurrent chemoradiation therapy or neoadjuvant chemotherapy (Conditional recommendation).
  + For patients with clinical stage IIIA (T1-T2, N2) disease, treatment options depend on nodal status from mediastinal biopsy.
    - For resectable T1-T3 (including T3 with multiple nodules in same lobe), N0-N1 disease, consider surgical exploration and resection plus mediastinal lymph node dissection or systematic sampling (Conditional recommendation), followed by adjuvant treatment based on postsurgical stage and resection margins.
    - For T1-T2 or T3 (other than invasive), N2 disease, initial treatment options include either:
      * Definitive concurrent chemoradiation, followed by durvalumab (Strong recommendation) (see Management of Unresectable Nonmetastatic Non-small Cell Lung Cancer for additional information)
      * Induction chemotherapy with or without radiation therapy (Conditional recommendation)
      * Follow-up treatment options depend on disease progression.
        + If there is no apparent progression, consider surgery with or without adjuvant radiation therapy if not previously given, with or without adjuvant chemotherapy (Conditional recommendation).
        + If there is local progression, consider radiation therapy if not previously given with or without chemotherapy (Conditional recommendation).
        + If there is systemic progression, manage as advanced disease.
  + For patients with separate pulmonary nodules on the same lobe (T3, N1) or on the ipsilateral non-primary lobe (T4, N0-N1), consider initial treatment with surgery (Conditional recommendation) followed by adjuvant treatment based on postsurgical stage and resection margins.
* See Management of Resectable Non-small Cell Lung Cancer for details.

#### **Management of Unresectable Nonmetastatic Disease**

* For patients with stage I and II inoperable disease:
  + For patients with inoperable stage IA with negative mediastinal lymph nodes, consider definitive radiation therapy including stereotactic body radiation therapy (SBRT) (Conditional recommendation).
  + For patients with inoperable stages IB-IIB with negative mediastinal lymph nodes (including minimally invasive nodal sampling):
    - If the patient has N0 disease after mediastinal node evaluation consider definitive radiation therapy, such as SBRT (Conditional recommendation). For high-risk stages IB-IIB, consider follow-up treatment with chemotherapy after definitive radiation therapy (Conditional recommendation).
    - If the patient has N1 disease after mediastinal node evaluation, consider definitive chemoradiation therapy (Conditional recommendation) and follow with consolidation durvalumab (Strong recommendation).
    - If there is positive mediastinal lymph nodal involvement, manage as stage III disease.
* For most patients with unresectable clinical stage IIIA-IIIC disease which is confirmed by minimally invasive nodal sampling, offer definitive concurrent chemoradiation therapy with platinum-based chemotherapy (Strong recommendation) and follow with consolidation durvalumab (Strong recommendation).
* See Management of Unresectable Nonmetastatic Non-small Cell Lung Cancer for details.

#### **Management of Advanced Disease**

* Offer early integrative palliative care, including discussion and shared decision-making with the patient, family, and caregivers with regard to treatment goals, care planning, and quality of life considerations (Strong recommendation).
* First-line therapy depends on the status of oncogenic driver mutations, PD-L1 expression, and histology.
* For patients with oncogenic driver mutations, offer first-line genotype-driven therapy. Complete or interrupt planned systemic therapy if the mutations are detected during first-line systemic therapy.
  + If a sensitizing EGFR mutation is detected, offer first-line EGFR-targeted therapy with any of osimertinib, erlotinib, afatinib, gefitinib, dacomitinib (Strong recommendation).
  + If an ALK rearrangement is detected, offer first-line ALK-targeted therapy with any of alectinib, brigatinib, ceritinib, or crizotinib (Strong recommendation). The preferred agent varies among guidelines.
  + If a ROS1 rearrangement is detected, offer first-line ROS1-targeted therapy with either crizotinib (Strong recommendation) or ceritinib (Conditional recommendation).
  + If a BRAF V600E mutation is detected, offer first-line BRAF-targeted therapy with dabrafenib plus trametinib (Conditional recommendation), or either vemurafenib alone or dabrafenib alone if the dabrafenib plus trametinib combination is not tolerated.
  + If a NTRK gene fusion is detected, larotrectinib is an option for first-line NTRK-targeted therapy (Conditional recommendation).
* For patients with high PD-L1 expression (defined as tumor proportion score [TPS] ≥ 50%), offer single-agent pembrolizumab as the preferred first-line therapy (Strong recommendation).
* For patients negative for oncogenic driver mutations and PD-L1 TPS < 50%, offer first-line systemic therapy.
  + For patients with nonsquamous histology:
    - If performance status is 0-1, offer platinum-based, pemetrexed-containing doublet chemotherapy in combination with pembrolizumab as the preferred option (Strong recommendation).
    - If performance status is 2, offer carboplatin-based doublet chemotherapy as the preferred option (Strong recommendation).
    - If performance status is 3-4, consider supportive care only (Conditional recommendation).
  + For patients with squamous histology:
    - If performance status is 0-1, offer pembrolizumab plus carboplatin plus either paclitaxel or albumin-bound paclitaxel as the preferred option (Strong recommendation).
    - If performance status is 2, offer carboplatin-based doublet chemotherapy as the preferred option (Strong recommendation).
    - If performance status is 3-4, consider supportive care only (Conditional recommendation).
* See Management of Advanced Non-small Cell Lung Cancer for details, including further lines of therapy; specific management of bone, brain, or oligometastases; and surveillance.

## **Background Information**

### **Description**

* Non-small cell lung cancer is a malignant tumor of the lung accounting for about 85%-90% of lung cancer cases.[1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ESMO2016)

### **Also Called**

* Other terms used to refer to non-small cell lung cancer are:
  + NSCLC
  + Non-small cell bronchogenic carcinoma

### **Definitions**

* The surgical pathological definitions are:[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__NCCN)
  + Complete resection (R0), defined as all of:
    - Free resection margins
    - Systematic node dissection or sampling
    - Highest mediastinal node negative for tumor
  + Incomplete resection (R1 for microscopically positive residual tissue or R2 for macroscopically positive residual tissue), defined as any of:
    - Positive resection margins
    - Unremoved positive lymph nodes
    - Positive pleural or pericardial effusions

### **Types**

* Non-small cell carcinoma subtypes include:[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__NCCN),[4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013B)
  + Nonsquamous carcinoma, including:
    - Adenocarcinoma
    - Large cell carcinoma
  + Squamous cell carcinoma

## **Epidemiology**

### **Who is Most Affected**

* Non-small cell lung cancer primarily affects adults ≥ 65 years old.[1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ESMO2016)
* Tobacco smokers are at higher risk. About 85%-90% of lung cancers caused by cigarette smoking.[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__NCCN)
* Male persons are more affected by lung cancer compared to female persons ([CA Cancer J Clin 2019 Jan;69(1):7](http://pubmed.ncbi.nlm.nih.gov/30620402?dopt=Abstract)[full-text](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551)).

### **Incidence/Prevalence**

* **globally, lung cancer was most commonly diagnosed cancer (excluding basal cell carcinoma) in 2018 with annual age-standardized incidence 31.5 per 100,000 male persons and 14.6 per 100,000 female persons**

Cohort Study[CA Cancer J Clin 2018 Nov;68(6):394](http://pubmed.ncbi.nlm.nih.gov/30207593?dopt=Abstract)[Full Text](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21492)

studySummary

* + based on population-based cancer registries, vital registration data, and mortality data from 185 countries with total population > 150,000 during 2018Cohort Study
  + incidence data regarding basal cell carcinoma excluded from analysis
  + lung cancer incidence
    - estimated new lung cancer cases 2,093,876 (11.6% of all new cancer cases, most commonly diagnosed cancer excluding basal cell carcinoma)
    - cumulative global lifetime risk of lung cancer (ages 0-74 years) 3.8% for male persons and 1.77% for female persons
    - age-standardized rates (ASRs) for incidence of lung cancer
      * overall ASR 31.5 per 100,000 male persons and 14.6 per 100,000 female persons
      * in more developed regions, ASR 40.4 for male persons and 19.1 for female persons
      * in less developed regions, ASR 11.8 for male persons and 4.6 for female persons
  + CA: a cancer journal for clinicians20181101CA Cancer J Clin686394394 Reference - GLOBOCAN 2018 ([CA Cancer J Clin 2018 Nov;68(6):394](http://pubmed.ncbi.nlm.nih.gov/30207593?dopt=Abstract)[full-text](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21492))
* **annual age-adjusted lung and bronchus cancer incidence 60.5 per 100,000 persons in United States in 2019**

Cohort Study[CA Cancer J Clin 2019 Jan;69(1):7](http://pubmed.ncbi.nlm.nih.gov/30620402?dopt=Abstract)[Full Text](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551)

Estimated Global Lung Cancer Incidence Varies by Global Region, 2018

| **Region** | **Age-Standardized Rates per 100,000** |
| --- | --- |
|  | Male | Female |
| **Americas** |
| North America | 39.1 | 30.7 |
| Central America | 7.2 | 4.5 |
| Caribbean | 23.5 | 14.2 |
| South America | 16.8 | 10.2 |
| **Africa** |
| Northern Africa | 16.9 | 3.4 |
| Western Africa | 2.4 | 1.2 |
| Middle Africa | 3.8 | 2.3 |
| Eastern Africa | 3.4 | 2.2 |
| Southern Africa | 26 | 8.9 |
| **Europe** |
| Western Europe | 43.3 | 25.7 |
| Northern Europe | 34 | 26.9 |
| Southern Europe | 43.1 | 15.7 |
| Eastern Europe | 49.3 | 11.9 |
| **Asia** |
| Western Asia | 38.8 | 7.8 |
| South Central Asia | 9.4 | 3.4 |
| Eastern Asia | 47.2 | 21.9 |
| South-Eastern Asia | 26.3 | 9.6 |
| **Oceana** |
| Australia/New Zealand | 28.4 | 24 |
| Melanesia | 17.1 | 8.9 |
| Micronesia/Polynesia | 52.2 | 24.3 |

studySummaryannual age-adjusted lung and bronchus cancer incidence 60.5 per 100,000 persons in United States in 2019 (CA Cancer J Clin 2019 Jan)08/15/2019 10:28:50 AMOncologic\_DiseasePulmonary\_DisordersOncologic\_Disease Pulmonary\_Disordersannual age-adjusted lung and bronchus cancer incidence 60.5 per 100,000 persons in United States in 2019 (CA Cancer J Clin 2019 Jan)08/15/2019 10:28:50 AM

* + based on annual report of cancer status in United States with data 2011-2015 for incidence ratesCohort Study
  + estimated 228,150 new cases (116,440 cases among male persons and 111,710 cases among female persons) of lung and bronchus cancer in 2019, the second most commonly diagnosed cancer in United States

|  | **Incidence Rates** |
| --- | --- |
| **Overall** | **Male** | **Female** |
| All races | 60.5 | 71.3 | 52.3 |
| Non-Hispanic White | 64.7 | 74.3 | 57.4 |
| Non-Hispanic Black | 63.8 | 85.4 | 49.2 |
| Asian/Pacific Islander | 34.9 | 44.5 | 27.8 |
| American Indian/Alaska Native | 61.5 | 69.3 | 55.7 |
| Hispanic | 30.7 | 39.2 | 24.6 |

* + CA: a cancer journal for clinicians20190101CA Cancer J Clin69177 Reference - [CA Cancer J Clin 2019 Jan;69(1):7](http://pubmed.ncbi.nlm.nih.gov/30620402?dopt=Abstract)[full-text](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551)
* Male and female incidence of lung cancer is reportedly similar among nonsmokers after adjusting for age.[1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ESMO2016)
* Age-standardized incidence rates of lung cancer in a prospective cohort study with 463,837 male and female persons aged 50-71 years in United States:
  + For current smokers who smoked > 2 packs/day:
    - Incidence was 1,259.2 per 100,000 person years in male persons.
    - Incidence was 1,308.9 per 100,000 person years in female persons.
  + For never-smokers:
    - Incidence was 20.3 per 100,000 person years in male persons.
    - Incidence was 25.3 per 100,000 person years in female persons.
  + Reference - [18556244Lancet Oncol 2008 Jul;9(7):649](http://pubmed.ncbi.nlm.nih.gov/18556244?dopt=Abstract), editorial can be found in [18598927Lancet Oncol 2008 Jul;9(7):609](http://pubmed.ncbi.nlm.nih.gov/18598927?dopt=Abstract)
* The incidence of lung cancer increased in Norway from 1988 to 2007, with a greater average increase in female persons.
  + Analysis was based on a national cohort study evaluating 40,118 cases of lung cancer diagnosed between 1988 and 2007.
  + There was a 64% increase in lung cancer incidence over the time period.
  + Age-adjusted annual average increase:
    - 4.9% in female persons
    - 1.4% in male persons
  + Female persons were more likely to be diagnosed with localized disease.
  + Reference - [21199818Thorax 2011 Apr;66(4):301](http://pubmed.ncbi.nlm.nih.gov/21199818?dopt=Abstract)

### **Risk Factors**

#### **Overview of Risk Factors**

* [Cigarette smoking](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#TOPIC_MKB_54V_5HB) is a major risk factor.
* Other risk factors include:
  + [Environmental tobacco smoke](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#TOPIC_UTB_54V_5HB)
  + [Environmental exposure to pollutants](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#TOPIC_CCC_54V_5HB), including:
    - Asbestos
    - Air particulate
    - Silica dust
    - Diesel exhaust
    - Coal smoke
    - Lewisite
    - Radon
    - General urban air pollutants and carbon-black dust
  + Other environmental exposure, such as cooking fumes
  + [Demographic factors and familial history](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#TOPIC_UYJ_W4V_5HB)
  + [Genetic predisposition](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#TOPIC_QFK_W4V_5HB)
  + [Medical comorbidities and medical history](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#TOPIC_EKK_W4V_5HB), including:
    - Chronic obstructive pulmonary disease (COPD)
    - HIV infection
    - Alpha-1 antitrypsin (AAT) deficiency
    - Exposure to radiation therapy
    - Exposure to computed tomography (CT)
    - Organ transplantation
  + [Dietary factors](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#TOPIC_CRK_W4V_5HB), including:
    - Total meat and red meat intake
    - Serum vitamin B6 and methionine levels

#### **Cigarette Smoking**

* Cigarette smoking greatly increases the risk of lung cancer.
  + **cigarette smoking associated with increased risk of all major histologic types of lung cancer compared to never smoking, with strongest risk increase for small cell lung cancer and squamous cell carcinoma**

Systematic Review[11165392Lung Cancer 2001 Feb-Mar;31(2-3):139](http://pubmed.ncbi.nlm.nih.gov/11165392?dopt=Abstract)

studySummary

* + - based on systematic reviewSystematic Review
    - systematic review of 1 cohort study and 27 case-control studies evaluating association between cigarette smoking and risk of different histologic types of lung cancer
    - comparing ever-smokers to never-smokers, ever-smokers associated with increased risk of
      * small cell lung cancer (odds ratio [OR] 12.9, 95% CI 9.8-17.1) in analysis of 22 studies
      * squamous cell carcinoma (OR 11.3, 95% CI 9.4-13.5) in analysis of 27 studies
      * large cell carcinoma (OR 5.6, 95% CI 4.2-7.7) in analysis of 8 studies
      * adenocarcinoma (OR 3.2, 95% CI 2.6-4) in analysis of 27 studies
    - PubMed11165392Lung cancer (Amsterdam, Netherlands)20010201Lung Cancer312-3139139Reference - [11165392Lung Cancer 2001 Feb-Mar;31(2-3):139](http://pubmed.ncbi.nlm.nih.gov/11165392?dopt=Abstract)
  + **cigarette smoking > 2 packs/day associated with > 50-fold increase in lung cancer compared to never smoking**

Cohort Study[18556244Lancet Oncol 2008 Jul;9(7):649](http://pubmed.ncbi.nlm.nih.gov/18556244?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2601691/)

studySummary

* + - based on age-standardized incidence rates in prospective cohort study with 463,837 persons aged 50-71 years in the United States Cohort Study
    - for current smokers who smoked > 2 packs/day
      * 1,259.2 per 100,000 person-years in male persons
      * 1,308.9 per 100,000 person-years in female persons
    - for never-smokers
      * 20.3 per 100,000 person-years in male persons
      * 25.3 per 100,000 person-years in female persons
    - PubMed18556244The Lancet. Oncology20080701Lancet Oncol97649649Reference - [18556244Lancet Oncol 2008 Jul;9(7):649](http://pubmed.ncbi.nlm.nih.gov/18556244?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2601691/), editorial can be found in [18598927Lancet Oncol 2008 Jul;9(7):609](http://pubmed.ncbi.nlm.nih.gov/18598927?dopt=Abstract)
  + **pipe smoking associated with increased risk of lung cancer, but cigarette smoking and combination of pipe or cigar with cigarette smoking appears associated with greater risk**

Cohort Study[20162568Int J Cancer 2010 Nov 15;127(10):2402](http://pubmed.ncbi.nlm.nih.gov/20162568?dopt=Abstract)[Full Text](https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.25252)

studySummary

* + - based on cohort of 102,395 male persons evaluated for cancer incidence and smoking history (cigar, pipe, or cigarette smoking alone or in combination)Cohort Study
    - median follow-up of 9 years
    - compared to persons who never smoked, increased risk of lung cancer associated with
      * exclusive pipe smoking (hazard ratio [HR] 9.8, 95% CI 5.2-18.5)
      * exclusive cigarette smoking (HR 15.3, 95% CI 10-23.4)
      * combined cigar and cigarette smoking (HR 15.2, 95% CI 9.1-25.5)
      * combined pipe and cigarette smoking (HR 14.1, 95% CI 8.8-22.4)
    - PubMed20162568International journal of cancer20101115Int J Cancer1271024022402Reference - [20162568Int J Cancer 2010 Nov 15;127(10):2402](http://pubmed.ncbi.nlm.nih.gov/20162568?dopt=Abstract)[full-text](https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.25252)
  + Medium-, low-, and very low-tar cigarettes were associated with an increased risk of lung cancer compared to not smoking in a cohort study with 940,774 persons ([14715602BMJ 2004 Jan 10;328(7431):72](http://pubmed.ncbi.nlm.nih.gov/14715602?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC314045/)).
  + Mentholated cigarettes may be associated with an increased risk of lung cancer compared to nonmentholated cigarettes in male persons in a cohort study with 11,761 persons ([7695461Arch Intern Med 1995 Apr 10;155(7):727](http://pubmed.ncbi.nlm.nih.gov/7695461?dopt=Abstract)).
* **in patients who currently smoke or formerly smoked, filtered cigarettes may be associated with decreased all-cause and lung cancer mortality compared to unfiltered cigarettes, but light/ultralight cigarettes may not be associated with decreased all-cause and lung cancer mortality compared to regular cigarettes (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[JAMA Intern Med 2019 Dec 1;179(12):1710](http://pubmed.ncbi.nlm.nih.gov/31633739)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6806424/)

Family\_Medicine Internal\_Medicine Primary\_Carein patients who currently smoke or formerly smoked, filtered cigarettes may be associated with decreased all-cause and lung cancer mortality compared to unfiltered cigarettes, but light/ultralight cigarettes may not be associated with decreased all-cause and lung cancer mortality compared to regular cigarettes (JAMA Intern Med 2019 Dec 1)12/10/2020 10:08:10 AMstudySummary

* + Cohort Study based on secondary cohort analysis of randomized trial
  + 14,123 patients (89%) from National Lung Screening Trial (50% current smokers, mean 55.9 pack-years of cigarette smoking history, mean age 66 years, 55% male, 92% White) who completed smoking questionnaires were assessed
    - 11.4% smoked unfiltered cigarettes, and 88.4% smoked filtered cigarettes
    - 44.1% smoked light/ultralight cigarettes, and 55.7% smoked regular cigarettes
    - 77.1% smoked unflavored cigarettes, and 22.7% smoked menthol-flavored cigarettes
  + comparing unfiltered vs. filtered cigarettes
    - all-cause mortality 11.5% vs. 6.8% (adjusted hazard ratio [HR] 1.28, 95% CI 1.09-1.5)
    - lung cancer mortality 3.9% vs. 1.6% (adjusted HR 1.96, 95% CI 1.46-2.64)
    - lung cancer in 6.3% vs. 3.9% (adjusted HR 1.37, 95% CI 1.1-1.71)
  + comparing light/ultralight vs. regular cigarettes
    - all-cause mortality 6.6% vs. 8% (not significant)
    - lung cancer mortality 1.7% vs. 1.9% (not significant)
    - lung cancer in 3.7% vs. 4.5% (adjusted HR 0.83, 95% CI 0.7-0.98)
  + comparing menthol-flavored vs. unflavored cigarettes, no significant differences in all-cause mortality, lung cancer mortality, or incidence of lung cancer
  + PubMed31633739JAMA internal medicineJAMA Intern Med20191201179121710-17121710Reference - [JAMA Intern Med 2019 Dec 1;179(12):1710](http://pubmed.ncbi.nlm.nih.gov/31633739)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6806424/)

#### **Environmental Tobacco Smoke**

* **environmental tobacco smoke increases risk of lung cancer**

Cohort Study[9365295BMJ 1997 Oct 18;315(7114):980](http://pubmed.ncbi.nlm.nih.gov/9365295?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2127653/)

studySummary

* + based on analysis of 37 epidemiologic studies of risk of lung cancer (4,626 cases) in nonsmokersCohort Study
  + 24% excess risk of lung cancer in nonsmokers who lived with a smoker compared to those who did not
  + dose-response relation found for environmental tobacco exposure
  + PubMed9365295BMJ (Clinical research ed.)19971018BMJ3157114980980Reference - [9365295BMJ 1997 Oct 18;315(7114):980](http://pubmed.ncbi.nlm.nih.gov/9365295?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2127653/), correction can be found in BMJ 1998 Oct 3;317(7163):951, commentary can be found in [9685291BMJ 1998 Aug 1;317(7154):346](http://pubmed.ncbi.nlm.nih.gov/9685291?dopt=Abstract)
  + estimated 3,000 deaths/year from lung cancer due to environmental tobacco smoke exposure ([Am Fam Physician 1998 Apr 1;57(7):1659](http://www.aafp.org/afp/1998/0401/p1659.html))
  + putting risk in individual perspective would mean that smoker quitting would lower spouse's risk of lung cancer from 0.25% to 0.17%, or 1,250 smokers would have to quit for 1 spouse to be saved from lung cancer (Evidence-Based Medicine 1998 Jul/Aug;3(4):126)
* **environmental tobacco smoke associated with increased risk of lung cancer and other respiratory diseases**

Cohort Study[BMJ 2005 Feb 5;330(7486):277](http://pubmed.ncbi.nlm.nih.gov/15681570)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC548173/)

studySummary

* + Cohort Study based on 7-year follow-up of prospective cohort of 123,479 persons who had never smoked or had stopped smoking for at least 10 years
  + frequent exposure to environmental tobacco smoke during childhood associated with lung cancer in adulthood
  + PubMed15681570BMJ (Clinical research ed.)BMJ200502053307486277277Reference - [BMJ 2005 Feb 5;330(7486):277](http://pubmed.ncbi.nlm.nih.gov/15681570)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC548173/), editorial can be found in [15695250BMJ 2005 Feb 5;330(7486):265](http://pubmed.ncbi.nlm.nih.gov/15695250?dopt=Abstract)
* **having a spouse who smokes may not increase risk of lung cancer**

Cohort Study[12750205BMJ 2003 May 17;326(7398):1057](http://pubmed.ncbi.nlm.nih.gov/12750205?dopt=Abstract)[Full Text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC155687/)

studySummary

* + based on cohort study with results limited by wide confidence intervalsCohort Study
  + 118,094 adults in California were followed for 39 years
  + 35,561 never-smokers married to ever-smokers were compared to never-smokers married to never-smokers
  + male and female persons analyzed separately
  + PubMed12750205BMJ (Clinical research ed.)20030517BMJ326739810571057Reference - [12750205BMJ 2003 May 17;326(7398):1057](http://pubmed.ncbi.nlm.nih.gov/12750205?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC155687/), editorial can be found in [12750182BMJ 2003 May 17;326(7398):1048](http://pubmed.ncbi.nlm.nih.gov/12750182?dopt=Abstract), commentary can be found in [BMJ 2003 Aug 30;327(7413):501](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC188396/?tool=pubmed)
  + Using the surrogate of marriage to spouse who smokes does not allow a valid conclusion about risk of environmental tobacco exposure.

#### **Environmental Exposure to Pollutants**

* Exposure to air pollutants can increase the risk for devoloping lung cancer.
  + Asbestos exposure:
    - Is associated with mesothelioma and lung carcinoma ([21534086J Toxicol Environ Health B Crit Rev 2011;14(1-4):76](http://pubmed.ncbi.nlm.nih.gov/21534086?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3118517/))
    - Is associated with an increased risk of lung cancer, with higher risk when combined with cigarette smoking in a systematic review of 17 observational studies with 75,147 persons ([26274395PLoS One 2015;10(8):e0135798](http://pubmed.ncbi.nlm.nih.gov/26274395?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4537132/))
  + Long-term exposure to combustion-related fine particulate air pollution is associated with an increased risk for cardiopulmonary mortality and lung cancer mortality ([11879110JAMA 2002 Mar 6;287(9):1132](http://pubmed.ncbi.nlm.nih.gov/11879110?dopt=Abstract), commentary can be found in [12186593JAMA 2002 Aug 21;288(7):830](http://pubmed.ncbi.nlm.nih.gov/12186593?dopt=Abstract)).
  + **occupational silica dust exposure associated with increased risk of lung cancer and death from lung cancer**

Systematic Review[27814719BMC Public Health 2016 Nov 4;16(1):1137](http://pubmed.ncbi.nlm.nih.gov/27814719?dopt=Abstract)

studySummary

* + - based on systematic review of observational studiesSystematic Review
    - systematic review of 96 observational studies (77 cohort studies, 17 case-control studies, and 2 proportional mortality studies) evaluating association between occupational silica exposure and risk of lung cancer in patients with or without silicosis
    - most studies included male persons only, but several studies included between 10% and 31% female persons
    - studies conducted worldwide (41 in Europe, 18 in the United States, 21 in Asia, 9 in Canada, 3 in Australia, and 1 in South Africa)
    - occupations included mining, foundry, pottery and ceramics, refractory brick and diatomaceous earth processing, granite (both sand and quarry), cement production, and construction
    - comparing persons with occupational silica dust exposure (with or without diagnosis of silicosis) to general population, occupational silica dust exposure associated with
      * increased risk of lung cancer (standardized incidence ratio 1.68, 95% CI 1.45-1.96) in analysis of 19 cohort studies, results limited by significant heterogeneity
      * increased risk of mortality due to lung cancer (standardized mortality ratio 1.55, 95% CI 1.38-1.75) in analysis of 63 cohort studies, results limited by significant heterogeneity
    - among industries evaluated, workers in mining industry had highest risk of death due to lung cancer comparing exposure to no exposure (standardized mortality ratio 1.48, 95% CI 1.18-1.86) in analysis of 18 studies, results limited by significant heterogeneity
    - PubMed27814719BMC public health20161104BMC Public Health16111371137Reference - [27814719BMC Public Health 2016 Nov 4;16(1):1137](http://pubmed.ncbi.nlm.nih.gov/27814719?dopt=Abstract)
  + **occupational exposure to diesel exhaust, silica dust, and paint may increase lung cancer risk**

Case-Control Study[21102581Br J Cancer 2011 Jan 4;104(1):208](http://pubmed.ncbi.nlm.nih.gov/21102581?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3039806/)

studySummary

* + - based on case-control study of 132 nonsmoking Chinese male persons with newly diagnosed lung cancer and 536 matched controlsCase-Control Study
    - all had lifetime work history collected
    - increased lung cancer risk associated with occupational exposure to
      * silica dust (odds ratio [OR] 2.58, 95% CI 1.11-6.01)
      * diesel exhaust (OR 3.47, 95% CI 1.08-11.14)
      * spray painting (OR 2.81, 95% CI 1.14-6.93)
      * nonspray painting (OR 2.36, 95% CI 1.04-5.37)
    - silica dust exposure associated with increased risk of adenocarcinoma (OR 2.91, 95% CI 1.1-7.68)
    - PubMed21102581British journal of cancer20110104Br J Cancer1041208208Reference - [21102581Br J Cancer 2011 Jan 4;104(1):208](http://pubmed.ncbi.nlm.nih.gov/21102581?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3039806/)
  + **domestic use of smoky coal associated with increased risk of lung cancer-related mortality compared to smokeless coal**

Cohort Study[22936785BMJ 2012 Aug 29;345:e5414](http://pubmed.ncbi.nlm.nih.gov/22936785?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3431444/)

studySummary

* + - based on retrospective cohort studyCohort Study
    - 37,272 persons using coal for household cooking or heating in China were followed up to 20 years
    - 73% used smoky coal and 27% used smokeless coal during lifetime
    - 6.4% died from lung cancer
    - smoky coal associated with increased risk of lung cancer-related mortality in (vs. smokeless coal in adjusted analyses)
      * male persons (hazard ratio 36.2, 95% CI 20.3-64.7)
      * female persons (hazard ratio 98.8, 95% CI 36.8-265.6)
    - PubMed22936785BMJ (Clinical research ed.)20120829BMJ345e5414e5414Reference - [22936785BMJ 2012 Aug 29;345:e5414](http://pubmed.ncbi.nlm.nih.gov/22936785?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3431444/)
  + Radon exposure is an environmental risk for developing lung cancer.
    - **radon concentrations in home associated with significantly increased risk of lung cancer**

Cohort Study[BMJ 2005 Jan 29;330(7485):223](http://pubmed.ncbi.nlm.nih.gov/15613366?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC546066/)

studySummary

* + - * based on collaborative analysis of individual data from 13 case-control studies from 9 European countries with 7,148 cases of lung cancer and 14,208 controlsCohort Study
      * PubMed15613366BMJ (Clinical research ed.)20050129BMJ3307485223223Reference - [BMJ 2005 Jan 29;330(7485):223](http://pubmed.ncbi.nlm.nih.gov/15613366?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC546066/), editorial can be found in [15613367BMJ 2005 Jan 29;330(7485):226](http://pubmed.ncbi.nlm.nih.gov/15613367?dopt=Abstract), commentary can be found in [15891242BMJ 2005 May 14;330(7500):1151](http://pubmed.ncbi.nlm.nih.gov/15891242?dopt=Abstract)
    - **residential radon exposure associated with increased risk for primary lung cancer**

Case-Control Study[10394313Am J Public Health 1999 Jul;89(7):1042](http://pubmed.ncbi.nlm.nih.gov/10394313?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1508843/)

studySummary

* + - * based on population-based case-control study of female persons aged 30-84 years in Missouri, United StatesCase-Control Study
      * PubMed10394313American journal of public health19990701Am J Public Health89710421042Reference - [10394313Am J Public Health 1999 Jul;89(7):1042](http://pubmed.ncbi.nlm.nih.gov/10394313?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1508843/)

#### **Demographic Factors and Familial History**

* **African American and Native Hawaiian ethnicities each associated with increased risk of lung cancer in persons smoking < 30 cigarettes/day**

Cohort Study[16436765N Engl J Med 2006 Jan 26;354(4):333](http://pubmed.ncbi.nlm.nih.gov/16436765?dopt=Abstract)[Full Text](https://www.nejm.org/doi/10.1056/NEJMoa033250?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov)

studySummary

* + based on prospective cohort studyCohort Study
  + 183,813 adults of African American, White, Japanese American, Hispanic, or Native Hawaiian ethnicity in California and Hawaii, United States, were followed for 8 years
  + mean 19.7% of male persons and 15.3% of female persons were current smokers
    - in male persons, current smoking ranged from 15.5% in Japanese Americans to 28.5% in African Americans
    - in female persons, current smoking ranged from 9.3% in Japanese Americans to 20.5% in African Americans
  + compared to African American male persons (analyses not adjusted for smoking history)
    - risk of lung cancer lower in
      * Hispanic adults (relative risk [RR] 0.29, 95% CI 0.23-0.38)
      * Japanese American adults (RR 0.31, 95% CI 0.25-0.38)
      * White adults (RR 0.83, 95% CI 0.71-0.98)
    - no significant difference in risk of lung cancer in Native Hawaiian adults (RR 1, 95% CI 0.8-1.25)
  + consistent findings in female persons
  + among current smokers smoking < 30 cigarettes/day, risk of lung cancer higher in African American and Native Hawaiian adults compared to White, Japanese American, and Hispanic smokers (p < 0.001 for each)
  + no significant difference in risk of lung cancer among ethnicities in current smokers smoking ≥ 30 cigarettes/day
  + PubMed16436765The New England journal of medicine20060126N Engl J Med3544333333Reference - [16436765N Engl J Med 2006 Jan 26;354(4):333](http://pubmed.ncbi.nlm.nih.gov/16436765?dopt=Abstract)[full-text](https://www.nejm.org/doi/10.1056/NEJMoa033250?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov), editorial can be found in [16436773N Engl J Med 2006 Jan 26;354(4):408](http://pubmed.ncbi.nlm.nih.gov/16436773?dopt=Abstract), commentary can be found in [16672710N Engl J Med 2006 May 4;354(18):1951](http://pubmed.ncbi.nlm.nih.gov/16672710?dopt=Abstract)
* Familial history can contribute to the risk of developing lung cancer.
  + **family history associated with increased risk of lung cancer**

Cohort Study[23257063BMJ 2012 Dec 20;345:e8076](http://pubmed.ncbi.nlm.nih.gov/23257063?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3527651/)

studySummary

* + - based on prospective cohort studyCohort Study
    - 7,904,092 persons aged 0-76 years in Sweden and their biological parents were analyzed
    - 183,200 persons had cancer and included in analysis
    - having parent affected with concordant cancer associated with increased risk of lung cancer compared to having no affected parent (adjusted hazard ratio 2.1, 95% CI 1.9-2.2) in overall analysis
    - having parent diagnosed with concordant cancer at early age associated with highest familial risk
    - PubMed23257063BMJ (Clinical research ed.)20121220BMJ345e8076e8076Reference - [23257063BMJ 2012 Dec 20;345:e8076](http://pubmed.ncbi.nlm.nih.gov/23257063?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3527651/)
  + **family history increases risk of lung cancer with strongest effect in early-onset disease**

Cohort Study[JAMA 2004 Dec 22;292(24):2977](http://pubmed.ncbi.nlm.nih.gov/15613665)

studySummary

* + - based on cohort of Icelandic Cancer Registry (2,756 patients diagnosed with lung cancer) records linked with extensive genealogical databaseCohort Study
    - relative with lung cancer associated with increased risk of lung cancer for
      * parents (risk ratio [RR] 2.69, 95% CI 2.2-3.23)
      * siblings (RR 2.02, 95% CI 1.77-2.23)
      * children (RR 1.96, 95% CI 1.53-2.39)
      * uncles/aunts (RR 1.34, 95% CI 1.15-1.49)
      * nephews/nieces (RR 1.28, 95% CI 1.1-1.43)
      * cousins (RR 1.14, 95% CI 1.05-1.22)
    - association strongest for relatives of patients with onset of disease at ≤ 60 years old
    - PubMed15613665JAMAJAMA20041222292242977-832977 Reference - [JAMA 2004 Dec 22;292(24):2977](http://pubmed.ncbi.nlm.nih.gov/15613665), correction can be found in JAMA 2005 Jan 12;293(2):163, editorial can be found in [15613673JAMA 2004 Dec 22;292(24):3026](http://pubmed.ncbi.nlm.nih.gov/15613673?dopt=Abstract)
  + Having first-degree relatives with early-onset lung cancer is associated with a higher risk of lung cancer in smokers ([15972566JAMA 2005 Jun 22;293(24):3036](http://pubmed.ncbi.nlm.nih.gov/15972566?dopt=Abstract)).

#### **Genetic Predisposition**

* genetic predisposition to lung cancer unclear because of confounding environmental factors ([27664245Ann Oncol 2016 Sep;27(suppl 5):v1](http://pubmed.ncbi.nlm.nih.gov/27664245?dopt=Abstract))
* increased genetic susceptibility may be associated with
  + oncogenic driver mutations, which are harbored in subset of advanced non-small cell lung cancer tumors and support their transformation, growth, and progression, including
    - epidermal growth factor receptor (EGFR) mutations (in 15%-20% of tumors)
    - anaplastic lymphoma kinase (ALK) rearrangements (in 5% of tumors)
    - c-ROS oncogene 1 (ROS1) rearrangements (in 1%-2% of tumors)
    - human epidermal growth factor receptor 2/erb-B2 receptor tyrosine kinase 2 (HER2/ERBB2) mutations (in 2%-3% of tumors)
    - serine/threonine-protein kinase B-raf (BRAF) V600E mutations (in 1%-3% of tumors)
    - mesenchymal epithelial transition factor proto-oncogene (MET) exon 14 skipping mutations (in 2%-4% of tumors) and amplification (in 1%-2% of tumors)
    - rearranged during transfection (RET) rearrangements (in 1% of tumors)
    - discoidin domain-containing receptor 2 (DDR2) mutations (in 4%-5% of lung squamous cell carcinomas)
    - Reference - [26620497Ther Adv Respir Dis 2016 Apr;10(2):113](http://pubmed.ncbi.nlm.nih.gov/26620497?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5933559/)
  + mutation of gene coding for nicotinic acetylcholine receptor
    - nicotinic acetylcholine receptor is protein on cell surface to which nicotine molecules latch and trigger cell change
    - mutation may result in increased vulnerability to nicotine addiction
    - Reference - [18452692Mayo Clin Proc 2008 May;83(5):584](http://pubmed.ncbi.nlm.nih.gov/18452692?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2718421)
  + other genetic locations
    - TP53 carrier status
    - variation in chromosomal regions 5p15.23, 6p21.33, 6q23-25, and 15q24-25
    - Reference - [cxh120982482pGenes (Basel) 2017 Jan 17;8(1):E36](http://pubmed.ncbi.nlm.nih.gov/28106732?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5295030/)
* evidence of genetic risk of lung cancer
  + gene variations in region of 15q25.1 associated with lung cancer (independent of smoking status) in case-control study with 1,154 cases and 1,137 controls ([18385676Nat Genet 2008 May;40(5):616](http://pubmed.ncbi.nlm.nih.gov/18385676?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2713680/))
  + polymorphism in matrix metalloproteinase 1 (MMP1) associated with increased risk of development and progression of lung cancer in case-control study with 825 cases and 825 controls ([21523769Cancer 2011 Nov 15;117(22):5172](http://pubmed.ncbi.nlm.nih.gov/21523769?dopt=Abstract)[full-text](https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.26154))

#### **Medical Comorbidities and Medical History**

* Evidence supports the impact of medical comorbidities on the risk of lung cancer:
  + **idiopathic pulmonary fibrosis may be associated with lung cancer**

Cohort Study[mnh30285867paph132126962t pa9h132126962t pafh132126962t pcxh132126962t pmdc30285867pRespir Res 2018 Oct 3;19(1):195](http://pubmed.ncbi.nlm.nih.gov/30285867?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6171146/)

studySummary

* + - based on population-based cohort study Cohort Study
    - 104,954 persons between 2000 and 2015 in Pennsylvania, United States, included
    - 1,108 persons had idiopathic pulmonary fibrosis, among whom 31 had lung cancer
    - standard incidence ratio 3.34 (95% CI 2.31-4.68) for lung cancer in patients with idiopathic pulmonary fibrosis compared to general population
    - PubMed30285867Respiratory research20181003Respir Res191195195 Reference - [mnh30285867paph132126962t pa9h132126962t pafh132126962t pcxh132126962t pmdc30285867pRespir Res 2018 Oct 3;19(1):195](http://pubmed.ncbi.nlm.nih.gov/30285867?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6171146/)
  + **chronic obstructive pulmonary disease (COPD) associated with increased risk of lung cancer**

Systematic Review[23029414PLoS One 2012;7(9):e46144](http://pubmed.ncbi.nlm.nih.gov/23029414?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3460937/)

studySummary

* + - based on systematic review of observational studies and case-control studySystematic Review
    - systematic review of 35 studies evaluating association between lung cancer and prior COPD or asthma in 22,010 patients with lung cancer and 44,438 patients without lung cancer
    - lung cancer risk increased with
      * COPD, including emphysema and chronic bronchitis, (odds ratio [OR] 2.76, 95% CI 1.85-4.11) in analysis of 21 studies
      * emphysema (OR 3.02, 95% CI 2.41-3.79) in analysis of 16 studies
      * chronic bronchitis (OR 1.88, 95% CI 1.49-2.36) in analysis of 17 studies
    - similar findings in case-control study with 1,069 patients with newly diagnosed lung cancer and 1,132 age-matched controls without lung cancer
    - PubMed23029414PloS one201201PLoS One79e46144e46144Reference - [23029414PLoS One 2012;7(9):e46144](http://pubmed.ncbi.nlm.nih.gov/23029414?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3460937/)
    - consistent results for visually detected emphysema in systematic review of 3 cohort and 4 case-control studies evaluating association between emphysema on computed tomography (CT) scan and risk of lung cancer in 7,368 persons ([22437042Lung Cancer 2012 Jul;77(1):58](http://pubmed.ncbi.nlm.nih.gov/22437042?dopt=Abstract))
  + Moderate-to-severe obstructive lung disease (forced expiratory volume in 1 second [FEV1] < 80% predicted and FEV1 to forced vital capacity ratio < 70%) was associated with a 2.8 times risk of incident lung cancer based on a study of 5,402 adults followed for up to 22 years, where 113 developed lung cancer ([12824098Arch Intern Med 2003 Jun 23;163(12):1475](http://pubmed.ncbi.nlm.nih.gov/12824098?dopt=Abstract)).
  + **HIV infection associated with increased risk of lung cancer**

Cohort Study[26436616Ann Intern Med 2015 Oct 6;163(7):507](http://pubmed.ncbi.nlm.nih.gov/26436616?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4711936/)

studySummary

* + - based on cohort studyCohort Study
    - 86,620 persons with HIV and 196,987 uninfected adults from the United States and Canada followed between 1996 and 2009
    - cumulative incidence of lung cancer by age 75 years 3.4% for persons with HIV infection vs. 2.8% for uninfected persons (p < 0.05)
    - PubMed26436616Annals of internal medicine20151006Ann Intern Med1637507507Reference - [26436616Ann Intern Med 2015 Oct 6;163(7):507](http://pubmed.ncbi.nlm.nih.gov/26436616?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4711936/)
  + **alpha-1 antitrypsin (AAT) deficiency associated with lung cancer risk**

Case-Control Study[18504338Arch Intern Med 2008 May 26;168(10):1097](http://pubmed.ncbi.nlm.nih.gov/18504338?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2562773/)

studySummary

* + - based on case-control studyCase-Control Study
    - 1,443 patients with incident lung cancer (cases), 902 cancer-free siblings, and 797 unrelated controls had genetic test for AAT enzyme deficiency
    - carriers of AAT deficiency gene
      * 13.4% in lung cancer cases
      * 9.9% in siblings (p < 0.01 vs. cases)
      * 7.8% in unrelated controls (p < 0.001 vs. cases)
    - PubMed18504338Archives of internal medicine20080526Arch Intern Med1681010971097Reference - [18504338Arch Intern Med 2008 May 26;168(10):1097](http://pubmed.ncbi.nlm.nih.gov/18504338?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2562773/)
* The medical history of a patient can affect their risk of lung cancer:
  + Radiation therapy for breast cancer increases the risk of lung cancer, especially in smokers ([8156488Cancer 1994 Mar 15;73(6):1615](http://pubmed.ncbi.nlm.nih.gov/8156488?dopt=Abstract), [7666469J Natl Cancer Inst 1995 Jan 4;87(1):60](http://pubmed.ncbi.nlm.nih.gov/7666469?dopt=Abstract), [14508821Cancer 2003 Oct 1;98(7):1362](http://pubmed.ncbi.nlm.nih.gov/14508821?dopt=Abstract)[full-text](https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.11655), [BMJ 2003 Oct 18;327(7420):938](http://www.bmj.com/content/327/7420/938.full)).
  + Full-body CT scan may be associated with an increased cancer risk.
    - Estimates were based on long-term cancer incidence among Hiroshima residents with radiation exposure similar to typical full-body CT.
    - Lung cancer was estimated to be the most common radiation-induced cancer.
    - Single full-body CT at age 45 years was estimated to cause fatal cancer in about 1 per 1,250 people.
    - 30 annual screenings from ages 45 to 75 years were estimated to cause fatal cancer in about 1 per 50 people.
    - Reference - [15273333Radiology 2004 Sep;232(3):735](http://pubmed.ncbi.nlm.nih.gov/15273333?dopt=Abstract)
  + Organ transplant was associated with an increased risk of lung cancer.
    - Analysis was based on a cohort study of 175,732 patients who had solid organ transplants.
    - Incidence was 173.4 per 100,000 person-years, with excess absolute risk of 85.3 per 100,000 person-years (95% CI 76.2-94.8)
    - Reference - ([22045767JAMA 2011 Nov 2;306(17):1891](http://pubmed.ncbi.nlm.nih.gov/22045767?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3310893/))

#### **Dietary Factors**

* **high total meat and high red meat intake each associated with increased risk of lung cancer**

Systematic Review[22855553Ann Oncol 2012 Dec;23(12):3163](http://pubmed.ncbi.nlm.nih.gov/22855553?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3501234/)

studySummary

* + based on systematic review of observational studiesSystematic Review
  + systematic review of 34 case-control and cohort studies evaluating meat consumption and risk of lung cancer
  + compared to low intake, high meat intake associated with increased risk of
    - lung cancer (overall)
      * risk ratio (RR) for total meat 1.35 (95% CI 1.08-1.69) in analysis of 22 studies
      * RR for red meat 1.34 (95% CI 1.18-1.52) in analysis of 18 studies
    - adenocarcinoma (RR for total meat 1.23, 95% CI 1.04-1.46) in analysis of 8 studies
    - squamous cell carcinoma (RR for total meat 1.47, 95% CI 1.31-1.66) in analysis of 6 studies
    - small cell lung cancer (RR for total meat 1.3, 95% CI 1.14-1.49) in analysis of 4 studies
  + PubMed22855553Annals of oncology : official journal of the European Society for Medical Oncology20121201Ann Oncol231231633163Reference - [22855553Ann Oncol 2012 Dec;23(12):3163](http://pubmed.ncbi.nlm.nih.gov/22855553?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3501234/)
* There is inconsistent evidence for an association between processed meat intake and the risk of lung cancer.
  + 494,036 persons who completed a baseline food frequency questionnaire were followed annually until they moved out of the study area, had cancer diagnosis, or died (mean 6.8 years).
    - The incidence of lung cancer was 1.7% (1,639 cases) in the highest quintile of processed meat intake vs. 1% in the lowest quintile (1,004 cases) (adjusted hazard ratio 1.16, 95% CI 1.06-1.26).
    - Reference - [18076279PLoS Med 2007 Dec;4(12):e325](http://pubmed.ncbi.nlm.nih.gov/18076279?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2121107/), editorial can be found in [18076281PLoS Med 2007 Dec;4(12):e345](http://pubmed.ncbi.nlm.nih.gov/18076281?dopt=Abstract)
  + 99,579 persons aged 55-74 years in Prostate, Lung, Colon, and Ovarian Cancer Screening trial were evaluated.
    - There were 782 incidents of lung cancer during 8-year follow-up.
    - Neither increased intake of red meat nor processed meat was associated with an increased risk of lung cancer in male or female persons after controlling for multiple variables including race, body mass index, education level, smoking status, and others.
    - Reference - [20232386Int J Cancer 2011 Jan 15;128(2):402](http://pubmed.ncbi.nlm.nih.gov/20232386?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2970721/)
* **lower serum levels of vitamin B6 and methionine may be associated with risk of lung cancer**

Case-Control Study[20551408JAMA 2010 Jun 16;303(23):2377](http://pubmed.ncbi.nlm.nih.gov/20551408?dopt=Abstract)

studySummary

* + based on nested case-control study in European Prospective Investigation into Cancer and Nutrition (EPIC) cohortCase-Control Study
  + 897 patients diagnosed with lung cancer and 1,770 matched controls
  + age-standardized incidence of lung cancer in male and female persons in entire EPIC cohort (rate per 100,000 person-years)
    - 6.6 and 7.1 for never-smokers
    - 44.9 and 23.9 for former smokers
    - 156.1 and 100.9 for current smokers
  + lower risk for lung cancer with (after adjusting for smoking)
    - elevated serum vitamin B6 (p < 0.0001 for trend)
    - elevated serum methionine (p < 0.0001 for trend)
  + similar risk with vitamin B6 and methionine observed in never, former, and current smokers
  + lower risk for lung cancer with elevated serum folate in former and current smokers (p = 0.001 for trend)
  + PubMed20551408JAMA20100616JAMA3032323772377Reference - [20551408JAMA 2010 Jun 16;303(23):2377](http://pubmed.ncbi.nlm.nih.gov/20551408?dopt=Abstract)

### **Factors Associated with Decreased Risk**

* Body weight as a factor associated with decreased risk:
  + **higher body mass index may be associated with lower incidence of lung cancer in never-smokers**

Systematic Review[mnh29866064paph129966465t pa9h129966465t pafh129966465t pcxh129966465t pmdc29866064pBMC Cancer 2018 Jun 5;18(1):635](http://pubmed.ncbi.nlm.nih.gov/29866064?dopt=Abstract)[Full Text](https://bmccancer.biomedcentral.com/articles/10.1186/s12885-018-4543-y)

studySummaryhigher body mass index (BMI) may be associated with lower incidence of lung cancer in never-smokers (BMC Cancer 2018 Jun 5)06/15/2018 09:27:00 AMOncologic\_DiseasePulmonary\_DisordersOncologic\_Disease Pulmonary\_Disordershigher body mass index (BMI) may be associated with lower incidence of lung cancer in never-smokers (BMC Cancer 2018 Jun 5)06/15/2018 09:27:00 AM29866064

* + - based on systematic review of observational studies Systematic Review
    - systematic review of 29 cohort and case-control studies assessing association between BMI and risk of lung cancer in 15 million never-smokers with > 10,000 cases of lung cancer
      * never-smoker defined as current nonsmoker with lifetime smoking < 100 cigarettes
      * follow-up > 5 years in most cohort studies
    - compared to normal weight, overweight or obesity (BMI ≥ 25 kg/m2) associated with reduced incidence of lung cancer (risk ratio [RR] 0.75, 95% CI 0.64-0.88) in analysis of 23 studies, results limited by significant heterogeneity
    - each 5 kg/m2 increase in BMI associated with reduced incidence of lung cancer (RR 0.89, 95% CI 0.83-0.96) in analysis of 28 studies, results limited by significant heterogeneity
    - association between 5 kg/m2 increases in BMI and incidence of lung cancer was significant in female persons in analysis of 13 studies but not in male persons in analysis of 12 studies
    - PubMed29866064BMC cancer20180605BMC Cancer181635635 Reference - [mnh29866064paph129966465t pa9h129966465t pafh129966465t pcxh129966465t pmdc29866064pBMC Cancer 2018 Jun 5;18(1):635](http://pubmed.ncbi.nlm.nih.gov/29866064?dopt=Abstract)[full-text](https://bmccancer.biomedcentral.com/articles/10.1186/s12885-018-4543-y)
  + **overweight and obesity may be associated with reduced risk of lung cancer regardless of smoking status**

Systematic Review[22777722Int J Cancer 2013 Mar 1;132(5):1162](http://pubmed.ncbi.nlm.nih.gov/22777722?dopt=Abstract)

studySummary

* + - based on systematic review of 31 studies with 26,066 lung cancer cases and 79,915,395 participants Systematic Review
    - patients stratified by normal weight (body mass index 18.5-24.9 kg/m2) vs. overweight and obesity (body mass index > 25 kg/m2)
    - compared to normal weight, overweight and obesity associated with decreased risk of lung cancer
      * overall (relative risk [RR] 0.79, 95% CI 0.73-0.85)
      * in current smokers (RR 0.63, 95% CI 0.57-0.7)
      * in former smokers (RR 0.73, 95% CI 0.58-0.91)
      * in nonsmokers (RR 0.83, 95% CI 0.7-0.98)
    - no significant difference in small cell lung cancer comparing normal weight vs. overweight and obesity in analysis of 2 trials
    - PubMed22777722International journal of cancer20130301Int J Cancer132511621162 Reference - [22777722Int J Cancer 2013 Mar 1;132(5):1162](http://pubmed.ncbi.nlm.nih.gov/22777722?dopt=Abstract)
* Dietary factors associated with decreased risk:
  + **high poultry intake associated with decreased risk of lung cancer**

Systematic Review[22855553Ann Oncol 2012 Dec;23(12):3163](http://pubmed.ncbi.nlm.nih.gov/22855553?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3501234/)

studySummary

* + - based on systematic review of observational studiesSystematic Review
    - systematic review of 23 case-control and 11 cohort studies evaluating association of meat consumption with risk of lung cancer
    - compared to low intake, high intake of poultry associated with decreased risk of lung cancer (risk ratio 0.91, 95% CI 0.85-0.97) in analysis of 11 studies
    - PubMed22855553Annals of oncology : official journal of the European Society for Medical Oncology20121201Ann Oncol231231633163 Reference - [22855553Ann Oncol 2012 Dec;23(12):3163](http://pubmed.ncbi.nlm.nih.gov/22855553?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3501234/)
* Pharmacologic factors associated with decreased risk:
  + **regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) associated with reduced risk of lung cancer**

Systematic Review[15764753Chest 2005 Mar;127(3):748](http://pubmed.ncbi.nlm.nih.gov/15764753?dopt=Abstract)

studySummary

* + - based on systematic review of observational studies Systematic Review
    - systematic review of 8 cohort and 6 case-control studies evaluating NSAID use and lung cancer
    - NSAID use associated with reduced lung cancer risk, all results limited by significant heterogeneity (p < 0.01)
      * (relative risk [RR] 0.79, 95% CI 0.66-0.95) overall
      * (RR 0.68, 95% CI 0.55-0.85) in analysis of 9 trials adjusted for smoking
      * (RR 0.78, 95% CI 0.62-0.98) in analysis of cohort studies
      * (RR 0.63, 95% CI 0.47-0.86) in analysis of case-control studies
    - risk of specific lung cancer type
      * (RR 0.48, 95% CI 0.3-0.75) for incidence of small cell lung cancer
      * (RR 0.66, 95% CI 0.56-0.79) for incidence of non-small cell lung cancer
    - causal relationship not established
    - PubMed15764753Chest20050301Chest1273748748 Reference - [15764753Chest 2005 Mar;127(3):748](http://pubmed.ncbi.nlm.nih.gov/15764753?dopt=Abstract)
  + **statin use may be associated with lower risk of lung cancer, but causal relationship not established (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Case-Control Study[17494779Chest 2007 May;131(5):1282](http://pubmed.ncbi.nlm.nih.gov/17494779?dopt=Abstract)

studySummary2

* + - based on retrospective case-control study Case-Control Study
    - retrospective study of 483,733 veterans in United States from 1998 to 2004
    - 7,280 (1.5%) patients had lung cancer diagnosis
    - statin used by 27.4% patients with lung cancer and 33.9% patients without lung cancer
    - statin use > 6 months associated with lower risk of lung cancer (adjusted odds ratio 0.45, 95% CI 0.42-0.48, p < 0.01)
    - PubMed17494779Chest20070501Chest131512821282 Reference - [17494779Chest 2007 May;131(5):1282](http://pubmed.ncbi.nlm.nih.gov/17494779?dopt=Abstract)
  + **postmenopausal hormone therapy may be associated with reduced risk for incident lung cancer**

Cohort Study[18349283Cancer Epidemiol Biomarkers Prev 2008 Mar;17(3):655](http://pubmed.ncbi.nlm.nih.gov/18349283?dopt=Abstract)[Full Text](http://cebp.aacrjournals.org/content/17/3/655.long)

studySummary

* + - based on cohort study Cohort Study
    - 72,772 female persons in Cancer Prevention Study II Nutrition Cohort followed from 1992 to 2003
    - 659 cases of incident lung cancer occurred
    - current use of postmenopausal hormonal therapy associated with decreased risk for lung cancer (rate ratio [RR] 0.76, 95% CI 0.62-0.92)
    - RR lower among never smokers (RR 0.56) than among current or former smokers (RR 0.76)
    - PubMed18349283Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology20080301Cancer Epidemiol Biomarkers Prev173655655 Reference - [18349283Cancer Epidemiol Biomarkers Prev 2008 Mar;17(3):655](http://pubmed.ncbi.nlm.nih.gov/18349283?dopt=Abstract)[full-text](http://cebp.aacrjournals.org/content/17/3/655.long)

### **Associated Conditions**

* Pulmonary hypertrophic osteoarthropathy or digital clubbing occurs in about 30% of lung cancer patients.
  + It is more common in female persons than male persons (40% vs. 19%) and in non-small cell than small cell lung cancer (35% vs. 4%).
  + Reference - [9872183Chest 1998 Dec;114(6):1535](http://pubmed.ncbi.nlm.nih.gov/9872183?dopt=Abstract)

## **Etiology and Pathogenesis**

### **Causes**

* Tobacco use is main cause of most lung cancers, with cigarette smoking causing about 85%-90% of cases.[1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ESMO2016),[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__NCCN)

### **Pathogenesis**

* Smoking may lead to diffuse tissue injury which in turn proceeds to epithelial clonal evolution. This may be characterized by:
  + Mutations in oncogenes, tumor suppressor genes, chromatin modifying genes
  + Gene rearrangements
  + Gene amplifications
  + Gene deletions
  + Epigenetic changes
  + Reference - [27168435N Engl J Med 2016 May 12;374(19):1864](http://pubmed.ncbi.nlm.nih.gov/27168435?dopt=Abstract), [18815398N Engl J Med 2008 Sep 25;359(13):1367](http://pubmed.ncbi.nlm.nih.gov/18815398?dopt=Abstract)

## **History and Physical**

History and Physical

### **Clinical Presentation**

* About 25% of patients may be asymptomatic, with detection by incidental finding on a chest x-ray.[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013A)
  + Small pulmonary nodules and less-advanced disease are more likely to be asymptomatic.
  + Larger pulmonary nodules, central tumors, and tumors with an endobronchial component are more likely to present with pulmonary symptoms.
* Common presenting symptoms of lung cancer include:[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__NCCN),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013A)
  + Cough, which is the most common presentation and may result from endobronchial irritation, parenchymal infiltration, or postobstructive pneumonia
  + Dyspnea
  + Chest pain
  + Hemoptysis
* Other symptoms may include:[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013A)
  + Wheezing, which may indicate endobronchial obstruction
  + Nonspecific chest discomfort or pleuritic chest pain, which may suggest invasion of pleura
* Patients with non-small cell lung cancer may present with:[4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013B)
  + A mass that infiltrates and encases mediastinal structures
  + No discretely visible mediastinal lymph nodes
* Patients with metastatic non-small cell lung cancer may present with:[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013A),[4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013B)
  + Constitutional symptoms, such as:
    - Fatigue
    - Weight loss
    - Malaise
    - Anorexia
  + Organ-specific symptoms, such as:
    - Bone pain
    - Headache
    - Seizures
    - Other neurologic symptoms
* Presentations that may precede a diagnosis of lung cancer:
  + Findings are based on a case-control study.
  + 247 patients > 40 years old with primary lung cancer and 1,235 matched controls in United Kingdom were analyzed in a review of primary care records for 2 years before diagnosis of lung cancer.
    - 64% had non-small cell cancer (32% squamous, 23% adenocarcinoma, 9% large cell carcinoma).
    - 21% had small cell cancer.
    - 11% had unspecified carcinoma.
    - 4% had no histology information available.
  + 10 findings were associated with lung cancer.
    - Hemoptysis
    - Weight loss
    - Loss of appetite
    - Dyspnea
    - Thoracic pain
    - Fatigue
    - Cough
    - Finger clubbing
    - Thrombocytosis
    - Abnormal spirometry
  + 3 findings were associated with lung cancer after excluding the final 180 days before diagnosis.
    - Hemoptysis
    - Dyspnea
    - Abnormal spirometry
  + All isolated findings had positive predictive values < 2% except hemoptysis (2.4% for single visit, 17% for multiple visits).
  + Reference - [16227326Thorax 2005 Dec;60(12):1059](http://pubmed.ncbi.nlm.nih.gov/16227326?dopt=Abstract)[full-text](http://thorax.bmj.com/content/60/12/1059.long)

### **History**

* Ask about constitutional symptoms, such as:[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__NCCN),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013A),[4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013B)
  + Weight loss ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE))
  + Anorexia
  + Fever
  + Malaise
  + Fatigue
* Ask about pulmonary symptoms, such as:[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__NCCN),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013A),[4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013B)
  + Cough
  + Dyspnea
  + Chest pain, location and quality
  + Hemoptysis, even in scant amounts, especially in patients with a history of smoking and/or chronic obstructive pulmonary disease
* Ask about organ specific symptoms suggesting metastases, such as:[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__NCCN),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013A),[4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013B)
  + Bone pain
  + Headaches

### **Physical**

* Perform a complete physical, including assessment for [performance status](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#PERFORMANCE_STATUS_SCALES) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__NCCN)
* Assess for:[2](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__NCCN),[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013A),[4](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013B)
  + Finger clubbing
  + Weakness
  + Wheeze or stridor
  + Signs of pneumonia
  + Signs of superior vena cava obstruction, such as facial and neck swelling
  + Lymphadenopathy, including signs of airway compression suggesting hilar adenopathy

## **Diagnosis and Staging**

Diagnosis\_and\_StagingDiagnosis\_and\_Staging

* In patients with a suspicious lung nodule ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)):
  + Determining the optimal diagnostic, treatment, and follow-up strategy requires a multidisciplinary evaluation, including thoracic surgeons, thoracic radiologists, and pulmonologists.
  + Perform risk assessment, including:
    - Patient factors such as age, smoking, medical, and family history
    - Initial imaging findings
  + Smoking cessation counseling is recommended.
* Initial testing to establish the diagnosis typically includes:
  + History and physical, including evaluation of performance status and weight loss ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE))
  + Imaging with computed tomography (CT) with contrast of the chest and upper abdomen, specifically the liver and adrenal glands ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE))
  + Biopsy and pathology review to establish tissue diagnosis ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)), including limited use of immunohistochemistry
  + Blood tests ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)), such as:
    - Complete blood count and platelets
    - Metabolic profile
* The initial staging test should be the least invasive and safest method from among the following options ([ACCP Grade 1C](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)):
  + Bronchoscopy with transbronchial needle aspiration
  + Endobronchial ultrasound-guided (EBUS) needle aspiration
  + Endoscopic ultrasound-guided (EUS) needle aspiration
  + Transthoracic needle aspiration
  + Mediastinoscopy
* After a diagnosis of non-small cell lung cancer is established, pretreatment testing aimed at confirming the stage typically includes:
  + Pulmonary function tests if not previously done ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE) for cardiopulmonary testing)
  + Bronchoscopy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE) for stages I-IIIA; [ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE) for confirmation of central lesion; [ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE) for diagnosis of centrally located tumors):
    - Intraoperative bronchoscopy is preferred for stage IA.
    - Perform further testing if bronchoscopy results are nondiagnostic and suspicion persists ([ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)).
  + Mediastinal lymph node evaluation using any of:
    - Mediastinoscopy ([ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE))
    - Mediastinotomy
    - EBUS-guided needle aspiration([ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE))
    - EUS-guided needle aspiration ([ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE))
    - CT-guided biopsy
  + Fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) scan, if not previously done and if available ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE))
* Additional pretreatment testing for ≥ stage IB includes:
  + Brain magnetic resonance imaging (MRI) with contrast is recommended for stage II-IV ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)), and optional for stage IB ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
  + For stage IIB and IIIA, consider MRI with contrast of the spine plus the thoracic inlet for superior sulcus lesions abutting the spine or subclavian vessels ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE))
  + For stage IIIB, consider pathologic confirmation of N3 disease by any of ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)):
    - Mediastinoscopy
    - Supraclavicular lymph node biopsy
    - Thoracoscopy
    - Needle biopsy
    - Mediastinotomy
    - EUS biopsy
    - EBUS biopsy
  + For stage IV with pleural or pericardial effusion, consider thoracentesis or pericardiocentesis with or without thoracoscopy if thoracentesis is indeterminate ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
* Pathological and molecular evaluation can be used in all patients with advanced disease to guide immunotherapy and/or genotype-driven treatment.
  + Perform programmed death ligand 1(PD-L1) testing ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)).
  + Perform molecular testing as part of broader molecular profiling.

| Table 3: Molecular Testing by Histology |
| --- |
| **Genetic Mutation** | **Squamous Cell Carcinoma** | **Non-squamous Cell Carcinoma** |
| **NCCN Recommendations** | **ESMO Recommendations** | **NCCN Recommendations** | **ESMO Recommendations** |
| EGFR | Consider testing only in never smokers or in patients with small biopsy specimens or mixed histology ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Perform testing only in patients with minimal, remote, or no history of smoking; otherwise testing not recommended ([ESMO Grade A, Level IV](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) | Perform testing ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Perform testing ([ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) |
| ALK | Consider testing only in never smokers or in patients with small biopsy specimens or mixed histology ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Perform testing only in patients with minimal, remote, or no history of smoking; otherwise testing not recommended ([ESMO Grade A, Level IV](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) | Perform testing ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Perform testing ([ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) |
| ROS1 | Consider testing only in patients with small biopsy specimens or mixed histology ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Perform testing ([ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) | Perform testing ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Perform testing ([ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) |
| BRAF | Consider testing only in patients with small biopsy specimens or mixed histology ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Perform testing ([ESMO Grade A, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) | Perform testing ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Perform testing ([ESMO Grade A, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) |
| Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, v-Raf murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; N/A, not available; NCCN, National Comprehensive Cancer Network; ROS1, c-ROS oncogene 1. |

* + Simultaneous broader molecular profiling ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE);[ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)), including NTRK testing, is strongly advised with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients about the availability of clinical trials.
  + See for additional information:
    - [Management of Advanced Non-small Cell Lung Cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-advanced-non-small-cell-lung-cancer)
    - [Genotype-driven Therapy for Non-small Cell Lung Cancer](https://dpa-pde-oxford.shinyapps.io/management/genotype-driven-therapy-for-non-small-cell-lung-cancer)
    - [Immunotherapy for Non-small Cell Lung Cancer](https://dpa-pde-oxford.shinyapps.io/management/immunotherapy-for-non-small-cell-lung-cancer)
* See [Non-small Cell Lung Cancer Diagnosis and Staging](https://dpa-pde-oxford.shinyapps.io/evaluation/non-small-cell-lung-cancer-diagnosis-and-staging) for details.

## **Management**

### **Management of Resectable Disease**

* For the management of clinical stage I and II disease:
  + If mediastinal nodes are negative on pretreatment evaluation and the patient can tolerate surgery, consider surgical resection plus mediastinal lymph node dissection or systematic sampling ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)).
  + There are specific considerations for the choice of procedure and extent of surgery.
    - Lobectomy considerations:
      * For patients with either stage I or II who are medically fit, lobectomy is recommended over sublobar resection ([ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)).
      * For patients with either stage I or II for whom complete resection can be achieved, sleeve or bronchoplastic resection is suggested over pneumonectomy ([ACCP Grade 2C](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)).
      * For patients with stage I, consider minimally invasive resection, such as video-assisted thoracic surgery (thoracoscopy) (VATS) over thoracotomy in experienced centers ([ACCP Grade 2C](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)).
    - Lymph node sampling or dissection considerations:
      * N1 and N2 node resection and mapping with at least 3 N2 stations and ≥ 1 node sampled from all mediastinal stations or complete lymph node dissection should be a routine part of any lung cancer resection. This includes sublobar resection, unless it is technically not possible without increased surgical risk.
      * For patients with either stage I or II, systematic mediastinal lymph node sampling or dissection at the time of anatomic resection is recommended over selective or no sampling ([ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)).
  + Follow-up treatment options after resection depend on postsurgical stage and resection margins.
    - For completely resected disease (R0), options include surveillance, adjuvant chemotherapy, or adjuvant sequential chemotherapy plus radiation therapy, depending on postsurgical stage and risk factors.
    - For incompletely resected disease (R1 or R2), options include re-resection with or without adjuvant chemotherapy, adjuvant radiation therapy, or adjuvant sequential or concurrent chemoradiation therapy, depending on postsurgical stage and resection margins.
* For patients with clinical stage IIIA (T3, N1) disease with negative mediastinal lymph nodes on pretreatment evaluation, initial treatment includes surgical exploration and resection plus mediastinal lymph node dissection or systematic sampling ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
* Follow-up treatment options after resection depend on postsurgical stage and resection margins.
  + For completely resected disease (R0), options include surveillance, adjuvant chemotherapy, or adjuvant sequential chemotherapy plus radiation therapy, depending on postsurgical stage and risk factors.
  + For incompletely resected disease (R1 or R2), options include re-resection with or without adjuvant chemotherapy, adjuvant radiation therapy, or adjuvant sequential or concurrent chemoradiation therapy, depending on postsurgical stage and resection margins.
* For patients with clinical stage IIIA disease and T3 (invasion), N1, or T4 (extension), N0-N1:
  + If the patient has a superior sulcus tumor (T3 invasion, N1), consider neoadjuvant concurrent chemoradiation, followed by surgery and adjuvant chemotherapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
  + If the patient has a superior sulcus tumor (T4 extension, N0-N1) and the tumor is deemed possibly resectable, consider initial treatment with neoadjuvant concurrent chemoradiation followed by re-evaluation to confirm resectability, followed by resection plus adjuvant chemotherapy if disease becomes resectable ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
  + If the tumor is in the chest wall, proximal airway, or mediastinum (T3 invasion, N1, or resectable T4 extension, N0-N1):
    - Initial treatment options include:
      * Surgery alone as the preferred treatment ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE))
      * Neoadjuvant concurrent chemotherapy radiation or chemotherapy alone, followed by surgery ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE))
    - Follow-up treatment after surgery depends on resection margins and initial treatment received.
* For patients with clinical stage IIIA (T1-T2, N2) disease, treatment options are based on nodal status from mediastinal biopsy.
  + If T1-T3 (including T3 with multiple nodules in the same lobe), N0-N1 disease on mediastinal biopsy, and disease is resectable:
    - Initial treatment includes surgical resection plus mediastinal lymph node dissection or systematic sampling ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
    - Adjuvant treatment is based on postsurgical stage and resection margins.
  + If T1-T2 or T3 (other than invasive), N2 disease on mediastinal biopsy, treatment options include either:
    - Definitive concurrent chemoradiation ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)), followed by [durvalumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/durvalumab) ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) (see [Management of Unresectable Nonmetastatic Non-small Cell Lung Cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-unresectable-nonmetastatic-non-small-cell-lung-cancer) for additional information)
    - Induction chemotherapy with or without radiation therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE))
    - Follow-up treatment options depend on disease progression.
      * If there is no apparent progression, consider surgery ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) with or without adjuvant radiation therapy if not previously given ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)), with or without adjuvant chemotherapy ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
      * If there is local progression, consider radiation therapy if not previously given with or without chemotherapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
      * If there is systemic progression, see [Management of Advanced Non-small Cell Lung Cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-advanced-non-small-cell-lung-cancer) for additional information.
  + If disease is T3 (invasion), N2 on mediastinal biopsy, see [Management of Unresectable Nonmetastatic Non-small Cell Lung Cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-unresectable-nonmetastatic-non-small-cell-lung-cancer) for additional information.
* For patients with separate pulmonary nodules, same lobe (T3, N1) or ipsilateral non-primary lobe (T4, N0-N1), the initial treatment option is surgery ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)). Adjuvant treatment recommendations are based on postsurgical stage and resection margins.
* See [Management of resectable non-small cell lung cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-resectable-non-small-cell-lung-cancer) for details.

### **Management of Unresectable Nonmetastatic Disease**

* For the management of stages I-II disease:
  + For patients with inoperable stage IA with negative mediastinal lymph nodes, consider definitive radiation therapy, including stereotactic body radiation therapy (SBRT) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ACCP Grade 2C](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)).
  + For patients with inoperable stages IB-IIB with negative mediastinal lymph nodes:
    - If N0 after mediastinal node evaluation:
      * Consider definitive radiation therapy, including SBRT ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE);[ACCP Grade 2C](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE) for stage I disease; [ESMO Grade A, Level III](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)).
      * If disease is high-risk stages IB-IIB, consider follow-up treatment with chemotherapy after definitive radiation therapy ([NCCN Category 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
    - If N1 after mediastinal node evaluation, consider definitive chemoradiation therapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade C, Level V](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)), followed by [durvalumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/durvalumab) ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
  + If the patient has positive mediastinal lymph nodes, see management of stage III disease.
* For the management of stages IIIA-IIIC disease (T1-T2, N2-N3, or T3, N1-N3, or T4, N0-N3):
  + For most patients with unresectable clinical stage IIIA-IIIC disease, offer definitive concurrent chemoradiation therapy with platinum-based chemotherapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE) for T3, N1 and T3 invasion, N2; [NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE) for T1-T2, T3 [other than invasive], N2, or T4, N0-N1, or T1-T3, N3; [ACCP Grade 1A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) followed by [durvalumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/durvalumab) ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
  + Patients who cannot tolerate or do not wish to have chemoradiation therapy should receive a fractionation pattern based on the physician's judgement and the patient's needs ([ACCP Grade 1C](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)).
* See [Management of unresectable nonmetastatic non-small cell lung cancer](https://dpa-pde-oxford.shinyapps.io/management/management-of-unresectable-nonmetastatic-non-small-cell-lung-cancer) for details.

### **Management of Advanced Disease**

* Offer early integrative palliative care ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE); [ACCP Grade 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)) including discussion and shared decision-making with the patient, family, and caregivers with regard to treatment goals, care planning, and quality of life considerations.
* For patients with oncogenic driver mutations, offer genotype-driven therapy.
  + As first-line therapy:
    - If driver mutations are discovered prior to first-line chemotherapy, regardless of histology:
      * First-line targeted therapy options depend on the types of mutations.

| Table 4: First-Line Targeted Therapy Options |
| --- |
| **EGFR Sensitizing Mutations** | **ALK Rearrangements** | **ROS1 Rearrangements** | **BRAF V600E Mutations** | **NTRK Gene Fusions** |
| Osimertinib (preferred) ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Alectinib (preferred) ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Crizotinib (preferred) ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) | Dabrafenib plus trametinib ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Larotrectinib ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) |
| Erlotinib ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE), with or without bevacizumab) | Brigatinib ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Ceritinib ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) | Vemurafenib or dabrafenib monotherapy (if dabrafenib plus trametinib is not tolerated) |
| Afatinib ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) | Ceritinib ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) |
| Gefitinib ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) | Crizotinib ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) |
| Dacomitinib ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) |
| Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, v-Raf murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor; ESMO, European Society of Medical Oncology; NCCN, National Comprehensive Cancer Network; NTRK, neurotrophic receptor tyrosine kinase; ROS1, c-ROS oncogene 1. |

* + - * In patients with BRAF V600E mutations or NTRK gene fusions, options also include cytotoxic chemotherapy with or without immune checkpoint inhibitor.
    - If driver mutations are discovered during first-line chemotherapy, regardless of histology, consider switching to one of the genotype-based targeted therapy options above ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)) after either completing chemotherapy (including maintenance therapy) or interrupting chemotherapy.
  + Options for second-line therapy and beyond are based on driver mutations, the number and location of lesions, and symptoms.
  + See [Genotype-driven Therapy for Non-small Cell Lung Cancer](https://dpa-pde-oxford.shinyapps.io/management/genotype-driven-therapy-for-non-small-cell-lung-cancer) for additional information.
* For patients with high PD-L1 expression (defined as tumor proportion score [TPS] ≥ 50%), offer immunotherapy.
  + As first-line therapy:
    - Regardless of histology, offer single-agent [pembrolizumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/pembrolizumab) as the preferred therapy ([ASCO Strong recommendation, High quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ASCO2017GRADE); [NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
    - If the tumor has nonsquamous histology, other options include:
      * Pembrolizumab plus [pemetrexed](https://dpa-pde-oxford.shinyapps.io/drug-monograph/pemetrexed) plus either [carboplatin](https://dpa-pde-oxford.shinyapps.io/drug-monograph/carboplatin) or [cisplatin](https://dpa-pde-oxford.shinyapps.io/drug-monograph/cisplatin) ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE))
      * [Atezolizumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/atezolizumab) plus [bevacizumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/bevacizumab) plus carboplatin plus [paclitaxel](https://dpa-pde-oxford.shinyapps.io/drug-monograph/paclitaxel) ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE))
    - If the tumor has squamous histology, other options include:
      * Pembrolizumab plus carboplatin plus either paclitaxel or albumin-bound paclitaxel ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE))
      * Pembrolizumab plus cisplatin plus either paclitaxel or albumin-bound paclitaxel ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE))
  + Options for second-line therapy and beyond are based on the previous therapy received.
  + See [Immunotherapy for Non-small Cell Lung Cancer](https://dpa-pde-oxford.shinyapps.io/management/immunotherapy-for-non-small-cell-lung-cancer) for additional information.
* For patients who are negative for oncogenic driver mutations and PD-L1 TPS < 50%, offer systemic therapy.
  + As first-line therapy:
    - For patients with nonsquamous histology:
      * If performance status is 0-1, offer platinum-based chemotherapy ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE) or [NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE) depending on options; [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE); [ACCP Grade 1A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)) containing [pemetrexed](https://dpa-pde-oxford.shinyapps.io/drug-monograph/pemetrexed) and [pembrolizumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/pembrolizumab) as the preferred option ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)).
      * Other options include platinum-based chemotherapy with or without the addition of [atezolizumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/atezolizumab) and/or [bevacizumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/bevacizumab).
      * If performance status is 2, offer platinum-based doublet chemotherapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE); [ACCP Grade 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)) with [carboplatin](https://dpa-pde-oxford.shinyapps.io/drug-monograph/carboplatin) as the preferred option ([ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)).
      * Other options include non-carboplatin doublet chemotherapy and single-agent chemotherapy.
      * If performance status is 3-4, consider supportive care only ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade B, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)).
    - For patients with squamous histology:
      * If performance status is 0-1, offer platinum-based chemotherapy ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE) or [NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE) depending on options; [ACCP Grade 1A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)) with [pembrolizumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/pembrolizumab) plus [carboplatin](https://dpa-pde-oxford.shinyapps.io/drug-monograph/carboplatin) plus [paclitaxel](https://dpa-pde-oxford.shinyapps.io/drug-monograph/paclitaxel) or albumin-bound paclitaxel as the preferred option ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)).
      * Other options include platinum-based doublet chemotherapy with or without pembrolizumab or [atezolizumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/atezolizumab).
      * If performance status is 2, offer platinum-based doublet chemotherapy ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE); [ACCP Grade 2B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)) with carboplatin as the preferred option ([ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)).
      * Other options include non-carboplatin doublet chemotherapy and single-agent chemotherapy.
      * If performance status is 3-4, consider supportive care only ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade B, Level II](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)).
  + Perform response evaluation after 2-3 cycles of first-line therapy or as clinically indicated ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ESMO Grade B, Level IV](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE)).
  + Follow-up options after response or stable disease after first-line therapy include continuation or a switch to maintenance therapy (NCCN grade and ESMO grade depending on options) or close observation ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
  + Second-line therapy and beyond is based on histology and previous therapy received.
  + Preferred options for subsequent-line therapy include [nivolumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/nivolumab), [atezolizumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/atezolizumab), and [pembrolizumab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/pembrolizumab) ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE) for second-line, [NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE) for third-line; [ESMO Grade A, Level I](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ESMOGRADE) for second-line) regardless of histology.
  + Other options for subsequent-line therapy include cytotoxic chemotherapy with or without targeted agents, or monotherapy with targeted agents.
* For patients with bone, brain, or oligometastases, specific treatment options are based on the site and/or extent of disease.

### **Prevention and Management of Complications**

* Prevention and management of malignancy-related complications:
  + For most common hormone-based [paraneoplastic syndromes](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-B8A8CB66-6550-4AD3-A05A-EDF0E9C6B991__ANC_1974581810), such as:[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013A)
    - [Hypercalcemia](https://dpa-pde-oxford.shinyapps.io/condition/hypercalcemia) of malignancy:
      * For mild hypercalcemia, oral hydration may be effective.
      * For moderate to severe hypercalcemia, rehydration with IV crystalloid fluids not containing calcium and loop diuretics, such as furosemide, may be used as needed after intravascular volume restoration.
      * Bisphosphonates, such as clodronate, [pamidronate](https://dpa-pde-oxford.shinyapps.io/drug-monograph/pamidronate), and [zoledronic acid](https://dpa-pde-oxford.shinyapps.io/drug-monograph/zoledronic-acid), may be used.
      * Consider glucocorticoids, [gallium nitrate](https://dpa-pde-oxford.shinyapps.io/topic/an:dmp2:T233415), and salmon calcitonin.
    - Carcinoid syndrome:
      * The risk of carcinoid crisis resulting from a massive release of serotonin due to an invasive procedure is difficult to predict.
      * Perioperative management is focused on prevention.
      * Carcinoid crisis may be prevented or treated with [octreotide acetate IV](https://dpa-pde-oxford.shinyapps.io/drug-monograph/octreotide-acetate).
      * To treat carcinoid syndrome, consider somatostatin analogs, serotonin receptor blockers, interferon, and antidiarrheal medications.
  + [Dermatomyositis](https://dpa-pde-oxford.shinyapps.io/condition/dermatomyositis) is generally treated with corticosteroids, [methotrexate](https://dpa-pde-oxford.shinyapps.io/drug-monograph/methotrexate), [cyclophosphamide](https://dpa-pde-oxford.shinyapps.io/drug-monograph/cyclophosphamide), [azathioprine](https://dpa-pde-oxford.shinyapps.io/drug-monograph/azathioprine), [mycophenolate](https://dpa-pde-oxford.shinyapps.io/topic/an:dmp2:T232904), [rituximab](https://dpa-pde-oxford.shinyapps.io/drug-monograph/rituximab), and immunoglobulin IV (IVIg).
* Prevention of postoperative complications:
  + PREVENTION\_AND\_MANAGEMENT\_OF\_COMPLICATIONS\_\_LI\_QJV\_B2P\_JVBEU11012211/01/2022 08:02:58 PMevidenceUpdatelowOncologic\_Diseasepreoperative exercise training may decrease risk of postoperative pulmonary complications and hospital length of stay in patients having surgery mostly for non-small cell lung cancer (Cochrane Database Syst Rev 2022 Sep 28)

**preoperative exercise training may decrease risk of postoperative pulmonary complications and hospital length of stay in patients having surgery mostly for non-small cell lung cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cochrane Review[Cochrane Database Syst Rev 2022 Sep 28;9:CD012020](https://pubmed.ncbi.nlm.nih.gov/36170564)

studySummary

* + - Cochrane Review based on Cochrane review of trials with methodologic or procedural limitations
    - systematic review of 10 randomized trials comparing preoperative exercise training vs. usual care with no formal exercise training in 636 patients (mean age 54-72 years) having surgery for lung cancer
    - 9 trials included patients with non-small cell lung cancer
    - preoperative exercise interventions varied across trials
      * interventions in all trials included aerobic exercise; additional interventions in some trials included breathing exercises, inspiratory muscle training, resistance training, or stretching
      * interventions ranged in frequency and duration from 3 times/day for 1 week to 5 times/week for 4 weeks
    - all trials had ≥ 1 limitation including unclear allocation concealment, small sample size, or lack of intention-to-treat analysis
    - preoperative exercise training associated with
      * decreased risk of postoperative pulmonary complications in analysis of 9 trials with 573 patients
        + risk ratio 0.45 (95% CI 0.33-0.61)
        + NNT 5-8 with pulmonary complications in 35% of no exercise training group
        + consistent results regardless of duration of intervention (≤ 2 weeks or > 2 weeks)
      * decreased hospital length of stay (mean difference -2.24 days, 95% CI -3.64 to -0.85 days) in analysis of 9 trials with 573 patients, results limited by significant heterogeneity
      * increased postintervention (preoperative) 6-minute walk distance (mean difference 29.55 meters, 95% CI 12.05-47.04 meters) in analysis of 6 trials with 474 patients
    - no significant differences in postintervention (preoperative) dyspnea or postoperative 6-minute walk distance in analyses of 3 trials with 95-141 patients
    - PubMed28589547The Cochrane database of systematic reviewsCochrane Database Syst Rev201706076CD012020CD012020Reference - [Cochrane Database Syst Rev 2022 Sep 28;9:CD012020](https://pubmed.ncbi.nlm.nih.gov/36170564)

## **Complications**

Complications and Prognosis

* Paraneoplastic syndromes have been reported in lung cancer.[3](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-F312CFCB-B7E6-401A-95B1-E0F2C5A57B47__ACCP2013A)
  + Hormone based paraneoplastic syndromes found in non-small cell lung cancer include:
    - [Hypercalcemia](https://dpa-pde-oxford.shinyapps.io/condition/hypercalcemia) of malignancy:
      * It is most commonly due to:
        + Ectopic production of parathyroid hormone-related protein (PTHrP) by the tumor
        + Increased concentration of the active metabolite of vitamin D (calcitriol)
        + Localized osteolytic hypercalcemia
      * Hypercalcemia of malignancy is reported in 10%-25% of patients with lung cancer. It is most common in squamous cell lung cancer.
      * For mild or moderate hypercalcemia, clinical symptoms may include polyuria, polydipsia, nausea, confusion, vomiting, abdominal pain, myalgia, and possibly severe dehydration and acute renal failure.
      * For severe hypercalcemia (> 14 mg/dL), clinical symptoms may include mental status changes, bradycardia, and hypotension.
      * Median survival of lung cancer patients with hypercalcemia of malignancy is reported to be 1 month.
    - Carcinoid syndrome:
      * It occurs as a result of ectopic serotonin production in about 1%-5% of bronchopulmonary neuroendocrine tumors.
      * Clinical symptoms include:
        + Skin flushing of upper thorax
        + Secretory diarrhea
        + Bronchoconstriction
        + Fibrosis of valves of rights side of heart in chronic cases, but extremely rare in lung carcinoids
      * Acute carcinoid crisis may occur as result of chemotherapy, biopsy, anesthesia, surgery, or adrenergic drugs, and symptoms include bronchospasm, hypotension, arrhythmias, and cardiopulmonary failure.
  + Immunologically based paraneoplastic syndromes in non-small cell lung cancer include [dermatomyositis](https://dpa-pde-oxford.shinyapps.io/condition/dermatomyositis) or polymyositis.
    - Such syndromes are associated with breast, ovarian, gastrointestinal, and lung cancers, with diagnosis generally within 1 year of cancer diagnosis.
    - Etiology is unknown, but it is likely to be autoimmune because immunosuppressive therapy is an effective treatment.
    - Clinical presentation may be characterized by progressive symmetrical proximal muscle weakness, elevated serum levels of muscle enzymes, abnormal electromyographs, abnormal muscle biopsy results, Gottron papules, and photodistributed heliotrope eruption with poikiloderma.
  + Other paraneoplastic syndromes in lung cancer include:
    - [Clubbing](https://dpa-pde-oxford.shinyapps.io/approach-to/clubbing-approach-to-the-patient) (hypertrophic osteoarthropathy)
    - Hematologic syndromes, such as:
      * Leukocytosis and eosinophilia
      * Leukemoid reactions
      * Thrombocytopenic purpura
      * Anemia
      * Thrombocytosis
    - Collagen-vascular syndromes, such as:
      * [Superior vena cava syndrome](https://dpa-pde-oxford.shinyapps.io/condition/superior-vena-cava-syndrome)
      * Vasculitis
      * [Systemic lupus erythematosus](https://dpa-pde-oxford.shinyapps.io/condition/systemic-lupus-erythematosus-sle-in-adults)
    - Cutaneous syndromes, such as:
      * Acquired hypertrichosis lanuginosa
      * Erythema gyratum repens
      * [Erythema multiforme](https://dpa-pde-oxford.shinyapps.io/condition/erythema-multiforme)
      * Tylosis
      * Red man syndrome
      * Exfoliative dermatitis
      * [Acanthosis nigricans](https://dpa-pde-oxford.shinyapps.io/condition/acanthosis-nigricans)
      * [Sweet syndrome](https://dpa-pde-oxford.shinyapps.io/condition/sweet-syndrome)
      * Pruritus and urticaria

## **Prognosis**

* Lung cancer was the most common cause of global cancer death with annual age-standardized mortality 27.1 per 100,000 male persons and 11.2 per 100,000 female persons in 2018.
* 5-year relative survival rates for lung and bronchus cancer in United States were:
  + 19% with disease at all stages
  + 56% with localized disease
  + 30% with regional disease
  + 5% with distant stage disease
* Commonly used prognostic factors for survival in non-small cell lung cancer include:
  + Early-stage disease at diagnosis
  + Performance status by Eastern Cooperative Oncology Group (ECOG) 0-2
  + No significant weight loss
  + Female sex
* Lifestyle factors that may affect prognosis include cigarette smoking.
* Medical factors that may affect prognosis include:
  + Tumor and microenvironment characteristics
  + Medical comorbidities
* Biomarkers for prognosis and/or predicting response to targeted therapy may include:
  + KRAS mutation
  + Driver mutations, such as:
    - EGFR mutations
    - ALK rearrangements
    - ROS1 rearrangements
    - HER2 (ERBB2) mutations
    - BRAF V600E mutations
    - RET gene rearrangements
    - High-level MET amplifications or MET exon 14 skipping mutations
  + PD-L1 expression level
* Genetic expression profiles for prognostication are under investigation, but they are not generally used in clinical practice. Such assays may include:
  + 14-gene assay predicts 5-year survival after resection for nonsquamous, non-small cell lung cancer ([level 1 [likely reliable] evidence](https://www.dynamed.com/home/editorial/editorial-process)).
  + 15-gene expression signature helps classify 5-year survival in patients with untreated stage IB or II non-small cell lung cancer ([level 1 [likely reliable] evidence](https://www.dynamed.com/home/editorial/editorial-process))
  + MicroRNA expression might predict postoperative survival in patients with lung adenocarcinoma ([level 2 [mid-level] evidence](https://www.dynamed.com/home/editorial/editorial-process)).
* See [Non-small Cell Lung Cancer Prognostication](https://dpa-pde-oxford.shinyapps.io/condition/non-small-cell-lung-cancer-prognostication) for details.
* Review of recurrence-free survival (RFS) in surgically-resected non-small cell lung cancer (NSCLC) patients can be found in [Chest 2023 Dec 6 early online](http://doi.org/10.1016/j.chest.2023.11.042).

## **Prevention and Screening**

Prevention and Screening

### **Prevention**

#### **Smoking Cessation**

##### **Smoking Cessation Strategies**

* American Cancer Society (ACS) recommends avoiding tobacco use and environmental tobacco smoke, as well as avoiding radon exposure to reduce the risk for lung cancer ([mnh22237782pcxh70249524pmdc22237782pCA Cancer J Clin 2012 Jan-Feb;62(1):30](http://pubmed.ncbi.nlm.nih.gov/22237782?dopt=Abstract)[full-text](http://onlinelibrary.wiley.com/doi/10.3322/caac.20140/abstract?systemMessage=Wiley+Online+Library+will+be+disrupted+on+4+August+from+10%3A00-12%3A00+BST+%2805%3A00-07%3A00+EDT%29+for+essential+maintenance)).
* All physicians should strongly advise every patient who smokes to quit. Physician advice to quit smoking increases abstinence rates ([PHS Strength of Evidence A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__PHSGRADE)).
  + In addition, treatment delivered by a variety of clinician types increases abstinence rates, so all clinicians should provide smoking cessation interventions ([PHS Strength of Evidence A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__PHSGRADE)).
  + 5-A strategy for advising patients recommended by United States Preventive Services Task Force (USPSTF):
    - Ask about tobacco use
    - Advise to quit through clear personalized messages
    - Assess willingness to quit
    - Assist to quit
    - Arrange follow-up and support
* A combination of counseling and medication is more effective than either alone, and both should be offered ([PHS Strength of Evidence A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__PHSGRADE)).
* First-line medication options include nicotine replacement therapy, varenicline, or bupropion ([PHS Strength of Evidence A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__PHSGRADE)).
* Other smoking cessation techniques that may be useful include cognitive behavioral therapy, acupuncture, mind-body interventions, and hypnotherapy.
* For individuals who are pregnant, offer face-to-face psychosocial interventions to quit ([PHS Strength of Evidence A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__PHSGRADE)) at the first prenatal visit and throughout pregnancy ([PHS Strength of Evidence B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__PHSGRADE)).
* See [Treatment for Tobacco Use](https://dpa-pde-oxford.shinyapps.io/management/treatment-for-tobacco-use-19) for details.

##### **Risk of Smoking on Cancer Mortality and Efficacy of Smoking Cessation**

* **smoking is the single largest population-attributable risk factor for cancer mortality worldwide**

Systematic Review[Lancet 2005 Nov 19;366(9499):1784](http://pubmed.ncbi.nlm.nih.gov/16298215/)

studySummary

* + Systematic Review based on comprehensive systematic review of population-attributable risk factors for cancer mortality
  + total 7,018,402 annual cancer deaths worldwide
  + 1,493,000 (21%) attributable to smoking
  + low fruit and vegetable intake associated with 5% population-attributable risk or 374,000 cancer deaths
  + alcohol associated with 5% population-attributable risk or 351,000 cancer deaths
  + PubMed16298215Lancet (London, England)Lancet2005111936694991784-931784Reference - [Lancet 2005 Nov 19;366(9499):1784](http://pubmed.ncbi.nlm.nih.gov/16298215/)
* **cancer sites associated with the highest proportion of smoking-attributable deaths include lung/bronchus/trachea, larynx, esophagus, oral cavity, and urinary bladder**

Cohort Study[cxh109299386pmdc26076120pJAMA Intern Med 2015 Sep 1;175(9):1574](http://pubmed.ncbi.nlm.nih.gov/26076120?dopt=Abstract)

studySummary

* + based on cohort study Cohort Study
  + 345,962 deaths in adults ≥ 35 years old in 2011 from 12 cancer sites evaluated
  + estimated 167,805 deaths (48.5%) attributed to smoking
  + largest proportion of smoking-attributable deaths for cancers of
    - lung, bronchus, and trachea (80.2%)
    - larynx (76.6%)
    - esophagus (50.7%)
    - oral cavity (47%)
    - urinary bladder (44.8%)
  + PubMed26076120JAMA internal medicine20150901JAMA Intern Med175915741574 Reference - [cxh109299386pmdc26076120pJAMA Intern Med 2015 Sep 1;175(9):1574](http://pubmed.ncbi.nlm.nih.gov/26076120?dopt=Abstract), editorial can be found in [cxh109299366pmdc26075733pJAMA Intern Med 2015 Sep 1;175(9):1516](http://pubmed.ncbi.nlm.nih.gov/26075733?dopt=Abstract)
  + consistent findings in prospective cohort study of 34,439 male persons with 50-year follow-up in Britain ([mnh15668706paph16009981pa9h16009981pbyh16009981pafh16009981pcxh16009981pmdc15668706pBr J Cancer 2005 Feb 14;92(3):426](http://pubmed.ncbi.nlm.nih.gov/15668706?dopt=Abstract)[full-text](https://www.nature.com/articles/6602359))
* Smoking was associated with an increased incidence of any cancer, including lung cancer, in a cohort study of 733,134 male persons ≥ 30 years old with 4-year follow-up in Korea ([15734213Cancer Detect Prev 2005;29(1):15](http://pubmed.ncbi.nlm.nih.gov/15734213?dopt=Abstract)).
* **former smokers may have reduced overall mortality compared to current smokers (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[26921675J Thorac Oncol 2016 May;11(5):693](http://pubmed.ncbi.nlm.nih.gov/26921675?dopt=Abstract)[Full Text](http://www.sciencedirect.com/science/article/pii/S1556086416004305)

studySummary2

* + based on cohort study Cohort Study
  + 3,381 adults ≥ 50 years old (median age 58 years, 69% men) who smoked cigarettes and were enrolled in low dose computed tomography (LDCT) screening programs were followed for median 9.7 years
  + 53% were active smokers during LDCT screening period or stopped smoking < 1 year before end of follow-up or death (current smokers) and 47% stopped smoking before LDCT screening or during follow-up (former smokers)
  + median smoking exposure 40 pack-years
  + overall mortality rate 7.9 deaths per 1,000 person-years
  + comparing former smokers vs. current smokers, overall mortality 5.1% vs. 6.4% (p = 0.05)
  + compared to current smokers
    - former smokers had adjusted hazard ratio (HR) for mortality 0.61 (95% CI 0.44-0.83)
    - former smokers who quit before LDCT screening had adjusted HR for mortality 0.57 (95% CI 0.38-0.85)
    - former smokers who quit during follow-up had adjusted HR for mortality 0.65 (95% CI 0.44-0.96)
  + PubMed26921675Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer20160501J Thorac Oncol115693693 Reference - [26921675J Thorac Oncol 2016 May;11(5):693](http://pubmed.ncbi.nlm.nih.gov/26921675?dopt=Abstract)[full-text](http://www.sciencedirect.com/science/article/pii/S1556086416004305)
* **former smokers may have decreased risk of lung cancer compared to current smokers (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[a9h122996558pcxh122996558pTob Induc Dis 2017 Jan 19;15:6](http://pubmed.ncbi.nlm.nih.gov/28123354?dopt=Abstract)[Full Text](https://tobaccoinduceddiseases.biomedcentral.com/articles/10.1186/s12971-017-0114-2)

studySummary2

* + based on retrospective cohort study Cohort Study
  + 5,509 adults (73% > 65 years old, 87% male) with confirmed primary lung cancer from Cancer Registry of Crete in 1992-2012 were evaluated for smoking habits
  + information on smoking status available in 92%
    - patients who currently smoke or formerly smoked 75.1%
    - patients who never smoked 16.8%
  + comparing patients who currently smoke vs. patients who never smoked, age-adjusted incidence rate (per 100,000 in 2013) of lung cancer 25.4 vs. 6.8 (p < 0.001)
  + age-adjusted incidence rate of lung cancer higher in ever smokers compared to former smokers (p = 0.02) and never smokers (p < 0.001)
  + PubMed28123354Tobacco induced diseases20170119Tob Induc Dis1566 Reference - [a9h122996558pcxh122996558pTob Induc Dis 2017 Jan 19;15:6](http://pubmed.ncbi.nlm.nih.gov/28123354?dopt=Abstract)[full-text](https://tobaccoinduceddiseases.biomedcentral.com/articles/10.1186/s12971-017-0114-2)
* **smoking cessation appears to reduce risk of lung cancer substantially (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Case-Control Study[10926586BMJ 2000 Aug 5;321(7257):323](http://pubmed.ncbi.nlm.nih.gov/10926586?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC27446/)

studySummary2

* + based on case-control study Case-Control Study
  + 982 inpatients < 75 years old with lung cancer and 3,185 matches from local population were compared for history of smoking and incidence of lung cancer

| Risk Ratios for Lung Cancer Compared With Current Smokers |
| --- |
| **Smoking Status** | **Risk Ratio in Men** | **Risk Ratio in Female Persons** |
| Never smoked\* | 0.03 | 0.05 |
| Quit smoking < 10 years ago | 0.66 | 0.69 |
| Quit smoking 10-19 years ago | 0.44 | 0.21 |
| Quit smoking 20-29 years ago | 0.2 | 0.05\*\* |
| Quit smoking > 30 years ago | 0.1 | NA |
| Abbreviation: NA, not applicable.  \* Risk ratio for persons who never smoked from large cohort study in United States ([aph9207204947ta9h9207204947tbyh9207204947tafh9207204947tbeh9207204947thch9207204947tnyh9207204947tnxh9207204947tbth9207204947tpbh9207204947tcxh9207204947tLancet 1992 May 23;339(8804):1268](http://pubmed.ncbi.nlm.nih.gov/1349675?dopt=Abstract)).  \*\* Risk ratio refers to female persons who quit smoking ≥ 20 years ago. |

* + PubMed10926586BMJ (Clinical research ed.)20000805BMJ3217257323323 Reference - [10926586BMJ 2000 Aug 5;321(7257):323](http://pubmed.ncbi.nlm.nih.gov/10926586?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC27446/), editorial can be found in [10926568BMJ 2000 Aug 5;321(7257):311](http://pubmed.ncbi.nlm.nih.gov/10926568?dopt=Abstract)[full-text](http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/10926568/)
* **smoking reduction may reduce risk of lung cancer, but not as effectively as smoking cessation (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[mdc16189363pJAMA 2005 Sep 28;294(12):1505](http://pubmed.ncbi.nlm.nih.gov/16189363?dopt=Abstract)

studySummary2

* + based on data combined from 3 longitudinal cohort studies in Denmark with 19,714 male persons and female persons aged 20-93 years followed for 5-10 years Cohort Study
  + 864 persons (4.4%) developed lung cancer
  + compared with persistent heavy smokers consuming > 15 cigarettes/day (absolute risk 7.8%)
    - reducers (heavy smokers who reduced smoking by > 50% without quitting) (adjusted hazard ratio [HR] 0.73, 95% CI 0.54-0.98) (absolute risk 6.3%)
    - continued light smokers (1-14 cigarettes/day) (HR 0.44, 95% CI 0.35-0.56) (absolute risk 3.3%)
    - quitters (during the study) (HR 0.5, 95% CI 0.36-0.69) (absolute risk 3.6%)
    - stable ex-smokers (having quit before study) (HR 0.17, 95% CI 0.13-0.23) (absolute risk 1.8%)
    - never smokers (HR 0.09, 95% CI 0.06-0.13) (absolute risk 0.7%)
  + PubMed16189363JAMA20050928JAMA2941215051505 Reference - [mdc16189363pJAMA 2005 Sep 28;294(12):1505](http://pubmed.ncbi.nlm.nih.gov/16189363?dopt=Abstract), editorial can be found in [mdc16189369pJAMA 2005 Sep 28;294(12):1550](http://pubmed.ncbi.nlm.nih.gov/16189369?dopt=Abstract), commentary can be found in [mdc16507799pJAMA 2006 Mar 1;295(9):1001](http://pubmed.ncbi.nlm.nih.gov/16507799?dopt=Abstract)
* **switching to chewing tobacco associated with higher risk of both overall mortality and lung cancer mortality compared to smoking cessation (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[17297069Tob Control 2007 Feb;16(1):22](http://pubmed.ncbi.nlm.nih.gov/17297069?dopt=Abstract)[Full Text](http://tobaccocontrol.bmj.com/content/16/1/22.long)

studySummary2

* + based on cohort study Cohort Study
  + 4,443 male switchers and 111,952 male abstainers followed for up to 20 years
  + 44,374 male persons died
  + compared to smoking cessation, switching to chewing tobacco or snuff associated with increased risk for
    - overall mortality (hazard ratio [HR] 1.08, 95% CI 1.01-1.15)
    - lung cancer mortality (HR 1.46, 95% CI 1.24-1.73)
    - coronary heart disease mortality (HR 1.13, 95% CI 1-1.29)
    - stroke mortality (HR 1.24, 95% CI 1.01-1.53)
  + PubMed17297069Tobacco control20070201Tob Control1612222 Reference - [17297069Tob Control 2007 Feb;16(1):22](http://pubmed.ncbi.nlm.nih.gov/17297069?dopt=Abstract)[full-text](http://tobaccocontrol.bmj.com/content/16/1/22.long)

#### **Chemoprevention (Including Supplementation)**

* American College of Chest Physicians (ACCP) recommendations for primary, secondary, and tertiary chemoprevention of lung cancer:
  + Beta-carotene supplementation is not recommended for persons with a smoking history > 20 pack years or a history of lung cancer ([ACCP Grade 1A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)).
  + In persons at risk of lung cancer or with a history of lung cancer:
    - The following agents are not recommended ([ACCP Grade 1A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE)):
      * [Vitamin E](https://dpa-pde-oxford.shinyapps.io/drug-monograph/vitamin-e)
      * Retinoids
      * [N-acetylcysteine](https://dpa-pde-oxford.shinyapps.io/drug-monograph/acetylcysteine)
      * [Isotretinoin](https://dpa-pde-oxford.shinyapps.io/drug-monograph/isotretinoin)
    - The following agents are not recommended outside of a well-designed clinical trial:
      * [Selenium](https://dpa-pde-oxford.shinyapps.io/drug-monograph/rituximab) for tertiary prevention ([ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE))
      * Aspirin ([ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE))
      * Inhaled steroids ([ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE))
      * Prostacyclin analogs, cyclo-oxygenase (COX)-2 inhibitors, or anethole dithiole thione ([ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE))
      * [Pioglitazone](https://dpa-pde-oxford.shinyapps.io/drug-monograph/pioglitazone) or myoinositol ([ACCP Grade 1B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE))
      * Tea extract or [metformin](https://dpa-pde-oxford.shinyapps.io/drug-monograph/metformin) ([ACCP Grade 2C](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCPGRADE))
  + Reference - ACCP evidence-based clinical practice guideline on lung cancer chemoprevention ([23649449Chest 2013 May;143(5 Suppl):e40S](http://pubmed.ncbi.nlm.nih.gov/23649449?dopt=Abstract))
* CHEMOPREVENTION\_\_LI\_WNH\_R12\_G5BEU07192207/19/2022 02:49:25 PMevidenceUpdatestandardFamily\_Medicine Internal\_Medicine Oncologic\_Diseasesupplementation with multivitamins may reduce risk of lung cancer, but supplementation with beta carotene may increase risk of lung cancer in community-dwelling adults (JAMA 2022 Jun 21)

**supplementation with multivitamins may reduce risk of lung cancer, but supplementation with beta carotene may increase risk of lung cancer in community-dwelling adults (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[JAMA 2022 Jun 21;327(23):2334](https://pubmed.ncbi.nlm.nih.gov/35727272)

studySummary

* + Systematic Review based on systematic review with trial-specific quality measures not reported
  + systematic review of 78 randomized trials and 6 cohort studies evaluating vitamin, mineral, and antioxidant supplementation in 739,803 community-dwelling adults (mean age 61 years) without chronic disease or vitamin, mineral, or nutritional deficiencies
  + 9 trials evaluated multivitamins and antioxidant supplements, and 8 trials evaluated beta carotene supplementation
  + compared to control
    - multivitamin supplementation associated with reduced risk of lung cancer (odds ratio 0.75, 95% CI 0.58-0.95) in analysis of 2 trials with 36,052 adults
    - beta carotene supplementation at 3.7-12 years of follow-up associated with increased risk of lung cancer (odds ratio 1.2, 95% CI 1.01-1.42) in analysis of 4 trials with 94.830 adults
  + PubMed35727272JAMAJAMA20220621327232334-23472334Reference - [JAMA 2022 Jun 21;327(23):2334](https://pubmed.ncbi.nlm.nih.gov/35727272)
* CHEMOPREVENTION\_\_LI\_KZQ\_J1S\_L4BEU01272101/27/2021 02:41:20 PMevidenceUpdatelowplusFamily\_Medicine Internal\_Medicine Primary\_Carevitamin A may increase risk of lung cancer in persons who smoked and had previous asbestos exposure, but not in low-risk persons (Cochrane Database Syst Rev 2020 Mar 4)

**vitamin A may increase risk of lung cancer in persons who smoked and had previous asbestos exposure, but not in low-risk persons (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cochrane Review[Cochrane Database Syst Rev 2020 Mar 4;3:CD002141](http://pubmed.ncbi.nlm.nih.gov/32130738-drugs-for-preventing-lung-cancer-in-healthy-people/?dopt=Abstract)

studySummary

* + Cochrane Review based on Cochrane review with no significant difference in high-quality trials for persons with high risk, and with wide confidence interval for persons with low-risk of developing lung cancer
  + systematic review of 12 randomized trials comparing vitamins, minerals, or other dietary supplements vs. placebo in healthy adults
  + 6 trials compared vitamin A to placebo
    - 3 trials included persons at high risk of developing lung cancer (smokers and previous exposure to asbestos)
    - 3 trials included persons at low risk of developing lung cancer
  + comparing vitamin A to placebo
    - in persons at high risk of developing lung cancer, vitamin A associated with
      * increased risk of lung cancer in analysis of 3 trials with 43,995 persons
        + risk ratio (RR) 1.1 (95% CI 1.01-1.2)
        + NNH 128-2,564 with lung cancer in 3.9% of placebo group
        + analysis included 3 high quality trials, with nonsignificant increase in risk of lung cancer in 2 trials, and no significant difference in risk in 1 trial
      * increased lung cancer mortality in analysis of 2 trials with 29,426 persons
        + RR 1.18 (95% CI 1.01-1.38)
        + NNH 131-5,000 with lung cancer mortality 2% in placebo group
      * increased all-cause mortality in analysis of 2 trials with 32,883 persons
        + RR 1.09 (95% CI 1.05-1.13)
        + NNH 33-87 with all-cause mortality 23% in placebo group
    - in persons at low risk of developing lung cancer, no significant differences in
      * risk of lung cancer (RR 0.99, 95% CI 0.69-1.42) in analysis of 3 trials with 168,319 persons
      * lung cancer mortality (RR 0.71, 95% CI 0.35-1.44) in analysis of 2 trials with 160,692 persons
      * both results not significant, but confidence interval includes possibility of benefit or harm
    - in 1 trial with 22,071 persons (mixed population)
      * yellowing of skin in 15.8% vs. 13.9% (p < 0.0001, NNH 52)
      * minor gastrointestinal symptoms in 2.4% vs. 1.1% (p < 0.0001, NNH 76)
  + PubMed32130738The Cochrane database of systematic reviewsCochrane Database Syst Rev202003043CD002141CD002141Reference - [Cochrane Database Syst Rev 2020 Mar 4;3:CD002141](http://pubmed.ncbi.nlm.nih.gov/32130738-drugs-for-preventing-lung-cancer-in-healthy-people/?dopt=Abstract)
* CHEMOPREVENTION\_\_LI\_TPX\_Y1S\_L4BEU01272101/27/2021 02:46:04 PMevidenceUpdatelowplusFamily\_Medicine Internal\_Medicine Primary\_Carevitamin C increases risk of lung cancer in women but may not increase risk of lung cancer in men (Cochrane Database Syst Rev 2020 Mar 4)

**vitamin C increases risk of lung cancer in female persons (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**) but may not increase risk of lung cancer in male persons (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cochrane Review[Cochrane Database Syst Rev 2020 Mar 4;3:CD002141](http://pubmed.ncbi.nlm.nih.gov/32130738-drugs-for-preventing-lung-cancer-in-healthy-people/?dopt=Abstract)

studySummary

* + Cochrane Review based on Cochrane review with wide confidence interval for lung cancer in men
  + systematic review of 12 randomized trials comparing vitamins, minerals, and other dietary supplements vs. placebo in healthy adults
  + 3 trials compared vitamin C (ascorbic acid) to placebo
  + mean follow-up ranged from 8-9 years
  + comparing vitamin C to placebo
    - incidence of lung cancer
      * 1.2% vs. 0.6% (p = 0.01, NNH 166) in 1 trial with 7,627 female persons
      * 1.3% vs. 1.4% (risk ratio 0.94, 95% CI 0.64-1.38) in 1 trial with 7,326 men, not significant, but confidence interval includes possibility of benefit or harm
    - no significant differences in lung cancer mortality or all-cause mortality in 1 trial with 7,326 men
  + PubMed32130738The Cochrane database of systematic reviewsCochrane Database Syst Rev202003043CD002141CD002141Reference - [Cochrane Database Syst Rev 2020 Mar 4;3:CD002141](http://pubmed.ncbi.nlm.nih.gov/32130738-drugs-for-preventing-lung-cancer-in-healthy-people/?dopt=Abstract)
* CHEMOPREVENTION\_\_LI\_GVV\_2BS\_L4BEU01272101/27/2021 02:47:32 PMevidenceUpdatestandardFamily\_Medicine Internal\_Medicine Primary\_Carevitamin E does not reduce risk of lung cancer, and vitamin D plus calcium and selenium each may not reduce risk of lung cancer in healthy adults (Cochrane Database Syst Rev 2020 Mar 4)

**vitamin E does not reduce risk of lung cancer (**[**level 1 [likely reliable] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**), and vitamin D plus calcium and selenium each may not reduce risk of lung cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**) in healthy adults**

Cochrane Review[Cochrane Database Syst Rev 2020 Mar 4;3:CD002141](http://pubmed.ncbi.nlm.nih.gov/32130738)

studySummary

* + Cochrane Review based on Cochrane review with wide confidence intervals for vitamin D plus calcium and selenium
  + systematic review of 12 randomized trials comparing vitamins, minerals, and other dietary supplements vs. placebo in healthy adults
  + 5 trials compared vitamin E (alpha-tocopherol) to placebo in healthy adults
  + comparing vitamin E to placebo
    - no significant differences in
      * lung cancer incidence (risk ratio [RR] 1.01, 95% CI 0.9-1.14) in analysis of 3 trials with 36,841 adults
      * lung cancer mortality (RR 0.96, 95% CI 0.77-1.18) in analysis of 2 trials with 29,214 adults
    - vitamin E associated with increased risk of hemorrhagic stroke (hazard ratio, 1.74, 95% CI 1.04-2.91) in 1 trial with 14,641 adults
  + 3 trials compared vitamin D plus calcium to placebo in healthy postmenopausal individuals
    - dose ranged from vitamin D3 400-2,000 units plus 1,000-1,500 mg calcium carbonate daily
    - mean follow-up ranged from 4-7 years
  + comparing vitamin D plus calcium to placebo, no significant differences in
    - risk of lung cancer in analysis of 3 trials with 37,601 female persons
      * RR 0.9 (95% CI 0.39 -2.08)
      * not significant, but confidence interval includes possibility of benefit or harm
    - risk of renal calculi in analysis of 2 trials with 2,931 female persons
  + 1 trial compared selenium to placebo in healthy adults
  + mean follow-up was 7 years
  + comparing selenium to placebo in 1 trial with 17,448 male persons
    - no significant differences in
      * risk of lung cancer (RR 1.11, 95% CI 0.8-1.54), not significant, but confidence interval includes possibility of benefit or harm
      * lung cancer mortality (RR 1.09, 95% CI 0.72-1.66)
    - selenium associated with increased risk of dermatitis and alopecia
  + PubMed32130738The Cochrane database of systematic reviewsCochrane Database Syst Rev202003043CD002141CD002141Reference - [Cochrane Database Syst Rev 2020 Mar 4;3:CD002141](http://pubmed.ncbi.nlm.nih.gov/32130738)
* **no vitamin supplements appear effective for lung cancer prevention while vitamin E use and long-term beta-carotene, lutein, or retinol use each appear to increase risk (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[Am J Epidemiol 2009 Apr 1;169(7):815](http://pubmed.ncbi.nlm.nih.gov/19208726/)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2842198/)Cohort Study[Am J Respir Crit Care Med 2008 Mar 1;177(5):524](http://pubmed.ncbi.nlm.nih.gov/17989343/)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2258445/)

studySummary

* + Cohort StudyCohort Study based on 2 analyses of data from Vitamins And Lifestyle (VITAL) cohort of > 77,000 adults aged 50-76 years
  + 77,126 adults aged 50-76 years completed baseline survey about supplement use during previous 10 years and were then followed for mean 4 years
    - 47% were never smokers
    - beta-carotene use > 4 years associated with increased risk for small cell lung cancer compared to no beta-carotene use (adjusted HR 3.22, 95% CI 1.29-8.07)
    - lutein use > 10 years as individual supplement associated with increased risk compared to no lutein use
      * for all lung cancer (adjusted HR 2.02, 95% CI 1.28-3.17)
      * for non-small cell lung cancer (adjusted HR 2.48, 95% CI 1.53-4.02)
    - retinol use > 4 years associated with increased risk compared to no retinol use
      * for all lung cancer (adjusted HR 1.53, 95% CI 1.12-2.08)
      * for non-small cell lung cancer (adjusted HR 1.8, 95% CI 1.29-2.52)
    - PubMed19208726American journal of epidemiologyAm J Epidemiol200904011697815-28815Reference - [Am J Epidemiol 2009 Apr 1;169(7):815](http://pubmed.ncbi.nlm.nih.gov/19208726/)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2842198/), commentary can be found in [19605516Am J Epidemiol 2009 Aug 1;170(3):401](http://pubmed.ncbi.nlm.nih.gov/19605516?dopt=Abstract)
  + 77,721 male persons and female persons aged 50-76 years were evaluated for supplement use (including multivitamin supplements, vitamin C, vitamin E, and folate) and incidence of lung cancer
    - lung cancer identified in 0.67%
    - adjusting for smoking, age, and sex, there was no association between lung cancer and any supplement
    - vitamin E associated with increased risk of lung cancer (HR 1.05 for every 100-mg/day increase in dose, 95% CI 1-1.09), especially for
      * current smokers (HR 1.11 for every 100-mg/day increase, 95% CI 1.03-1.19)
      * non-small cell lung cancer (HR 1.07 for every 100-mg/day increase, 95% CI 1.02-1.12)
    - PubMed17989343American journal of respiratory and critical care medicineAm J Respir Crit Care Med200803011775524-30524 Reference - [Am J Respir Crit Care Med 2008 Mar 1;177(5):524](http://pubmed.ncbi.nlm.nih.gov/17989343/)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2258445/), editorial can be found in [18296467Am J Respir Crit Care Med 2008 Mar 1;177(5):470](http://pubmed.ncbi.nlm.nih.gov/18296467?dopt=Abstract)
* **regular aspirin use does not appear to reduce risk of lung cancer in female persons or male persons (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Randomized Trial[JAMA 2005 Jul 6;294(1):47](http://pubmed.ncbi.nlm.nih.gov/15998890/)

studySummary

* + Randomized Trial based on 1 randomized trial with low adherence rate and 1 cohort study
  + 39,876 healthy female persons > 45 years old who completed 3-month placebo run-in period were randomized to [aspirin](https://dpa-pde-oxford.shinyapps.io/drug-monograph/aspirin) 100 mg vs. placebo orally every other day (and also randomized to [vitamin E](https://dpa-pde-oxford.shinyapps.io/drug-monograph/vitamin-e) 600 units vs. placebo orally every other day) for mean 10 years (range 8-11 years)
    - 13% of female persons were current smokers and 36% were past smokers
    - 76% of female persons reported taking at least two-thirds of assigned aspirin or placebo tablets at 5 years (67% at 10 years)
    - 79% of female persons reported taking at least two-thirds of assigned vitamin E dosage or placebo at 5 years (72% at 10 years)
    - comparing aspirin vs. placebo, incidence of lung cancer 0.45% vs. 0.58% (p = 0.08)
  + PubMed15998890JAMAJAMA20050706294147-5547Reference - Women's Health Study ([JAMA 2005 Jul 6;294(1):47](http://pubmed.ncbi.nlm.nih.gov/15998890/)), editorial can be found in [JAMA 2005 Jul 6;294(1):105](http://pubmed.ncbi.nlm.nih.gov/15998897/), commentary can be found in [Am Fam Physician 2005 Nov 15;72(10):2087](http://www.aafp.org/afp/2005/1115/p2087.html), [mdc16287949pJAMA 2005 Nov 16;294(19):2432](http://pubmed.ncbi.nlm.nih.gov/16287949?dopt=Abstract), or in [mnh16388558tmdc16388558tACP J Club 2006 Jan-Feb;144(1):8](http://pubmed.ncbi.nlm.nih.gov/16388558?dopt=Abstract)
* In a prospective cohort study of 49,383 male physicians aged 40-75 years in United States:
  + 328 developed lung cancer during 601,453 person-years of follow-up.
  + Regular use of aspirin twice or more per week (dose information not available) was not associated with a reduced risk of lung cancer (adjusted RR 1.13, 95% CI 0.89-1.43) compared to nonusers.
  + Reference - [mnh14583773paph11234752pa9h11234752pbyh11234752pafh11234752pcxh11234752pmdc14583773pBr J Cancer 2003 Nov 3;89(9):1705](http://pubmed.ncbi.nlm.nih.gov/14583773?dopt=Abstract)[full-text](https://www.nature.com/bjc/journal/v89/n9/full/6601343a.html)

#### **Dietary Measures**

* **increased cruciferous vegetable consumption associated with decreased risk of lung cancer in female persons (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[23553059Ann Oncol 2013 Jul;24(7):1918](http://pubmed.ncbi.nlm.nih.gov/23553059?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3690909/)

studySummary2

* + based on systematic review of observational studies Systematic Review
  + systematic review of 10 observational studies evaluating association between cruciferous vegetable consumption with risk of lung cancer in female persons
  + compared to lowest quartile, highest quartile of cruciferous vegetable consumption associated with reduced risk of lung cancer (relative risk 0.75, 95% CI 0.63-0.89), results limited by significant heterogeneity
  + PubMed23553059Annals of oncology : official journal of the European Society for Medical Oncology20130701Ann Oncol24719181918 Reference - [23553059Ann Oncol 2013 Jul;24(7):1918](http://pubmed.ncbi.nlm.nih.gov/23553059?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3690909/)
* **weekly cruciferous vegetable consumption associated with decreased risk of lung cancer in persons with null GSTM1 or GSTT1 genes (implicated in elimination of isothiocyanates) but not in persons with positive GSTM1 and GSTT1 genes (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Case-Control Study[mnh16257343paph18680367pa9h18680367pbyh18680367pafh18680367pbeh18680367phch18680367pnyh18680367pnxh18680367pbth18680367ppbh18680367pcxh18680367pmdc16257343pLancet 2005 Oct 29;366(9496):1558](http://pubmed.ncbi.nlm.nih.gov/16257343?dopt=Abstract)

studySummary2

* + based on case-control study Case-Control Study
  + 2,141 patients with lung cancer were compared to 2,168 controls
  + weekly consumption of cruciferous vegetables associated with reduced risk for lung cancer in persons with
    - GSTM1 null (OR 0.67, 95% CI 0.49-0.91)
    - GSTT1 null (OR 0.63, 0.37-1.07)
    - null for both (OR 0.28, 0.11-0.67)
  + PubMed16257343Lancet (London, England)20051029Lancet366949615581558 Reference - [mnh16257343paph18680367pa9h18680367pbyh18680367pafh18680367pbeh18680367phch18680367pnyh18680367pnxh18680367pbth18680367ppbh18680367pcxh18680367pmdc16257343pLancet 2005 Oct 29;366(9496):1558](http://pubmed.ncbi.nlm.nih.gov/16257343?dopt=Abstract)
* **increased soy food intake associated with decreased risk of lung cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Cohort Study[23097255Am J Epidemiol 2012 Nov 15;176(10):846](http://pubmed.ncbi.nlm.nih.gov/23097255?dopt=Abstract)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3626060/)

studySummary2

* + based on prospective cohort study Cohort Study
  + 71,550 female persons in China were followed for usual soy food intake over mean 9.1 years and stratified to quintiles of soy intake
  + 0.5% developed lung cancer
  + highest quintile of soy food intake associated with lower risk of lung cancer vs. lowest quintile (hazard ratio 0.63, 95% CI 0.44-0.9)
  + PubMed23097255American journal of epidemiology20121115Am J Epidemiol17610846846 Reference - [23097255Am J Epidemiol 2012 Nov 15;176(10):846](http://pubmed.ncbi.nlm.nih.gov/23097255?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3626060/)
* **increased phytoestrogen intake associated with decreased risk of lung cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Case-Control Study[mdc16189362pJAMA 2005 Sep 28;294(12):1493](http://pubmed.ncbi.nlm.nih.gov/16189362?dopt=Abstract)

studySummary2

* + based on case-control studyCase-Control Study
  + 1,674 lung cancer patients were compared to 1,735 matched healthy controls in United States
  + highest quartiles of total phytosterols, isoflavones, lignans, and phytoestrogens were associated with reduced risk for lung cancer ranging from 21% for phytosterols (odds ratio [OR] 0.79, 95% CI 0.64-0.97) to 46% for total phytoestrogens from food sources only (OR 0.54, 95% CI 0.42-0.7)
  + PubMed16189362JAMA20050928JAMA2941214931493 Reference - [mdc16189362pJAMA 2005 Sep 28;294(12):1493](http://pubmed.ncbi.nlm.nih.gov/16189362?dopt=Abstract), correction can be found in JAMA 2005 Dec 7;294(21):2700, editorial can be found in [mdc16189369pJAMA 2005 Sep 28;294(12):1550](http://pubmed.ncbi.nlm.nih.gov/16189369?dopt=Abstract), commentary can be found in [mdc16478894pJAMA 2006 Feb 15;295(7):755](http://pubmed.ncbi.nlm.nih.gov/16478894?dopt=Abstract)
* Neither tomato nor lycopene intake was associated with a decreased risk of lung cancer in an FDA review for premarket approval of a qualified health claim ([17623802J Natl Cancer Inst 2007 Jul 18;99(14):1074](http://pubmed.ncbi.nlm.nih.gov/17623802?dopt=Abstract)).

### **Screening**

* General information:
  + The lifetime risk of developing lung and bronchus cancer was 6.7% for male persons and 5.9% for female persons in United States in 2019.
  + The goal of screening is to benefit individuals by increasing life expectancy and quality of life but with low false-positive results to prevent additional, unnecessary testing.
  + Low-dose computed tomography (LDCT) screening detects lung cancer in about 1%-2% of patients who smoke or have other risk factors for lung cancer.
* Risk stratification:
  + Patients are considered low risk if they are < 50 years old and/or have < 20 pack-year history of smoking ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
  + Patients are considered moderate risk if they are ≥ 50 years old and have ≥ 20 pack-year history of smoking or second-hand smoke exposure and no additional risk factors ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
  + Patients are considered high risk if either of the following:
    - Age 55-74 years, ≥ 30 pack-year history of smoking, and smoking cessation < 15 years ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE))
    - Age ≥ 50 years, ≥ 20 pack-year history of smoking, and the presence of additional risk factors that increase the risk of lung cancer to ≥ 1.3%:
      * Additional risk factors include a personal history of cancer or lung disease, family history of lung cancer, radon exposure, or relevant occupational exposure ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
      * Second-hand smoke exposure is not an additional risk factor in this circumstance.
* [Recommendations](https://dpa-pde-oxford.shinyapps.io/prevention/lung-cancer-screening#GUID-8FD39E44-7F74-448A-B3C5-447EC400656E):
  + Screening of lung cancer using low-dose computed tomography (LDCT) is recommended or suggested in patients with:
    - Age 55-74 years, ≥ 30 pack-year history of smoking, and smoking cessation < 15 years ([NCCN Category 1](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ACCP Weak recommendation, Moderate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCP2018GRADE) also includes patients 75-77 years old; [USPSTF Grade B](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__USPSTFGRADE), also includes patients 75-80 years old)
    - Age ≥ 50 years, ≥ 20 pack-year history of smoking, and the presence of additional risk factors that increase risk of lung cancer to ≥ 1.3% ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)):
      * Additional risk factors include a personal history of cancer or lung disease, family history of lung cancer, radon exposure, or relevant occupational exposure.
      * Second-hand smoke exposure is not an additional risk factor in this circumstance.
  + Routine lung cancer screening with LDCT is not recommended or suggested in patients who:
    - Are asymptomatic, do not meet the above criteria, and are at high risk based on clinical prediction calculators ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ACCP Weak recommendation, Low-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCP2018GRADE))
    - Do not meet the above criteria and are not at high risk based on clinical prediction calculators ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE); [ACCP Strong recommendation, Moderate-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCP2018GRADE))
    - Have severe comorbidities which would preclude the evaluation of findings or potentially definitive treatment, or limit life expectancy ([ACCP Strong recommendation, Low-quality evidence](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__ACCP2018GRADE))
* Considerations for shared decision-making:
  + Shared decision-making should include the discussion of potential benefits and harms.
    - Benefits may include decreased lung cancer mortality, improved quality of life from screening and early detection (compared to standard detection), and detection of other serious health issues.
    - Harms may include overdiagnosis, anxiety due to test findings, physical complications, false-positive or false-negative results, unnecessary testing and procedures, radiation exposure, increased cost, and incidental findings.
  + A video-based decision aid may improve patient knowledge of the lung cancer screening decision ([level 3 [lacking direct] evidence](https://www.dynamed.com/home/editorial/editorial-process)).
  + Lung cancer screening is reported to reduce the quality of life in patients with an unfavorable preference toward screening and life expectancy < 10.5 years regardless of annual lung cancer risk ranging from 0.07% to 2.67% ([level 3 [lacking direct] evidence](https://www.dynamed.com/home/editorial/editorial-process)).
* Effects of screening on lung cancer mortality:
  + LDCT screening reduces lung cancer mortality and all-cause mortality compared to chest x-ray screening in high-risk patients (age 55-74 years, ≥ 30 pack-year history of smoking, and smoking cessation < 15 years) ([level 1 [likely reliable] evidence](https://www.dynamed.com/home/editorial/editorial-process)), but may not reduce lung cancer mortality in patients with ≥ 20 pack years of cigarette smoking history ([level 2 [mid-level] evidence](https://www.dynamed.com/home/editorial/editorial-process)).
  + Annual screening with chest x-ray does not appear to reduce lung cancer mortality ([level 2 [mid-level] evidence](https://www.dynamed.com/home/editorial/editorial-process)).
  + The addition of sputum cytology every 4 months to annual chest x-ray does not appear to reduce lung cancer mortality ([level 2 [mid-level] evidence](https://www.dynamed.com/home/editorial/editorial-process)).
* [Diagnostic accuracy of LDCT](https://dpa-pde-oxford.shinyapps.io/prevention/lung-cancer-screening#DX_ACCURACY_CT):
  + LDCT screening has high sensitivity and moderate specificity for lung cancer ([level 1 [likely reliable] evidence](https://www.dynamed.com/home/editorial/editorial-process)), but may be associated with a high rate of false-positives, leading to unnecessary, invasive follow-up procedures.
  + LDCT is reported to be as accurate as standard-dose computed tomography (CT) for detection of solid nodules, but it is reported to be less sensitive for detection of very low-density nonsolid nodules or ground-glass opacity nodules (GGOs).
* [Follow-up testing based on LDCT findings](https://dpa-pde-oxford.shinyapps.io/prevention/lung-cancer-screening#GUID-E2CE6C5B-9D2D-42FC-9998-87E4C5FA31BE)
  + Follow-up testing after baseline screening LDCT:
    - If no nodule is detected, consider follow-up LDCT annually until the patient is no longer eligible for definitive treatment. It is uncertain how long person should continue being screened and the age at which screening should stop ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
    - If a nodule is found, follow up is based on the size and characteristics of a single solid, part-solid, or ground-glass opacity (GGO)/ground-glass nodule (GGN)/nonsolid nodule, or multiple nodules.
  + Follow-up testing after annual or follow-up LDCT:
    - If a new nodule with mean diameter ≥ 3 mm is detected and there is infection/inflammation suspected, consider a repeat LDCT in 1-3 months ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)). Nodules rapidly increasing in size suggest inflammation or malignancy other than non-small cell lung cancer.
    - If a new nodule with mean diameter ≥ 3 mm is detected and there is no suspicion of infection or inflammation, follow-up as per size and characteristics for single solid nodule, part-solid nodule, or GGO/GGN/nonsolid nodule, or multiple nodules ([NCCN Category 2A](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-3B11520F-ABF9-4B1D-93C3-1D1F71AAD7F8__NCCNGRADE)).
* See [Lung Cancer Screening](https://dpa-pde-oxford.shinyapps.io/prevention/lung-cancer-screening) for details.

## **Lung Cancer in Female Persons**

ManagementManagement

### **General Information**

* Oncologic\_Diseasereview of lung cancer in women (Clin Chest Med 2020 Mar)07/14/2020 01:01:48 PMFemale persons are [less affected by lung cancer](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#INCIDENCE_PREVALENCE) compared to male persons, but the incidence of lung cancer in female persons is declining at a slower rate compared to male persons PubMed32008629Clinics in chest medicineClin Chest Med2020030141153-6553([Clin Chest Med 2020 Mar;41(1):53](http://pubmed.ncbi.nlm.nih.gov/32008629)).
* Lung cancer is reported to be the leading cause of cancer deaths in female persons in 28 countries PubMed32008629Clinics in chest medicineClin Chest Med2020030141153-6553([Clin Chest Med 2020 Mar;41(1):53](http://pubmed.ncbi.nlm.nih.gov/32008629)).
* PubMed24216523Seminars in thoracic and cardiovascular surgerySemin Thorac Cardiovasc Surg2013070125287-9487Adenocarcinoma is the most common type of non-small cell lung cancer found in female persons ([Clin Chest Med 2020 Mar;41(1):53](http://pubmed.ncbi.nlm.nih.gov/32008629), [Semin Thorac Cardiovasc Surg 2013 Summer;25(2):87](http://pubmed.ncbi.nlm.nih.gov/24216523)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3827695/)).

### **Comparative Lung Cancer Risk in Female Persons vs. Male Persons**

* Smoking remains the most important risk factor for lung cancer in both male and female persons.
  + There was a reported 16.8-fold increase in deaths from lung cancer in female persons over a 50-year period from 1959 to 2010 in the United States.
    - The prevalence of cigarette smoking was 15.5% in 2016 (13.5% in female persons and 17.5% in male persons) compared to 42% in 1964.
    - The difference in smoking prevalence comparing female persons to male persons in young cohorts is progressively decreasing due to converging female and male smoking initiation rates and decreasing smoking cessation rates in female persons.
  + Incidence of tobacco-related lung cancer in female persons in the United States during 2010-2014:
    - 54.3% in White female persons
    - 49.2% in Black female persons
    - 39% in American Indian and Alaskan native female persons
    - 27.9% in Asian Pacific Islander female persons
    - PubMed30383737Morbidity and mortality weekly report. Surveillance summaries (Washington, D.C. : 2002)MMWR Surveill Summ2018110267121-421Reference - [MMWR Surveill Summ 2018 Nov 2;67(12):1](http://pubmed.ncbi.nlm.nih.gov/30383737)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6220819/)
  + Female persons with lung cancer are reported to be younger, to have started smoking at later age, and to smoke less intensively compared to male persons.
  + Comparing female persons vs. male persons, the reported relative risk for all lung cancers was:
    - 12.7 vs. 9.1 for ever-smoking
    - 27.9 vs. 9.6 for level of smoking
  + Reference - [Clin Chest Med 2020 Mar;41(1):53](http://pubmed.ncbi.nlm.nih.gov/32008629)
* In nonsmokers, the annual cases of non-small cell lung cancer in the United States was reported to be more common in female persons vs. male persons (17.5% vs. 6.9%, p < 0.001).
* Other risk factors in female persons compared to male persons may include:
  + Hormonal factors include:
    - Estrogen receptors may be overexpressed and play role in the modulation of gene expression and carcinogenesis through the formation of DNA adducts, growth factor gene stimulation, angiogenesis, and acceleration of smoke-related carcinogens.
    - Progesterone may have a protective effect by inhibiting cell proliferation and inducing apoptosis.
  + Prior radiation therapy for breast cancer associated with an increased risk of secondary lung cancer
  + Higher molecular changes causing cancer including:
    - DNA adducts in smokers
    - P53 mutation in smokers
    - K-ras mutation
    - Gastrin-releasing peptide receptor mRNA expression
  + PubMed32008629Clinics in chest medicineClin Chest Med2020030141153-6553Reference - [Clin Chest Med 2020 Mar;41(1):53](http://pubmed.ncbi.nlm.nih.gov/32008629)
* **postmenopausal individuals may have higher risk of developing lung cancer compared to premenopausal individuals**

Systematic Review[Medicine (Baltimore) 2017 Jun;96(26):e7065](http://pubmed.ncbi.nlm.nih.gov/28658099)[Full Text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5500021/)

studySummary

* + Systematic Review based on systematic review of observational studies
  + systematic review of 3 cohort studies and 5 case-control studies evaluating menopausal status and risk of lung cancer in 390,301 individuals
  + 3,608 patients had or developed lung cancer
  + postmenopausal individuals had higher risk of developing lung cancer compared to premenopausal individuals (risk ratio [RR] 1.44, 95% CI 1.12-1.85)
  + increased risk after adjusting for age and smoking (RR 1.52, 95% CI 1.06-2.17)
  + PubMed28658099MedicineMedicine (Baltimore)201706019626e7065e7065Reference - [Medicine (Baltimore) 2017 Jun;96(26):e7065](http://pubmed.ncbi.nlm.nih.gov/28658099)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5500021/)

### **Treatment Outcomes**

* Compared to male persons, female persons may have:
  + Less advanced lung cancer
  + Improved outcomes following treatment:
    - Outcomes may include lower mortality rates and improved response to chemotherapy.
    - Improved outcomes may be due to increased frequency of EGFR mutations.
  + Higher rates of adverse events after radiation therapy
  + PubMed32008629Clinics in chest medicineClin Chest Med2020030141153-6553References - [Clin Chest Med 2020 Mar;41(1):53](http://pubmed.ncbi.nlm.nih.gov/32008629), [Semin Thorac Cardiovasc Surg 2013 Summer;25(2):87](http://pubmed.ncbi.nlm.nih.gov/24216523)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3827695/)
* **female persons with stage III-IV non-small cell lung cancer treated with platinum chemotherapy may have improved survival and response rates compared to male persons**

individual patient data meta-analysis[Ann Oncol 2010 Oct;21(10):2023](http://pubmed.ncbi.nlm.nih.gov/20332134)

studySummary

* + individual patient data meta-analysis based on pooled analysis of individual patient data without assessment of trial quality
  + pooled analysis of individual patient data from 5 randomized trials with 2,349 patients with stage III-IV non-small cell lung cancer comparing outcomes in female persons vs. male persons
  + 793 patients (34%) were female persons
  + all patients received first-line treatment with platinum-based chemotherapy
  + median follow-up was 8.6 months
  + comparing female persons vs. male persons
    - median survival 9.6 months vs. 8.6 months (p = 0.002)
    - 1-year survival 41% vs. 35% (no p value reported)
    - 3-year survival 8% vs. 5% (no p value reported)
    - overall response in 42% vs. 40% (p = 0.01)
    - nausea and vomiting
      * any grade, in 62% vs. 54% (p = 0.0004)
      * severe grade, in 11% vs. 6% (p < 0.0001)
    - mucositis any grade in 39% vs. 34% (p = 0.03)
  + in multivariate analysis, factors associated with improved survival include
    - female sex (hazard ratio [HR] 0.83, 95% CI 0.74-0.92)
    - stage III disease (HR 0.75, 95% CI 0.68-0.82)
    - good performance status (HR 0.56, 95% CI 0.49-0.63)
  + PubMed20332134Annals of oncology : official journal of the European Society for Medical OncologyAnn Oncol2010100121102023-82023Reference - [Ann Oncol 2010 Oct;21(10):2023](http://pubmed.ncbi.nlm.nih.gov/20332134)
* **immune checkpoint inhibitors associated with improved overall survival in patients with advanced or metastatic cancers including non-small cell lung cancer, but efficacy appears lower in female persons compared to male persons (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[Lancet Oncol 2018 Jun;19(6):737](http://pubmed.ncbi.nlm.nih.gov/29778737)

studySummary

* + Systematic Review based on systematic review limited by clinical heterogeneity
  + systematic review of 20 randomized trials evaluating efficacy of immune checkpoint inhibitors in 11,351 patients with advanced or metastatic disease
  + 3,705 patients (33%) were female persons
  + 3,482 patients (31%) had non-small cell lung cancer and 3,632 (32%) had melanoma; other cancers included small-cell lung cancer, mesothelioma, head and neck cancer, renal cell carcinoma, urothelial tumors, and gastric tumors
  + immune checkpoint inhibitors included PD-1 inhibitors (nivolumab or pembrolizumab), CTLA-4 inhibitors (ipilimumab or tremelimumab), and PD-1 plus CTLA-4 (ipilimumab plus nivolumab)
  + compared to other treatments, immune checkpoint inhibitors associated with improved overall survival
    - for all cancers in analysis of all trials
      * in female persons (hazard ratio [HR] 0.86, 95% CI 0.79-0.93)
      * in male persons (HR 0.72, 95% CI 0.65-0.79), results limited by significant heterogeneity
    - for non-small cell lung cancer in analysis of 6 trials
      * in female persons (HR 0.89, 95% CI 0.71-1.11)
      * in male persons (HR 0.72, 95% CI 0.61-0.86)
  + immune checkpoint inhibitors associated with increased efficacy in male persons compared to female persons (HR 0.85, 95% CI 0.77-0.94)
  + PubMed29778737The Lancet. OncologyLancet Oncol20180601196737-746737Reference - [Lancet Oncol 2018 Jun;19(6):737](http://pubmed.ncbi.nlm.nih.gov/29778737), editorial can be found in [Lancet Oncol 2018 Jun;19(6):716](http://pubmed.ncbi.nlm.nih.gov/29778735), commentaries can be found in [Eur Urol 2018 Dec;74(6):e139](http://pubmed.ncbi.nlm.nih.gov/30031571" \t "_blank), [Transl Lung Cancer Res 2018 Sep;7(Suppl 3):S211](http://pubmed.ncbi.nlm.nih.gov/30393604" \t "_blank)
* **use of hormone therapy does not appear to increase survival in female persons with lung cancer (**[**level 2 [mid-level] evidence**](https://www.dynamed.com/home/editorial/editorial-process)**)**

Systematic Review[Steroids 2017 Feb;118:47](http://pubmed.ncbi.nlm.nih.gov/27964943)

studySummary

* + Systematic Review based on systematic review limited by heterogeneity
  + systematic review of 8 cohort studies and 3 post-hoc analyses of randomized trials evaluating hormone therapy and lung cancer mortality in female persons with lung cancer
  + no significant difference in lung cancer mortality with hormone therapy in analysis of all trials, results limited by heterogeneity
    - no significant difference with estrogen therapy
    - no significant difference with estrogen plus progesterone therapy
  + PubMed27964943SteroidsSteroids2017020111847-5447Reference - [Steroids 2017 Feb;118:47](http://pubmed.ncbi.nlm.nih.gov/27964943)

## **Guidelines and Resources**

GuidelinesGuidelines

### **Guidelines**

#### **International Guidelines**

* College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology (CAP/IASLC/AMP) updated guideline on molecular testing for selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors can be found in [29355391Arch Pathol Lab Med 2018 Mar;142(3):321](http://pubmed.ncbi.nlm.nih.gov/29355391?dopt=Abstract)[full-text](http://www.archivesofpathology.org/doi/10.5858/arpa.2017-0388-CP).
* American Thoracic Society/European Respiratory Society (ATS/ERS) statement on role of pulmonologist in diagnosis and management of lung cancer can be found in [23947517Am J Respir Crit Care Med 2013 Aug 15;188(4):503](http://pubmed.ncbi.nlm.nih.gov/23947517?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5448508/).
* International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) international multidisciplinary classification of lung adenocarcinoma can be found in [21252716J Thorac Oncol 2011 Feb;6(2):244](http://pubmed.ncbi.nlm.nih.gov/21252716?dopt=Abstract), executive summary can be found in [21926387Proc Am Thorac Soc 2011 Sep;8(5):381](http://pubmed.ncbi.nlm.nih.gov/21926387?dopt=Abstract), editorial can be found in [21252714J Thorac Oncol 2011 Feb;6(2):239](http://pubmed.ncbi.nlm.nih.gov/21252714?dopt=Abstract), commentary can be found in [21847046J Thorac Oncol 2011 Jul;6(7):1298](http://pubmed.ncbi.nlm.nih.gov/21847046?dopt=Abstract), [21847068J Thorac Oncol 2011 Aug;6(8):1451](http://pubmed.ncbi.nlm.nih.gov/21847068?dopt=Abstract).
* Society for Immunotherapy (SITC) consensus statement on immunotherapy for treatment of non-small cell lung cancer can be found in [J Immunother Cancer 2018 Jul 17;6(1):75](http://pubmed.ncbi.nlm.nih.gov/30012210?dopt=Abstract)[full-text](https://jitc.biomedcentral.com/articles/10.1186/s40425-018-0382-2).
* INTERNATIONAL\_GUIDELINES\_\_LI\_W14\_YYB\_PXBGNU05262305/26/2023 09:28:21 AMguidelineNotationUpdatelowOncologic\_DiseaseAmerican Society for Radiation Oncology/European Society for Radiotherapy and Oncology (ASTRO/ESTRO) guideline on treatment of oligometastatic non-small cell lung cancer (ASTRO/ESTRO 2023 Apr)American Society for Radiation Oncology/European Society for Radiotherapy and Oncology (ASTRO/ESTRO) guideline on treatment of oligometastatic non-small cell lung cancer can be found at [ASTRO/ESTRO 2023 Apr](https://www.astro.org/Patient-Care-and-Research/Clinical-Practice-Statements/Clinical-Practice-Guidelines/Oligometastatic-NSCLC).

#### **United States Guidelines**

* UNITES\_STATES\_GUIDELINES\_\_LI\_K4C\_PDD\_5XBGNU061323\_106/13/2023 10:23:57 AMguidelineNotationUpdatelowOncologic\_DiseaseNational Comprehensive Cancer Network (NCCN) statement on mitigating the impacts of anticancer drug shortages (NCCN 2023 Jun 7)National Comprehensive Cancer Network (NCCN) statement on mitigating the impacts of anticancer drug shortages can be found at [NCCN 2023 Jun 7 PDF](https://www.nccn.org/docs/default-source/oncology-policy-program/NCCN-Statement-on-Anti-Cancer-Drug-Shortages.pdf).
* National Comprehensive Cancer Network (NCCN) guidelines on:
  + Non-small cell lung cancer can be found at [NCCN website](http://www.nccn.org/professionals/physician_gls/) (free registration required).
  + Lung cancer screening can be found at [NCCN website](http://www.nccn.org/professionals/physician_gls/) (free registration required).
  + Smoking cessation for patients with cancer can be found at [NCCN website](http://www.nccn.org/professionals/physician_gls/) (free registration required).
* American College of Chest Physicians (ACCP):
  + Executive summary of ACCP evidence-based clinical practice guidelines on diagnosis and management of lung cancer can be found in [23649434Chest 2013 May;143(5 Suppl):7S](http://pubmed.ncbi.nlm.nih.gov/23649434?dopt=Abstract).
  + Evidence-based clinical practice guidelines on:
    - Chemoprevention of lung cancer can be found in [23649449Chest 2013 May;143(5 Suppl):e40S](http://pubmed.ncbi.nlm.nih.gov/23649449?dopt=Abstract).
    - Treatment of tobacco use in lung cancer can be found at [23649454Chest 2013 May;143(5 Suppl):e61S](http://pubmed.ncbi.nlm.nih.gov/23649454?dopt=Abstract).
    - Screening for lung cancer can be found in [23649455Chest 2013 May;143(5 Suppl):e78S](http://pubmed.ncbi.nlm.nih.gov/23649455?dopt=Abstract).
    - Evaluation of individuals with pulmonary nodules can be found in [23649456Chest 2013 May;143(5 Suppl):e93S](http://pubmed.ncbi.nlm.nih.gov/23649456?dopt=Abstract).
    - Clinical and organizational factors in initial evaluation of patients with lung cancer can be found in [23649435Chest 2013 May;143(5 Suppl):e121S](http://pubmed.ncbi.nlm.nih.gov/23649435?dopt=Abstract).
    - Establishing diagnosis of lung cancer can be found in [23649436Chest 2013 May;143(5 Suppl):e142S](http://pubmed.ncbi.nlm.nih.gov/23649436?dopt=Abstract).
    - Physiologic evaluation of patient with lung cancer being considered for resectional surgery can be found in [23649437Chest 2013 May;143(5 Suppl):e166S](http://pubmed.ncbi.nlm.nih.gov/23649437?dopt=Abstract).
    - Methods for staging non-small cell lung cancer can be found in [23649440Chest 2013 May;143(5 Suppl):e211S](http://pubmed.ncbi.nlm.nih.gov/23649440?dopt=Abstract).
    - Diagnostic surgical pathology in lung cancer can be found in [23649441Chest 2013 May;143(5 Suppl):e251S](http://pubmed.ncbi.nlm.nih.gov/23649441?dopt=Abstract).
    - Diagnosis and treatment of bronchial intraepithelial neoplasia and early lung cancer of central airways can be found in [23649442Chest 2013 May;143(5 Suppl):e263S](http://pubmed.ncbi.nlm.nih.gov/23649442?dopt=Abstract).
    - Treatment of stage I and II non-small cell lung cancer can be found in [23649443Chest 2013 May;143(5 Suppl):e278S](http://pubmed.ncbi.nlm.nih.gov/23649443?dopt=Abstract).
    - Treatment of stage III non-small cell lung cancer can be found in [23649445Chest 2013 May;143(5 Suppl):e314S](http://pubmed.ncbi.nlm.nih.gov/23649445?dopt=Abstract).
    - Treatment of stage IV non-small cell lung cancer can be found in [23649446Chest 2013 May;143(5 Suppl):e341S](http://pubmed.ncbi.nlm.nih.gov/23649446?dopt=Abstract).
    - Special treatment issues in non-small cell lung cancer can be found in [23649447Chest 2013 May;143(5 Suppl):e369S](http://pubmed.ncbi.nlm.nih.gov/23649447?dopt=Abstract).
    - Complementary therapies and integrative medicine in lung cancer can be found in [23649450Chest 2013 May;143(5 Suppl):e420S](http://pubmed.ncbi.nlm.nih.gov/23649450?dopt=Abstract).
    - Follow-up and surveillance of patient with lung cancer after curative-intent therapy can be found in [23649451Chest 2013 May;143(5 Suppl):e437S](http://pubmed.ncbi.nlm.nih.gov/23649451?dopt=Abstract).
    - Symptom management in patients with lung cancer can be found at [23649452Chest 2013 May;143(5 Suppl):e455S](http://pubmed.ncbi.nlm.nih.gov/23649452?dopt=Abstract).
    - Palliative and end-of-life care in lung cancer can be found in [23649453Chest 2013 May;143(5 Suppl):e498S](http://pubmed.ncbi.nlm.nih.gov/23649453?dopt=Abstract).
    - Symptomatic treatment of cough among adult patients with lung cancer can be found in [Chest 2017 Apr;151(4):861](http://pubmed.ncbi.nlm.nih.gov/28108179?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6026217/).
* UNITES\_STATES\_GUIDELINES\_\_LI\_BW2\_ZN5\_CWBGNU01092301/09/2023 11:12:00 AMguidelineNotationUpdatelowOncologic\_DiseaseAmerican Thoracic Society (ATS) guideline on stakeholder research priorities to promote implementation of shared decision-making for lung cancer screening (Am J Respir Crit Care Med 2022 Mar 15)American Thoracic Society (ATS) guideline on stakeholder research priorities to promote implementation of shared decision-making for lung cancer screening can be found in [Am J Respir Crit Care Med 2022 Mar 15;205(6):619](https://pubmed.ncbi.nlm.nih.gov/35289730).
* American College of Chest Physicians/Society of Thoracic Surgeons (ACCP/STS) consensus statement on evaluation and management for high-risk patients with stage I non-small cell lung cancer can be found in [23208335Chest 2012 Dec;142(6):1620](http://pubmed.ncbi.nlm.nih.gov/23208335?dopt=Abstract).
* American College of Radiology (ACR) Appropriateness Criteria for:
  + UNITES\_STATES\_GUIDELINES\_\_LI\_CZM\_N4J\_3XBGNU05022305/02/2023 09:52:52 AMguidelineNotationUpdatelowOncologic\_DiseaseAmerican College of Radiology (ACR) Appropriateness Criteria for incidentally detected indeterminate pulmonary nodule (ACR 2023)Incidentally detected indeterminate pulmonary nodule can be found at [ACR 2023 PDF](https://acsearch.acr.org/docs/69455/Narrative).
  + Nonsurgical treatment for locally advanced non-small cell lung cancer: good performance status/definitive intent can be found at [ACR 2014 PDF](https://acsearch.acr.org/docs/69394/Narrative/).
  + Early-stage non-small-cell lung cancer can be found at [ACR 2013 PDF](https://acsearch.acr.org/docs/3082798/Narrative/).
  + Induction and adjuvant therapy for N2 non-small-cell lung cancer can be found at [ACR 2013 PDF](https://acsearch.acr.org/docs/69393/Narrative/).
  + Nonsurgical treatment for non-small cell lung: poor performance status or palliative intent can be found at [ACR 2012 PDF](https://acsearch.acr.org/docs/69349/Narrative/).
  + Noninvasive clinical staging of bronchogenic carcinoma can be found at [ACR 2013 PDF](https://acsearch.acr.org/docs/69456/Narrative).
  + Metastatic bone disease can be found at [ACR 2012 PDF](https://acsearch.acr.org/docs/69431/Narrative/).
  + Nonspine bone metastases can be found at [ACR 2014 PDF](https://acsearch.acr.org/docs/69354/Narrative/).
  + Hemoptysis can be found at [ACR 2014 PDF](https://acsearch.acr.org/docs/69449/Narrative/).
* American Society for Radiation Oncology (ASTRO):
  + Guideline on stereotactic body radiotherapy for early-stage non-small cell lung cancer can be found in [28596092Pract Radiat Oncol 2017 Sep - Oct;7(5):295](http://pubmed.ncbi.nlm.nih.gov/28596092?dopt=Abstract).
  + Evidence-based clinical practice guideline on palliative thoracic radiotherapy in lung cancer can be found in [25740118Pract Radiat Oncol 2011 Apr-Jun;1(2):60](http://pubmed.ncbi.nlm.nih.gov/25740118?dopt=Abstract)[full-text](http://www.sciencedirect.com/science/article/pii/S1879850011000919).
* ASTRO/ACR practice parameter on performance of stereotactic body radiation therapy can be found at [ACR 2014 Jun PDF](https://www.acr.org/-/media/ACR/Files/Practice-Parameters/sbrt-ro.pdf).
* UNITES\_STATES\_GUIDELINES\_\_LI\_D1K\_12D\_5XBGNU061323\_106/13/2023 10:27:54 AMguidelineNotationUpdatelowOncologic\_DiseaseASCO position on prioritization of antineoplastic agents in limited supply for first intervention (ASCO 2023 Jun 13)American Society of Clinical Oncology (ASCO) position on prioritization of antineoplastic agents in limited supply for first intervention can be found at [ASCO](https://old-prod.asco.org/practice-patients/practice-support/drug-shortages/clinical-guidance), accessed 2023 Jun 13.
* American Society of Clinical Oncology (ASCO):
  + Clinical practice guidelines:
    - UNITES\_STATES\_GUIDELINES\_\_LI\_C2T\_ZVD\_51CGNU03182403/18/2024 09:55:06 AMguidelineNotationUpdatelowOncologic\_DiseaseAmerican Society of Clinical Oncology (ASCO) guideline on therapy for stage IV non-small cell lung cancer with driver alterations (J Clin Oncol 2024 Feb 28) on therapy for stage IV non-small cell lung cancer with driver alterations can be found in [38417091J Clin Oncol 2024 Feb 28;:JCO2302744](http://pubmed.ncbi.nlm.nih.gov/38417091?dopt=Abstract).
    - UNITES\_STATES\_GUIDELINES\_\_LI\_PVD\_TWD\_51CGNU03182403/18/2024 10:01:03 AMguidelineNotationUpdatelowOncologic\_DiseaseAmerican Society of Clinical Oncology (ASCO) guideline on therapy for stage IV non-small cell lung cancer without driver alterations (J Clin Oncol 2024 Feb 28)on therapy for stage IV non-small cell lung cancer without driver alterations can be found in [38417098J Clin Oncol 2024 Feb 28;:JCO2302746](http://pubmed.ncbi.nlm.nih.gov/38417098?dopt=Abstract).
    - PubMed34936470Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol20211222JCO2102528JCO2102528On management of stage III non-small-cell lung cancer can be found at [ASCO 2023 Jun](https://old-prod.asco.org/practice-patients/guidelines/thoracic-cancer#/168762).
    - UNITES\_STATES\_GUIDELINES\_\_LI\_HNJ\_MSF\_HSBGNU01182201/18/2022 11:05:00 AMguidelineNotationUpdatelowOncologic\_DiseaseASCO guideline on adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIA resectable non-small-cell lung cancers can be found at (ASCO 2022 Jan)On adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIA resectable non-small-cell lung cancers can be found at [ASCO 2022 Jan](https://www.asco.org/practice-patients/guidelines/thoracic-cancer#/10226).
    - Update on systemic therapy for stage IV non-small cell lung cancer can be found in [cxh125742193pmdc28806116pJ Clin Oncol 2017 Oct 20;35(30):3484](http://pubmed.ncbi.nlm.nih.gov/28806116?dopt=Abstract), summary can be found in [J Oncol Pract 2017 Dec;13(12):832](http://pubmed.ncbi.nlm.nih.gov/28850309?dopt=Abstract).
  + Endorsement of ASTRO evidence-based guideline on stereotactic body radiotherapy for early-stage non-small cell lung cancer can be found in [J Clin Oncol 2018 Mar 1;36(7):710](http://pubmed.ncbi.nlm.nih.gov/29106810?dopt=Abstract).
* PubMed33591844Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol202103203991040-10911040ASCO/Cancer Care Ontario (CCO) joint guideline update on therapy for stage IV non-small cell lung cancer with driver alterations can be found in [J Clin Oncol 2021 Mar 20;39(9):1040](http://pubmed.ncbi.nlm.nih.gov/33591844).
* American Society for Gastrointestinal Endoscopy (ASGE) guideline on role of endoscopic ultrasound (EUS) for evaluation of mediastinal adenopathy can be found in [21802583Gastrointest Endosc 2011 Aug;74(2):239](http://pubmed.ncbi.nlm.nih.gov/21802583?dopt=Abstract).
* United States Public Health Service (USPHS) clinical practice guideline on treating tobacco use and dependence can be found at [USPHS 2008 May](https://www.ncbi.nlm.nih.gov/books/NBK63952/)[PDF](https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08.pdf) or in [Spanish](https://www.ncbi.nlm.nih.gov/books/NBK47499/" \t "_blank)[PDF](https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08_sp.pdf).
* American Cancer Society (ACS):
  + Guideline on nutrition and physical activity for cancer prevention can be found in [CA Cancer J Clin 2020 Jul;70(4):245](http://pubmed.ncbi.nlm.nih.gov/32515498)[full-text](https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21591).
  + Guideline on nutrition and physical activity for cancer survivors can be found in [22539238CA Cancer J Clin 2012 Jul;62(4):242](http://pubmed.ncbi.nlm.nih.gov/22539238?dopt=Abstract)[full-text](http://onlinelibrary.wiley.com/doi/10.3322/caac.21142/full), correction can be found in CA Cancer J Clin 2013 May;63(3):215.
  + Review of guidelines and issues in cancer screening can be found in [mnh25581023pcxh100399216t pmdc25581023pCA Cancer J Clin 2015 Jan-Feb;65(1):30](http://pubmed.ncbi.nlm.nih.gov/25581023?dopt=Abstract)[full-text](http://onlinelibrary.wiley.com/doi/10.3322/caac.21261/full).
* American Association for Thoracic Surgery (AATS) guideline on lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups can be found in [22710039J Thorac Cardiovasc Surg 2012 Jul;144(1):33](http://pubmed.ncbi.nlm.nih.gov/22710039?dopt=Abstract)[full-text](http://www.sciencedirect.com/science/article/pii/S0022522312006009?via%3Dihub).
* United States Public Health Service (USPHS) clinical practice guideline on treating tobacco use and dependence can be found at [USPHS 2008 May](https://www.ncbi.nlm.nih.gov/books/NBK63952/)[PDF](https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08.pdf) or in [Spanish](https://www.ncbi.nlm.nih.gov/books/NBK47499/" \t "_blank)[PDF](https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08_sp.pdf).
* UNITES\_STATES\_GUIDELINES\_\_LI\_E3K\_RBM\_3BCGNU05082405/08/2024 02:23:14 PMguidelineNotationUpdatelowOncologic\_DiseaseCollege of American Pathologists (CAP) guideline on PD-L1 and TMB testing of patients with lung cancer for immunooncology therapies (CAP 2024 Apr 16)College of American Pathologists (CAP) guideline on PD-L1 and TMB testing of patients with lung cancer for immunooncology therapies can be found at [CAP 2024 Apr 16](https://www.cap.org/protocols-and-guidelines/current-cap-guidelines/pd-l1-testing-of-patients-with-lung-cancer-for-immunooncology-therapies).

#### **United Kingdom Guidelines**

* National Institute for Health and Care Excellence (NICE):
  + UNITED\_KINGDOM\_GUIDELINES\_\_LI\_I35\_52Q\_P5BGNU08222208/22/2022 11:14:33 AMguidelineNotationUpdatelowOncologic\_DiseaseNational Institute for Health and Care Excellence (NICE) guideline on diagnosis and management of lung cancer (NICE 2024 Mar 8)Guideline on diagnosis and management of lung cancer can be found at [NICE 2019 Mar 28:NG122, last updated 2024 Mar 8](https://www.nice.org.uk/guidance/ng122)[PDF](https://www.nice.org.uk/guidance/ng122/resources/lung-cancer-diagnosis-and-management-pdf-66141655525573).
  + Oncologic\_DiseaseNICE guideline on recognition and referral of suspected cancer (NICE 2015 Jun 23)11/04/2015 01:07:00 PMGuideline on recognition and referral of suspected cancer can be found at [NICE 2015 Jun 23:NG12, last updated 2021 Dec 15](http://www.nice.org.uk/guidance/ng12)[PDF](http://www.nice.org.uk/guidance/ng12/resources/suspected-cancer-recognition-and-referral-1837268071621).
  + Specific NICE guidelines on:
    - Selpercatinib for untreated RET fusion-positive advanced non-small cell lung cancer can be found at [NICE 2023 Jul 26:TA911](https://www.nice.org.uk/guidance/ta911)[PDF](https://www.nice.org.uk/guidance/ta911/resources/selpercatinib-for-untreated-ret-fusionpositive-advanced-nonsmallcell-lung-cancer-pdf-82615482098629).
    - Lorlatinib for untreated ALK-positive advanced non-small cell lung cancer can be found at [NICE 2023 Jul 12:TA909](https://www.nice.org.uk/guidance/ta909)[PDF](https://www.nice.org.uk/guidance/ta909/resources/lorlatinib-for-untreated-alkpositive-advanced-nonsmallcell-lung-cancer-pdf-82615435069381).
    - AI-derived computer-aided detection (CAD) software for detecting and measuring lung nodules in CT scan images can be found at [NICE 2023 Jul 5:DG55](https://www.nice.org.uk/guidance/dg55)[PDF](https://www.nice.org.uk/guidance/dg55/resources/aiderived-computeraided-detection-cad-software-for-detecting-and-measuring-lung-nodules-in-ct-scan-images-pdf-1053873334213).
    - Dabrafenib plus trametinib for treating BRAF V600 mutation-positive advanced non-small cell lung cancer can be found at [NICE 2023 Jun 14:TA898](https://www.nice.org.uk/guidance/ta898)[PDF](https://www.nice.org.uk/guidance/ta898/resources/dabrafenib-plus-trametinib-for-treating-braf-v600-mutationpositive-advanced-nonsmallcell-lung-cancer-pdf-82613800803013).
    - Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small cell lung cancer can be found at [NICE 2023 Mar 22:TA876](https://www.nice.org.uk/guidance/ta876)[PDF](https://www.nice.org.uk/guidance/ta876/resources/nivolumab-with-chemotherapy-for-neoadjuvant-treatment-of-resectable-nonsmallcell-lung-cancer-pdf-82613676511429).
    - Mobocertinib for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy can be found at [NICE 2023 Jan 4:TA855](https://www.nice.org.uk/guidance/ta855)[PDF](https://www.nice.org.uk/guidance/ta855/resources/mobocertinib-for-treating-egfr-exon-20-insertion-mutationpositive-advanced-nonsmallcell-lung-cancer-after-platinumbased-chemotherapy-pdf-82613553899461).
    - Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy can be found at [NICE 2022 Dec 14:TA850](https://www.nice.org.uk/guidance/ta850)[PDF](https://www.nice.org.uk/guidance/ta850/resources/amivantamab-for-treating-egfr-exon-20-insertion-mutationpositive-advanced-nonsmallcell-lung-cancer-after-platinumbased-chemotherapy-pdf-82613545501381).
    - Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer can be found at [NICE 2022 Sept 28:TA823](https://www.nice.org.uk/guidance/ta823)[PDF](https://www.nice.org.uk/guidance/ta823/resources/atezolizumab-for-adjuvant-treatment-of-resected-nonsmallcell-lung-cancer-pdf-82613369141701).
    - Pralsetinib for treating RET fusion-positive advanced non-small cell lung cancer can be found at [NICE 2022 Aug 3:TA812](https://www.nice.org.uk/guidance/ta812)[PDF](https://www.nice.org.uk/guidance/ta812/resources/pralsetinib-for-treating-ret-fusionpositive-advanced-nonsmallcell-lung-cancer-pdf-82613306995909).
    - UNITED\_KINGDOM\_GUIDELINES\_\_LI\_R41\_Q2R\_BTBGNU04012204/01/2022 02:07:30 PMguidelineNotationUpdatelowOncologic\_DiseaseNational Institute for Health and Care Excellence (NICE) guideline on sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (NICE 2022 Mar 30)Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer can be found at [NICE 2022 Mar 30:TA781](https://www.nice.org.uk/guidance/ta781)[PDF](https://www.nice.org.uk/guidance/ta781/resources/sotorasib-for-previously-treated-kras-g12c-mutationpositive-advanced-nonsmallcell-lung-cancer-pdf-82611551797189).
    - UNITED\_KINGDOM\_GUIDELINES\_\_LI\_RSX\_CL5\_VSBGNU03112203/11/2022 12:59:28 PMguidelineNotationUpdatelowOncologic\_DiseaseNational Institute for Health and Care Excellence (NICE) guideline on pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (NICE 2022 Feb 9)Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer can be found at [NICE 2022 Feb 9:TA770](https://www.nice.org.uk/guidance/ta770)[PDF](https://www.nice.org.uk/guidance/ta770/resources/pembrolizumab-with-carboplatin-and-paclitaxel-for-untreated-metastatic-squamous-nonsmallcell-lung-cancer-pdf-82611489651397).
    - UNITED\_KINGDOM\_GUIDELINES\_\_LI\_TBS\_PSZ\_SSBGNU03012203/01/2022 01:00:57 PMguidelineNotationUpdatelowOncologic\_DiseaseNational Institute for Health and Care Excellence guideline on microwave ablation for primary or metastatic cancer in the lung (NICE 2022 Feb 2:IPG716)Microwave ablation for primary or metastatic cancer in the lung can be found at [NICE 2022 Feb 2:IPG716](https://www.nice.org.uk/guidance/ipg716)[PDF](https://www.nice.org.uk/guidance/ipg716/resources/microwave-ablation-for-primary-or-metastatic-cancer-in-the-lung-pdf-1899876102318277).
    - Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection can be found at [NICE 2022 Jan 19:TA761](https://www.nice.org.uk/guidance/ta761)[PDF](https://www.nice.org.uk/guidance/ta761/resources/osimertinib-for-adjuvant-treatment-of-egfr-mutationpositive-nonsmallcell-lung-cancer-after-complete-tumour-resection-pdf-82611430864837).
    - Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer can be found at [NICE 2022 Jan 12:TA760](https://www.nice.org.uk/guidance/ta760)[PDF](https://www.nice.org.uk/guidance/ta760/resources/selpercatinib-for-previously-treated-ret-fusionpositive-advanced-nonsmallcell-lung-cancer-pdf-82611429185221).
    - Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer can be found at [NICE 2021 Sep 8:TA724](https://www.nice.org.uk/guidance/ta724)[PDF](https://www.nice.org.uk/guidance/ta724/resources/nivolumab-with-ipilimumab-and-chemotherapy-for-untreated-metastatic-nonsmallcell-lung-cancer-pdf-82611194038981).
    - Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer can be found at [NICE 2021 Jun 2:TA705](https://www.nice.org.uk/guidance/ta705)[PDF](https://www.nice.org.uk/guidance/ta705/resources/atezolizumab-monotherapy-for-untreated-advanced-nonsmallcell-lung-cancer-pdf-82611074786245).
    - Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer can be found at [NICE 2021 Mar 10:TA683](https://www.nice.org.uk/guidance/ta683)[PDF](https://www.nice.org.uk/guidance/ta683/resources/pembrolizumab-with-pemetrexed-and-platinum-chemotherapy-for-untreated-metastatic-nonsquamous-nonsmallcell-lung-cancer-pdf-82609378374085).
    - Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor can be found at [NICE 2021 Jan 27:TA670](https://www.nice.org.uk/guidance/ta670)[PDF](https://www.nice.org.uk/guidance/ta670/resources/brigatinib-for-alkpositive-advanced-nonsmallcell-lung-cancer-that-has-not-been-previously-treated-with-an-alk-inhibitor-pdf-82609312869061).
    - Nivolumab for advanced non-squamous non-small-cell cancer after chemotherapy can be found at [NICE 2021 Jul 7:TA713](https://www.nice.org.uk/guidance/ta713)[PDF](https://www.nice.org.uk/guidance/ta713/resources/nivolumab-for-advanced-nonsquamous-nonsmallcell-lung-cancer-after-chemotherapy-pdf-82611131893189).
    - Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy can be found at [NICE 2020 Oct 21:TA655](https://www.nice.org.uk/guidance/ta655)[PDF](https://www.nice.org.uk/guidance/ta655/resources/nivolumab-for-advanced-squamous-nonsmallcell-lung-cancer-after-chemotherapy-pdf-82609200334789).
    - Durvalumab for treating locally advanced unresectable non-small cell lung cancer after platinum-based chemoradiation can be found at [NICE 2019 May 1:TA578](https://www.nice.org.uk/guidance/ta578)[PDF](https://www.nice.org.uk/guidance/ta578/resources/durvalumab-for-treating-locally-advanced-unresectable-nonsmallcell-lung-cancer-after-platinumbased-chemoradiation-pdf-82607149523653).
    - Guideline on osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer can be found at [NICE 2020 Jan 22:TA621](https://www.nice.org.uk/guidance/ta621)[PDF](https://www.nice.org.uk/guidance/ta621/resources/osimertinib-for-untreated-egfr-mutationpositive-nonsmallcell-lung-cancer-pdf-82609012217797).
    - Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small cell lung cancer can be found at [NICE 2019 Sep 11:TA600](https://www.nice.org.uk/guidance/ta600)[PDF](https://www.nice.org.uk/guidance/ta600/resources/pembrolizumab-with-carboplatin-and-paclitaxel-for-untreated-metastatic-squamous-nonsmallcell-lung-cancer-pdf-82608889605829).
    - Pembrolizumab for untreated PD-L1 positive metastatic non-small cell lung cancer can be found at [NICE 2018 Jul 18:TA531](https://www.nice.org.uk/guidance/ta531)[PDF](https://www.nice.org.uk/guidance/ta531/resources/pembrolizumab-for-untreated-pdl1positive-metastatic-nonsmallcell-lung-cancer-pdf-82606895901637).
    - Pembrolizumab for treating PD-L1 positive non-small cell lung cancer in adults who have had chemotherapy [NICE 2017 Jan 11:TA428](https://www.nice.org.uk/guidance/ta428/)[PDF](https://www.nice.org.uk/guidance/ta428/resources/pembrolizumab-for-treating-pdl1positive-nonsmallcell-lung-cancer-after-chemotherapy-pdf-82604670410437).
    - Nivolumab for previously treated non-squamous non-small cell lung cancer can be found at [NICE 2017 Nov 1:TA484](https://www.nice.org.uk/guidance/ta484)[PDF](https://www.nice.org.uk/guidance/ta484/resources/nivolumab-for-previously-treated-nonsquamous-nonsmallcell-lung-cancer-pdf-82605026489029).
    - Nivolumab for previously treated squamous non-small-cell lung cancer can be found at [NICE 2017 Nov 1:TA483](https://www.nice.org.uk/guidance/ta483)[PDF](https://www.nice.org.uk/guidance/ta483/resources/nivolumab-for-previously-treated-squamous-nonsmallcell-lung-cancer-pdf-82605024809413).
    - Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy can be found at [NICE 2018 May 16:TA520](https://www.nice.org.uk/guidance/ta520)[PDF](https://www.nice.org.uk/guidance/ta520/resources/atezolizumab-for-treating-locally-advanced-or-metastatic-nonsmallcell-lung-cancer-after-chemotherapy-pdf-82606833755845).
    - Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer can be found at [NICE 2019 Jun 5:TA584](https://www.nice.org.uk/guidance/ta584).
    - Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer [NICE 2016 Oct 26:TA416](https://www.nice.org.uk/guidance/ta416)[PDF](https://www.nice.org.uk/guidance/ta416/resources/osimertinib-for-treating-locally-advanced-or-metastatic-egfr-t790m-mutationpositive-nonsmallcell-lung-cancer-82604606585029).
    - Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small cell lung cancer can be found at [NICE 2014 Apr 23:TA310](http://www.nice.org.uk/guidance/TA310)[PDF](http://www.nice.org.uk/guidance/ta310/resources/afatinib-for-treating-epidermal-growth-factor-receptor-mutationpositive-locally-advanced-or-metastatic-nonsmallcell-lung-cancer-82602419724997).
    - Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy can be found at [NICE 2015 Dec 16:TA374](https://www.nice.org.uk/guidance/ta374)[PDF](https://www.nice.org.uk/guidance/ta374/resources/erlotinib-and-gefitinib-for-treating-nonsmallcell-lung-cancer-that-has-progressed-after-prior-chemotherapy-82602789240517).
    - Alectinib for untreated ALK-positive advanced non-small cell lung cancer can be found at [NICE 2018 Aug 8:TA536](https://www.nice.org.uk/guidance/ta536).
    - Ceritinib for second-line treatment of ALK-positive non-small cell lung cancer can be found at [NICE 2016 Jun 22:TA395](https://www.nice.org.uk/guidance/ta395)[PDF](https://www.nice.org.uk/guidance/ta395/resources/ceritinib-for-previously-treated-anaplastic-lymphoma-kinase-positive-nonsmallcell-lung-cancer-82602911852485).
    - Crizotinib for untreated ALK-positive advanced non-small cell lung cancer can be found at [NICE 2016 Sep 28:TA406](https://www.nice.org.uk/guidance/ta406)[PDF](https://www.nice.org.uk/guidance/ta406/resources/crizotinib-for-untreated-anaplastic-lymphoma-kinasepositive-advanced-nonsmallcell-lung-cancer-82604546118853).
    - Crizotinib for previously treated ALK-positive advanced non-small-cell lung cancer can be found at [NICE 2016 Dec 21:TA422](https://www.nice.org.uk/guidance/ta422)[PDF](https://www.nice.org.uk/guidance/ta422/resources/crizotinib-for-previously-treated-anaplastic-lymphoma-kinasepositive-advanced-nonsmallcell-lung-cancer-pdf-82604660332741).
    - Crizotinib for treating ROS1-positive advanced non-small cell lung cancer can be found at [NICE 2018 Jul 4:TA529](https://www.nice.org.uk/guidance/ta529)[PDF](https://www.nice.org.uk/guidance/ta529/resources/crizotinib-for-treating-ros1positive-advanced-nonsmallcell-lung-cancer-pdf-82606848872389).
    - Entrectinib for treating ROS1-positive advanced non-small cell lung cancer can be found at [NICE 2020 Aug 12:TA643](https://www.nice.org.uk/guidance/ta643)[PDF](https://www.nice.org.uk/guidance/ta643/resources/entrectinib-for-treating-ros1positive-advanced-nonsmallcell-lung-cancer-pdf-82609136509381).
    - Necitumumab for untreated advanced or metastatic squamous non-small cell lung cancer can be found at [NICE 2016 Sep 28:TA411](https://www.nice.org.uk/guidance/ta411)[PDF](https://www.nice.org.uk/guidance/ta411/resources/necitumumab-for-untreated-advanced-or-metastatic-squamous-nonsmallcell-lung-cancer-82604598186949).
    - Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small cell lung cancer can be found at [NICE 2015 Jul 22:TA347](http://www.nice.org.uk/guidance/ta347)[PDF](http://www.nice.org.uk/guidance/ta347/resources/nintedanib-for-previously-treated-locally-advanced-metastatic-or-locally-recurrent-nonsmallcell-lung-cancer-82602612880837).
    - Ramucirumab for second-line therapy of locally advanced or metastatic non-small cell lung cancer can be found at [NICE 2016 Aug 24:TA403](https://www.nice.org.uk/guidance/ta403)[PDF](https://www.nice.org.uk/guidance/ta403/resources/ramucirumab-for-previously-treated-locally-advanced-or-metastatic-nonsmallcell-lung-cancer-82604541080005).
    - Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin can be found at [NICE 2016 Aug 24:TA402](https://www.nice.org.uk/guidance/ta402)[PDF](https://www.nice.org.uk/guidance/ta402/resources/pemetrexed-maintenance-treatment-for-nonsquamous-nonsmallcell-lung-cancer-after-pemetrexed-and-cisplatin-82604539400389).
* Scottish Intercollegiate Guidelines Network (SIGN) national clinical guideline on management of lung cancer can be found at [SIGN 2014 Feb PDF](http://www.sign.ac.uk/assets/sign137.pdf).
* British Thoracic Society (BTS) guidelines on:
  + Diagnostic flexible bronchoscopy in adults: accredited by the National institute for Health and Care Excellence (NICE) can be found in [23860341Thorax 2013 Aug;68 Suppl 1:i1](http://pubmed.ncbi.nlm.nih.gov/23860341?dopt=Abstract).
  + Advanced diagnostic and therapeutic flexible bronchoscopy in adults can be found in [21987439Thorax 2011 Nov;66 Suppl 3:iii1](http://pubmed.ncbi.nlm.nih.gov/21987439?dopt=Abstract), summary can be found in [22003155Thorax 2011 Nov;66(11):1014](http://pubmed.ncbi.nlm.nih.gov/22003155?dopt=Abstract).

#### **Canadian Guidelines**

* PubMed37504336Current oncology (Toronto, Ont.)Curr Oncol202307063076473-64966473Expert Canadian consensus recommendations on the management of KRAS G12C-mutated NSCLC can be found in [Curr Oncol 2023 Jul 6;30(7):6473](https://pubmed.ncbi.nlm.nih.gov/37504336)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10377814/).
* CANADIAN\_GUIDELINES\_\_LI\_SBH\_M21\_FSBGNU01102201/10/2022 01:11:03 PMguidelineNotationUpdatelowOncologic\_DiseaseCanadian Expert Panel recommendation on the management of MET-altered NSCLC (Curr Oncol 2021 Nov 9)PubMed34898564Current oncology (Toronto, Ont.)Curr Oncol202111092864552-45764552Canadian Expert Panel (CEP) consensus recommendation on the management of MET-altered non-small cell lung cancer (NSCLC) can be found in [Curr Oncol 2021 Nov 9;28(6):4552](https://pubmed.ncbi.nlm.nih.gov/34898564)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/34898564/).
* Cancer Care Ontario (CCO):
  + CCO Program in Evidence-Based Care guidelines on:
    - CANADIAN\_GUIDELINES\_\_LI\_LRG\_VGP\_TWBGNU03102303/10/2023 12:33:30 PMguidelineNotationUpdatelowOncologic\_DiseaseCancer Care Ontario guideline on role of high dose rate brachytherapy in the palliation of symptom in patients with non-small cell lung cancer (CCO 2022 Dec)Role of high dose rate brachytherapy in the palliation of symptom in patients with non-small cell lung cancer can be found at [CCO 2022 Dec](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/791).
    - Therapy for stage IV non–small-cell lung cancer without driver alterations can be found at [CCO 2020 Jan](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/62681).
    - Invasive mediastinal staging of non-small cell lung cancer can be found at [CCO 2018 May PDF](https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/pebc17-6f.pdf).
    - Treatment of patients with stage III (N2 or N3) non-small cell lung cancer can be found at [CCO 2017 Sep](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/43311).
    - Systemic treatment for patients with advanced non-small cell lung cancer can be found at [CCO 2016 Nov](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31811).
    - Use of systemic treatment in the maintenance of patients with non-small cell lung cancer can be found at [CCO 2015 Aug](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/831).
    - Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer can be found at [CCO 2012 Oct](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2411).
    - Use of epidermal growth factor receptor inhibitors gefitinib (Iressa), erlotinib (Tarceva), afatinib, dacomitinib, or icotinib in treatment of non-small cell lung cancer can be found at [CCO 2014 May](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1066).
    - Radiotherapy with curative intent in patients with early stage, medically inoperable, non-small cell lung cancer can be found at [CCO 2016 May](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/526).
    - Focal tumor ablation for early-stage primary lung cancer and lung metastases can be found at [CCO 2016 Aug](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/4106).
    - Role of intensity-modulated radiation therapy (IMRT) in lung cancer can be found at [CCO 2010 Nov](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2186).
    - Role of high-dose rate brachytherapy in palliation of symptom in patients with non-small cell lung cancer can be found at [CCO 2018 Jun](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/791).
    - Follow-up and surveillance of curatively treated lung cancer patients can be found at [CCO 2014 Aug](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/261).
  + CCO best practices on oncologic pathology secondary review: lung cancer can be found at [CCO 2014 Jun](https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/406).
* PubMed33591844Journal of clinical oncology : official journal of the American Society of Clinical OncologyJ Clin Oncol202103203991040-10911040American Society of Clinical Oncology (ASCO)/CCO joint guideline update on therapy for stage IV non-small cell lung cancer with driver alterations can be found in [J Clin Oncol 2021 Mar 20;39(9):1040](http://pubmed.ncbi.nlm.nih.gov/33591844).
* Alberta Health Services (AHS) clinical practice guidelines on:
  + Non-small cell lung cancer staging can be found at [AHS 2009 Jul PDF](http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-nsclc-staging.pdf).
  + Non-small cell lung cancer stage I can be found at [AHFS 2014 Jul PDF](http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lu001-nsclc-stage1.pdf).
  + Non-small cell lung cancer stage II can be found at [AHFS 2014 Jul PDF](http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lu002-nsclc-stage2.pdf).
  + Non-small cell lung cancer stage III can be found at [AHS 2012 Apr PDF](http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lu003-nlscs-stage3.pdf).
  + Non-small cell lung cancer stage IV can be found at [AHS 2013 Nov PDF](http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lu004-nsclc-stage4.pdf).
  + Superior sulcus (Pancoast) tumors can be found at [AHFS 2012 Jan PDF](http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lu005-super-sulcus-tumours.pdf).

#### **European Guidelines**

* European Society for Medical Oncology (ESMO):
  + ESMO clinical practice guidelines on:
    - EUROPEAN\_GUIDELINES\_\_LI\_HLD\_5HQ\_KWBGNU02062302/06/2023 11:41:29 AMguidelineNotationUpdatelowOncologic\_DiseaseESMO clinical practice guideline on non-oncogene-addicted metastatic non-small-cell lung cancer (ESMO 2023 Jan)Non-oncogene-addicted metastatic non-small-cell lung cancer can be found at [ESMO 2023 Jan](https://www.esmo.org/guidelines/guidelines-by-topic/lung-and-chest-tumours/non-oncogene-addicted-metastatic-non-small-cell-lung-cancer).
    - EUROPEAN\_GUIDELINES\_\_LI\_OBS\_P3W\_P5BGNU08232208/23/2022 07:32:01 AMguidelineNotationUpdatelowOncologic\_DiseaseEuropean Society for Medical Oncology (ESMO) clinical practice guideline on management of EGFR mutant non-small-cell lung cancer (Ann Oncol 2022 May)PubMed35176458Annals of oncology : official journal of the European Society for Medical OncologyAnn Oncol20220501335466-487466Management of EGFR mutant non-small-cell lung cancer can be found in [Ann Oncol 2022 May;33(5):466](https://pubmed.ncbi.nlm.nih.gov/35176458).
    - PubMed30715168Annals of oncology : official journal of the European Society for Medical OncologyAnn Oncol20190501305863-870863Diagnosis, treatment and follow-up: metastatic non-small cell lung cancer can be found in [Ann Oncol. 2018 Oct 1;29(Supplement\_4):iv192-iv237](http://pubmed.ncbi.nlm.nih.gov/30285222?dopt=Abstract)[PDF](https://iris.unito.it/retrieve/handle/2318/1677658/441047/OP-ANNO180277%20192..237.pdf); correction can be found in [Ann Oncol 2019 May 1;30(5):863](http://pubmed.ncbi.nlm.nih.gov/30715168?dopt=Abstract).
    - Diagnosis, treatment and follow-up: early-stage and locally advanced non-small cell lung cancer can be found in [28881918Ann Oncol 2017 Jul 1;28(suppl\_4):iv1](http://pubmed.ncbi.nlm.nih.gov/28881918?dopt=Abstract)[full-text](https://academic.oup.com/annonc/article/28/suppl_4/iv1/3958156).
    - Bone health in cancer patients can be found in [24782453Ann Oncol 2014 Sep;25 Suppl 3:iii 124](http://pubmed.ncbi.nlm.nih.gov/24782453?dopt=Abstract).
  + ESMO consensus guidelines on:
    - Locally advanced stage III non-small cell lung cancer can be found in [25897013Ann Oncol 2015 Aug;26(8):1573](http://pubmed.ncbi.nlm.nih.gov/25897013?dopt=Abstract).
    - Pathology and molecular biomarkers for non-small cell lung cancer can be found in [Ann Oncol 2015 Aug;26(8):1573](http://pubmed.ncbi.nlm.nih.gov/25897013?dopt=Abstract)[PDF](https://iris.unito.it/retrieve/handle/2318/1675626/435836/untitled.pdf).
* EUROPEAN\_GUIDELINES\_\_LI\_W2V\_G5V\_TVBGNU12082212/08/2022 11:00:37 AMguidelineNotationUpdatelowOncologic\_DiseaseEuropean Respiratory Society (ERS) guideline on various aspects of quality in lung cancer care (Eur Respir J 2023 Feb)PubMed36396145The European respiratory journalEur Respir J20221117European Respiratory Society (ERS) guideline on various aspects of quality in lung cancer care can be found in [Eur Respir J 2023 Feb;61(2):doi:10.1183/13993003.03201-2021](https://pubmed.ncbi.nlm.nih.gov/36396145" \t "_blank).
* Norwegian Directorate of Health (NDH) guideline on ​diagnosis, treatment, and follow-up of lung cancer, mesothelioma, and thymoma can be found at [NDH 2021 Apr](https://www.helsebiblioteket.no/retningslinjer/lungekreft/forord) [Norwegian].
* Dutch Federation of Medical Specialists Guidelines Database (Federatie Medisch Specialisten Richtlijnendatabase) guideline on non-small cell lung carcinoma can be found at [Richtlijnendatabase 2020 Jan 24](https://richtlijnendatabase.nl/richtlijn/niet_kleincellig_longcarcinoom/startpagina_-_niet-kleincelling_longcarcinoom.html" \t "_blank) [Dutch].
* Central European Cooperative Oncology Group (CECOG) consensus on systematic treatment of non-small cell lung cancer can be found in [21940784Ann Oncol 2012 May;23(5):1223](http://pubmed.ncbi.nlm.nih.gov/21940784?dopt=Abstract).
* Cardiovascular and Interventional Radiological Society of Europe (CIRSE) guideline on thermal ablation of primary and secondary lung tumors can be found in [22271076Cardiovasc Intervent Radiol 2012 Apr;35(2):247](http://pubmed.ncbi.nlm.nih.gov/22271076?dopt=Abstract), correction can be found in Cardiovasc Intervent Radiol 2012 Apr;35(2):444.
* European consensus on EGFR mutation testing in non-small cell lung cancer can be found in [20871269J Thorac Oncol 2010 Oct;5(10):1706](http://pubmed.ncbi.nlm.nih.gov/20871269?dopt=Abstract).
* European clinical oncologists and lung cancer specialists expert guideline on bisphosphonate use in patients with lung cancer and bone metastases can be found in [19701109J Thorac Oncol 2009 Oct;4(10):1280](http://pubmed.ncbi.nlm.nih.gov/19701109?dopt=Abstract).
* European Lung Cancer Working Party (ELCWP) guideline on treatment of metastatic non-small cell lung cancer can be found in [25102581Rev Med Brux 2014 May-Jun;35(3):145](http://pubmed.ncbi.nlm.nih.gov/25102581?dopt=Abstract) [French].
* Italian Association of Medical Oncologists (Associazione Italiana Oncologi Medici) (AIOM) guideline on tumors of the elderly can be found at Sistema Nazionale Linee Guida dell’Istituto Superiore di Sanità [(SNLG-ISS) Sep 2020 PDF](https://snlg.iss.it/wp-content/uploads/2020/09/LG-283-Tumori-Anziano.pdf) [Italian].
* Italian Association of Medical Oncologists (Associazione Italiana Oncologi Medici) (AIOM) guideline on lung cancers can be found at Sistema Nazionale Linee Guida dell’Istituto Superiore di Sanità [(SNLG-ISS) Mar 2020, updated 2021 Oct PDF](https://snlg.iss.it/wp-content/uploads/2021/11/LG-149_Polmone_agg2021.pdf) [Italian].
* Italian Association of Medical Oncology/Italian Society of Anatomic Pathology and Diagnostic Cytopathology (AIOM/SIAPeC) recommendations on mutational analysis of EGFR in lung carcinoma can be found in [21171518Pathologica 2010 Jun;102(3):119](http://pubmed.ncbi.nlm.nih.gov/21171518?dopt=Abstract) [English, Italian].
* National Board of Health and Welfare (NBHW [Socialstyrelsen]) guideline on lung cancer care and treatment can be found at [NBHW 2011 Mar](http://www.socialstyrelsen.se/nationalguidelines/nationalguidelinesforlungcancercareandtreatment)[PDF](http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18241/2011-3-2.pdf) [Swedish].
* EUROPEAN\_GUIDELINES\_\_LI\_WBB\_4Z3\_Y1CGNU04022404/02/2024 10:06:32 AMguidelineNotationUpdatelowOccupational\_and\_Environmental\_MedicineDeutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V./Deutsche Krebsgesellschaft e.V. (German Society for Pulmonology and Respiratory Medicine/German Cancer Society eV) (DGP/DKG) guideline on prävention, diagnostik, therapie und nachsorge des lungenkarzinoms (prevention, diagnosis, therapy and aftercare of lung cancer) (AWMF 2024 Mar 20)Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V./Deutsche Krebsgesellschaft e.V. (German Society for Pulmonology and Respiratory Medicine/German Cancer Society eV) (DGP/DKG) guideline on prävention, diagnostik, therapie und nachsorge des lungenkarzinoms (prevention, diagnosis, therapy and aftercare of lung cancer) can be found at Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften [(AWMF) 2024 Mar 20 PDF](https://register.awmf.org/assets/guidelines/020-007OLl_S3_Praevention-Diagnostik-Therapie-Nachsorge-Lungenkarzinom_2024-03.pdf) [German].
* Nemzeti Erőforrás Minisztérium (Department of Human Resources [NEFMI]) basic principles on prevention, diagnosis, and therapy of lung cancer can be found in [22724157Magy Onkol 2012 May;56(2):114](http://pubmed.ncbi.nlm.nih.gov/22724157?dopt=Abstract)[PDF](http://huon.hu/2012/56/2/0114/0114a.pdf) [Hungarian].
* Haute Autorité de Santé conseils pour cancer du poumon et mésothéliome pleural malin se trouvent sur le site [Haute Autorité de Santé 2009 Mai](http://www.has-sante.fr/portail/jcms/c_820058/ald-n-30-cancer-du-poumon-et-mesotheliome-pleural-malin) [French].
* Haute Autorité de Santé/Institut National du Cancer conseils pour cancer primitif non à petites cellules du poumon: pratiques chirurgicales se trouvent sur le site [Haute Autorité de Santé 2008 Dec](http://www.has-sante.fr/portail/jcms/c_966330/label-conjoint-has-inca-cancer-primitif-non-a-petites-cellules-du-poumon-pratiques-chirurgicales) ou [Institut National du Cancer 2008 Dec](http://www.e-cancer.fr/soins/recommandations/cancers-bronchopulmonaires-et-pleuraux" \t "_blank) [French].
* Spanish Society of Medical Oncology (SEOM):
  + Guideline on treatment of non-small cell lung cancer can be found in [20974565Clin Transl Oncol 2010 Nov;12(11):735](http://pubmed.ncbi.nlm.nih.gov/20974565?dopt=Abstract).
  + Clinical guideline on using molecular markers in clinical practice can be found in [21821495Clin Transl Oncol 2011 Aug;13(8):587](http://pubmed.ncbi.nlm.nih.gov/21821495?dopt=Abstract).
* Spanish Society of Medical Oncology/Spanish Society of Pathology (SEOM/SEAP) guideline on biomarker testing in advanced non-small cell lung cancer can be found in [22551539Clin Transl Oncol 2012 May;14(5):338](http://pubmed.ncbi.nlm.nih.gov/22551539?dopt=Abstract).
* Sociedad Española Neumología y Cirugía Torácica (Spanish Society of Pulmonology and Thoracic Surgery [SEPAR]) guideline on lung cancer staging can be found in [21824707Arch Bronconeumol 2011 Sep;47(9):454](http://pubmed.ncbi.nlm.nih.gov/21824707?dopt=Abstract) [English, Spanish], commentary can be found in [22100701Arch Bronconeumol 2012 Jan;48(1):32](http://pubmed.ncbi.nlm.nih.gov/22100701?dopt=Abstract) [English, Spanish].
* Norwegian Directorate of Health (DOH) national guideline on treatment and follow-up of lung cancer, mesothelioma and thymoma can be found at [DOH 2018 Jul PDF](https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/1400/IS-2745%20-%20Lungekrefthandlingsprogram%20170718.pdf) [Norwegian].
* Austrian Society of Pathology (ASP) consensus statement on histology-based algorithm in molecular diagnosis of mutations of Epidermal Growth Factor Receptor (EGFR) in non-small cell lung cancer can be found in [cxh61464606pmdc21604158pWien Klin Wochenschr 2011 May;123(9-10):316](http://pubmed.ncbi.nlm.nih.gov/21604158?dopt=Abstract) [German].
* Polish Respiratory Society (Polskie Towarzystwo Chorób Płuc [PTCHP]) recommendations on palliative care in chronic lung diseases can be found in [22187179Pneumonol Alergol Pol 2012;80(1):41](http://pubmed.ncbi.nlm.nih.gov/22187179?dopt=Abstract) [Polish], commentary can be found in [22187173Pneumonol Alergol Pol 2012;80(1):1](http://pubmed.ncbi.nlm.nih.gov/22187173?dopt=Abstract).

#### **Asian Guidelines**

* Chinese Society of Clinical Oncology-European Society of Medical Oncology Pan-Asian guidelines for management of metastatic non-small cell lung cancer can be found in [Ann Oncol 2019 Feb 1;30(2):171](http://pubmed.ncbi.nlm.nih.gov/30596843?dopt=Abstract)[PDF](https://www.annalsofoncology.org/article/S0923-7534(19)31046-4/pdf).
* Asian Oncology Summit 2009 consensus statement on first-line systemic treatment of advanced stage non-small cell lung cancer in Asia can be found in [19880064Lancet Oncol 2009 Nov;10(11):1102](http://pubmed.ncbi.nlm.nih.gov/19880064?dopt=Abstract).
* expert consensus on epidermal growth factor receptor gene mutation detection in non-small cell lung cancer can be found in [22321552Zhonghua Bing Li Xue Za Zhi 2011 Oct;40(10):700](http://pubmed.ncbi.nlm.nih.gov/22321552?dopt=Abstract) [Chinese].
* Japan Lung Cancer Society (JLCS) 2005 clinical guideline on lung cancer can be found at [Minds guideline listing (医療情報サービスマインズ)](http://minds.jcqhc.or.jp/stc/0007/1/0007_G0000073_GL.html) (Japanese 日本語).
* Research group on methods and evaluation on cancer screening (funded by Ministry of Health, Labour and Welfare) 2005 clinical guideline on lung cancer screening can be found at [Minds guideline listing (医療情報サービスマインズ)](http://minds.jcqhc.or.jp/stc/0041/1/0041_G0000119_GL.html) (Japanese 日本語).

#### **Mexican Guidelines**

* Grupos de Desarrollo de las Instituciones Públicas del Sistema Nacional de Salud de México (Secretaría de Salud, IMSS, ISSSTE, SEDENA, SEMAR, DIF, PEMEX) guías de práctica clínica en prevención y detección temprana del cáncer de pulmón en el primer nivel de atención se pueden encontrar en [Secretaría de Salud-México 2013 PDF](http://www.cenetec.salud.gob.mx/descargas/gpc/CatalogoMaestro/022_GPC_Ca_Pulmonar1erNivel/SSA_022_08_EyR.pdf" \t "_blank) [Spanish].

#### **Middle Eastern Guidelines**

* National Comprehensive Cancer Network (NCCN) guideline on non-small cell lung cancer modified for Middle East and North Africa region can be found at [NCCN website](https://www.nccn.org/global/international_adaptations.aspx) (free registration required).
* Saudi Lung Cancer Guidelines Committee 2012 guideline on lung cancer management can be found in [23244186J Infect Public Health 2012 Dec;5 Suppl 1:S4](http://pubmed.ncbi.nlm.nih.gov/23244186?dopt=Abstract)[full-text](https://www.sciencedirect.com/science/article/pii/S1876034112001220?via%3Dihub).
* Expert guideline on multimodality radiological staging of lung cancer can be found in [23244181J Infect Public Health 2012 Dec;5 Suppl 1:S14](http://pubmed.ncbi.nlm.nih.gov/23244181?dopt=Abstract)[full-text](http://www.sciencedirect.com/science/article/pii/S1876034112001207?via%3Dihub).
* Expert guideline on EGFR mutation testing in non-small cell lung cancer (NSCLC) can be found in [23244184J Infect Public Health 2012 Dec;5 Suppl 1:S31](http://pubmed.ncbi.nlm.nih.gov/23244184?dopt=Abstract)[full-text](https://www.sciencedirect.com/science/article/pii/S1876034112001190?via%3Dihub).
* Expert guideline on role of fluorodeoxyglucose positron emission tomography/computed tomography in lung cancer management can be found in [23244185J Infect Public Health 2012 Dec;5 Suppl 1:S35](http://pubmed.ncbi.nlm.nih.gov/23244185?dopt=Abstract)[full-text](https://www.sciencedirect.com/science/article/pii/S1876034112000974?via%3Dihub).

### **Review Articles**

* Review of precision and diagnosis and treatment for advanced non-small cell lung cancer can be found in [N Engl J Med 2017 Aug 31;377(9):849](http://pubmed.ncbi.nlm.nih.gov/28854088?dopt=Abstract).
* PubMed35559635American family physicianAm Fam Physician202205011055487-494487Review of diagnosis, treatment principles, and screening of lung cancer can be found in [Am Fam Physician 2022 May 1;105(5):487](https://pubmed.ncbi.nlm.nih.gov/35559635).
* PubMed34742731The Annals of thoracic surgeryAnn Thorac Surg2022110111451965-19731965Review of lung cancer in women can be found in [Ann Thorac Surg 2022 Nov;114(5):1965](https://pubmed.ncbi.nlm.nih.gov/34742731).
* PubMed35040882JAMAJAMA202201183273264-273264Review of evaluating the patient with a pulmonary nodule can be found in [JAMA 2022 Jan 18;327(3):264](https://pubmed.ncbi.nlm.nih.gov/35040882).
* REVIEW\_ARTICLES\_\_LI\_QSF\_DL3\_PSBRAU02162202/16/2022 10:31:49 AMreviewArticleUpdatelowOncologic\_Diseasereview of lung cancer (Lancet 2021 Aug 7)PubMed32008629Clinics in chest medicineClin Chest Med2020030141153-6553Review of lung cancer can be found in [Lancet 2021 Aug 7;398(10299):535](https://pubmed.ncbi.nlm.nih.gov/34273294).
* Review of lung cancer in women can be found in [Clin Chest Med 2020 Mar;41(1):53](http://pubmed.ncbi.nlm.nih.gov/32008629).
* Reviews of management:
  + Review of treatment of non-small cell lung cancer can be found in [27413711Transl Lung Cancer Res 2016 Jun;5(3):288](http://pubmed.ncbi.nlm.nih.gov/27413711?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4931124/).
  + Review of systemic treatment for lung cancer can be found in [Curr Opin Pulm Med 2018 Jul;24(4):355](http://pubmed.ncbi.nlm.nih.gov/29697418?dopt=Abstract).
  + Review of new horizons in systemic anti-cancer therapy in older people can be found in [29617715Age Ageing 2018 May 1;47(3):340](http://pubmed.ncbi.nlm.nih.gov/29617715?dopt=Abstract).
  + Review of current and targeted therapies of lung cancer can be found in [Lancet 2017 Jan 21;389(10066):299](http://pubmed.ncbi.nlm.nih.gov/27574741?dopt=Abstract)[PDF](https://iris.unito.it/retrieve/handle/2318/1623632/445761/Lung%20cancer_%20current%20therapies%20and%20new%20targeted%20treatments.pdf).
  + Review of targeted therapies for treatment of non-small cell lung cancer can be found in [27831000Hum Vaccin Immunother 2017 Apr 3;13(4):843](http://pubmed.ncbi.nlm.nih.gov/27831000?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5404364/).
  + Review of new and emerging targeted treatments in advanced non-small-cell lung cancer can be found in [Lancet 2016 Sep 3;388(10048):1012](http://pubmed.ncbi.nlm.nih.gov/27598681?dopt=Abstract).
  + Review of recent developments in management of non-small cell lung cancer can be found in [23972814Lancet 2013 Aug 24;382(9893):709](http://pubmed.ncbi.nlm.nih.gov/23972814?dopt=Abstract).
  + Review of resistance to molecularly targeted therapy in non-small cell lung cancer can be found in [Respir Investig 2019 Jan;57(1):20](http://pubmed.ncbi.nlm.nih.gov/30293943?dopt=Abstract).
  + Review of maintenance chemotherapy for advanced non-small cell lung cancer can be found in [cxh85930232pmdc23401441pJ Clin Oncol 2013 Mar 10;31(8):1009](http://pubmed.ncbi.nlm.nih.gov/23401441?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3589699/).
  + Review of stereotactic ablative radiation therapy in lung cancer can be found in [Curr Opin Pulm Med 2018 Jul;24(4):335](http://pubmed.ncbi.nlm.nih.gov/29521657?dopt=Abstract).
* Reviews of diagnosis and molecular testing:
  + Review of rebiopsy of histological tumor samples in advanced non-small cell lung cancer can be found in [Int J Clin Oncol 2019 Jan;24(1):41](http://pubmed.ncbi.nlm.nih.gov/30159691?dopt=Abstract).
  + Geriatrics Oncologic\_Disease Pulmonary\_Disordersreview of utility of cytologic and histologic samples obtained through minimally invasive pulmonary procedures (Am J Respir Crit Care Med 2018 Jul 1)06/01/2018 10:40:00 AMReview of utility of cytologic and histologic samples obtained through minimally invasive pulmonary procedures can be found in [29756991Am J Respir Crit Care Med 2018 Jul 1;198(1):24](http://pubmed.ncbi.nlm.nih.gov/29756991?dopt=Abstract).
  + Review of immunohistochemical markers in subclassification of non-small cell lung cancer can be found in [Semin Cancer Biol 2018 Oct;52(Pt 1):103](http://pubmed.ncbi.nlm.nih.gov/29183778?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5970946/).
  + Review of emerging biomarkers for immune checkpoint inhibition in lung cancer can be found in [Semin Cancer Biol 2018 Oct;52(Pt 2):269](http://pubmed.ncbi.nlm.nih.gov/29782924?dopt=Abstract).
  + Review of challenges in molecular testing in non-small cell lung cancer patients with advanced disease can be found in [27598680Lancet 2016 Sep 3;388(10048):1002](http://pubmed.ncbi.nlm.nih.gov/27598680?dopt=Abstract).
  + Review of genetics and biomarkers in personalization of lung cancer treatment can be found in [23972815Lancet 2013 Aug 24;382(9893):720](http://pubmed.ncbi.nlm.nih.gov/23972815?dopt=Abstract).
  + Review of KRAS in lung cancer can be found in [Eur J Cancer 2018 Aug;99:20](http://pubmed.ncbi.nlm.nih.gov/29894909?dopt=Abstract" \t "_blank).
* Review of familial risk for lung cancer can be found in [a9h120638966pcxh120638966pOncol Lett 2017 Feb;13(2):535](http://pubmed.ncbi.nlm.nih.gov/28356926?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5351216/).
* Review of clinical implications of genomic discoveries in lung cancer can be found in [27168435N Engl J Med 2016 May 12;374(19):1864](http://pubmed.ncbi.nlm.nih.gov/27168435?dopt=Abstract).

### **MEDLINE Search**

* To search MEDLINE for (Non-Small Cell Lung Cancer) with targeted search (Clinical Queries), click [therapy](https://pubmed.ncbi.nlm.nih.gov/?term=(non%20small%20cell%20lung%20cancer)%20AND%20(randomized%20controlled%20trial%5bPublication%20Type%5d%20OR%20(randomized%5bTitle/Abstract%5d%20AND%20controlled%5bTitle/Abstract%5d%20AND%20trial%5bTitle/Abstract%5d))), [diagnosis](https://pubmed.ncbi.nlm.nih.gov/?term=(non%20small%20cell%20lung%20cancer)%20AND%20(specificity%5bTitle/Abstract%5d)), or [prognosis](https://pubmed.ncbi.nlm.nih.gov/?term=(non%20small%20cell%20lung%20cancer)%20AND%20(prognos*%5bTitle/Abstract%5d%20OR%20(first%5bTitle/Abstract%5d%20AND%20episode%5bTitle/Abstract%5d)%20OR%20cohort%5bTitle/Abstract%5d)).

## **References**

### **General References Used**

The references listed below are used in this DynaMed topic primarily to support background information and for guidance where evidence summaries are not felt to be necessary. Most references are incorporated within the text along with the evidence summaries.

1. Novello S, Barlesi F, Califano R, et al; ESMO Guidelines Committee. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. [Ann Oncol. 2016 Sep;27(suppl 5):v1-v27](http://pubmed.ncbi.nlm.nih.gov/27664245?dopt=Abstract).
2. Ettinger DS, Wood DE, Aisner DL, et al. Non-small cell lung cancer. Version 3.2019. In: National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines). NCCN 2019 Jan from [NCCN website](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp) (free registration required) .
3. Ost DE, Yeung SC, Tanoue LT, Gould MK. 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. [Chest. 2013 May;143(5 Suppl):e121S-41S](http://pubmed.ncbi.nlm.nih.gov/23649435?dopt=Abstract)[full-text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4694609/).
4. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. [Chest. 2013 May;143(5 Suppl):e142S-65S](http://pubmed.ncbi.nlm.nih.gov/23649436?dopt=Abstract).

### **Recommendation Grading Systems Used**

* American College of Chest Physicians (ACCP) uses Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to recommendations since 2018:
  + Recommendations:
    - Strong - benefits outweigh risk and burdens, or vice versa; recommend
    - Weak - conditional, benefits closely balanced with risks and burden; suggest
    - Ungraded - consensus based, uncertainty due to lack of evidence, expert opinion that benefits outweigh risk and burdens, or vice versa; insufficient evidence for a graded recommendation
  + Quality of evidence:
    - High - confidence that true effect lies close to estimate of effect from the estimate of effect
    - Moderate - moderate confidence in effect estimate, true effect likely to be close to the estimate of the effect, but possibility it is substantially different
    - Low - confidence in the effect estimate is limited, true effect may be substantially different from estimate of effect
    - Very low - little confidence in the effect estimate. true effect is likely to be substantially different
  + Reference - screening for lung cancer: CHEST guideline and expert panel report ([Chest 2018 Apr;153(4):954](http://pubmed.ncbi.nlm.nih.gov/29374513?dopt=Abstract))
* ACCP 2013 grading system for recommendations:
  + Grade 1 - strong recommendation based on clear risk/benefit balance
  + Grade 2 - weak recommendation based on unclear or close risk/benefit balance
  + Grade A - high-quality evidence based on consistent evidence from randomized trials without important limitations or exceptionally strong evidence from observational studies
  + Grade B - moderate-quality evidence based on randomized trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise results) or very strong evidence from observational studies
  + Grade C - low- or very low-quality evidence based on observational studies, case series, or randomized trials with serious flaws or indirect evidence
  + Reference - ACCP evidence-based clinical practice guidelines methodology for development of guidelines for lung cancer ([23649432Chest 2013 May;143(5 Suppl):41S](http://pubmed.ncbi.nlm.nih.gov/23649432?dopt=Abstract))
* American Society of Clinical Oncology (ASCO) grading of recommendations:
  + Strength of recommendations:
    - Strong - high confidence that recommendation reflects best practice based on strong evidence for true net effect, consistent results with no or minor exceptions, minor or no concerns about study quality, and/or extent of panelists' agreement
    - Moderate - moderate confidence that recommendation reflects best practice based on good evidence for true net effect, consistent results with minor and/or few exceptions, minor and/or few concerns about study quality, and/or extent of panelists' agreement
    - Weak - some confidence that recommendation offers best current guidance for practice based on limited evidence for true net effect, consistent results but with important exceptions, concerns about study quality, and/or extent of panelists' agreement
  + Quality of evidence:
    - High - high confidence available evidence reflects true magnitude and direction of net effect (balance of benefits vs. harms), further research very unlikely to change either magnitude or direction of net effect
    - Intermediate - moderate confidence available evidence reflects true magnitude and direction of net effect; further research unlikely to alter direction net effect; might alter the magnitude of net effect
    - Low - low confidence available evidence reflects true magnitude and direction of net effect; further research may change either magnitude and/or direction of net effect
    - Insufficient - insufficient evidence to discern true magnitude and direction of net effect; further research may better inform the topic; consensus of opinion of experts reasonable to inform outcomes related to topic
  + Types of recommendation:
    - Evidence-based - sufficient evidence from published studies to inform recommendation to guide clinical practice
    - Formal consensus - available evidence deemed insufficient to inform recommendation to guide clinical practice; expert panel used formal consensus process to reach recommendation
    - Informal consensus:
      * Available evidence deemed insufficient to inform recommendation to guide clinical practice
      * Recommendation is considered best current guidance for practice based on informal consensus of expert panel
      * Expert panel agreed formal consensus process not necessary
    - No recommendation - insufficient evidence, confidence, or agreement to provide recommendation to guide clinical practice at this time; expert panel deemed available evidence insufficient and concluded it unlikely formal consensus process would achieve level of agreement needed for recommendation
  + Reference - ASCO systemic therapy for stage IV non-small cell lung cancer clinical practice guideline update ([cxh125742193pmdc28806116pJ Clin Oncol 2017 Oct 20;35(30):3484](http://pubmed.ncbi.nlm.nih.gov/28806116?dopt=Abstract))
* European Society for Medical Oncology (ESMO) grades of recommendation:
  + Grades of recommendation:
    - Grade A - strong evidence for efficacy with substantial clinical benefit, strongly recommended
    - Grade B - strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
    - Grade C - insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages, optional
    - Grade D - moderate evidence against efficacy or for adverse outcomes, generally not recommended
    - Grade E - strong evidence against efficacy or for adverse outcomes, never recommended
  + Levels of evidence:
    - Level I - evidence from ≥ 1 large, randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
    - Level II - small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
    - Level III - prospective cohort studies
    - Level IV - retrospective cohort studies or case-control studies
    - Level V - studies without control group, case reports, expert opinions
  + Reference - Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up ([27664245Ann Oncol 2016 Sep;27(suppl 5):v1](http://pubmed.ncbi.nlm.nih.gov/27664245?dopt=Abstract))
* National Comprehensive Cancer Network (NCCN) categories for recommendations:
  + Category 1 - based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
  + Category 2A - based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
  + Category 2B - based on lower-level evidence, there is NCCN consensus that the intervention is appropriate
  + Category 3 - based on any level of evidence, there is major NCCN disagreement that the intervention is appropriate
  + Reference - [NCCN Categories of Evidence and Consensus](https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines#:~:text=and%20patient%20preferences.-,Definitions%20for%20NCCN%20Categories,-The%20specific%20definitions)
* United States Department of Health and Human Services, Public Health Service (PHS) guideline panel grading system:
  + Strength of evidence ratings:
    - Strength of Evidence A - multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings
    - Strength of Evidence B - some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal
    - Strength of Evidence C - reserved for important clinical situations in which Panel achieved consensus on recommendation in the absence of relevant randomized controlled trials
  + Reference - PHS clinical practice guideline on treating tobacco use and dependence ([USPHS 2008 May](https://www.ncbi.nlm.nih.gov/books/NBK63952/)[PDF](https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08.pdf) or in [Spanish](https://www.ncbi.nlm.nih.gov/books/NBK47499/" \t "_blank)[PDF](https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08_sp.pdf)), endorsed by American Academy of Pediatrics [Pediatrics 2008 Aug;122(2):471])
* United States Preventive Services Task Force (USPSTF) grades of recommendation:
  + Grade A - USPSTF recommends the service with high certainty of substantial net benefit
  + Grade B - USPSTF recommends the service with high certainty of moderate net benefit or moderate certainty of moderate-to-substantial net benefit
  + Grade C - USPSTF recommends selectively offering or providing the service (based on professional judgment and patient preference) with at least moderate certainty of small net benefit
  + Grade D - USPSTF recommends against providing the service with moderate-to-high certainty of no net benefit or harms outweighing benefits
  + Grade I - insufficient evidence to assess balance of benefits and harms
  + Reference - [USPSTF Grade Definitions](https://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions)
* United States Preventive Services Task Force (USPSTF) grades of recommendation (prior to May 2007):
  + Grade A - USPSTF strongly recommends that clinicians provide the service to eligible patients, based on good evidence that the service improves important health outcomes and that benefits substantially outweigh harms
  + Grade B - USPSTF recommends that clinicians provide the service to eligible patients, based on at least fair evidence that the service improves important health outcomes and that benefits outweigh harms
  + Grade C - USPSTF makes no recommendation for or against routinely providing the service, based on at least fair evidence that the service can improve health outcomes but the balance of benefits and harms is too close to justify a general recommendation
  + Grade D - USPSTF recommends against routinely providing the service to asymptomatic patients, based on at least fair evidence that the service is ineffective or that harms outweigh benefits
  + Grade I - USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing the service
  + Reference - [USPSTF Grade Definitions](https://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions)

### **Synthesized Recommendation Grading System for DynaMed Content**

* The DynaMed Team systematically monitors clinical evidence to continuously provide a synthesis of the most valid relevant evidence to support clinical decision-making (see [7-Step Evidence-Based Methodology](https://www.ebsco.com/clinical-decisions/dynamed-solutions/about/evidence-based-process/methodology)).
* Guideline recommendations summarized in the body of a DynaMed topic are provided with the recommendation grading system used in the original guideline(s) and allow users to quickly see where guidelines agree and where guidelines differ from each other and from the current evidence.
* In DynaMed content, we synthesize the current evidence, current guidelines from leading authorities, and clinical expertise to provide recommendations to support clinical decision-making in the [Overview & Recommendations section](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-C9212C1D-81EB-40D7-A690-A950909FF66E).
* We use the [Grading of Recommendations Assessment, Development and Evaluation (GRADE)](http://www.gradeworkinggroup.org/) approach to classify synthesized recommendations as Strong or Conditional.
  + **Strong recommendations** may be used when, based on the available evidence, clinicians (without conflicts of interest) consistently have a high degree of confidence that the desirable consequences (health benefits, decreased costs and burdens) outweigh the undesirable consequences (harms, costs, burdens).
  + **Conditional recommendations** may be used when, based on the available evidence, clinicians believe that desirable and undesirable consequences are finely balanced, or appreciable uncertainty exists about the magnitude of expected consequences (benefits and harms).
  + **Conditional recommendations** may be used when clinicians disagree in judgments of the relative benefit and harm or have limited confidence in their judgments.
  + **Conditional recommendations** may also be used when the range of patient values and preferences suggests that informed patients are likely to make different choices.
* DynaMed synthesized recommendations (in the [Overview & Recommendations section](https://dpa-pde-oxford.shinyapps.io/Phenotyping_ESBCO_Shiny/_w_1d5cbdd8/#GUID-C9212C1D-81EB-40D7-A690-A950909FF66E)) are determined with a systematic methodology.
  + Recommendations are explicitly labeled as **Strong recommendations** or **Conditional recommendations** when a qualified organization has explicitly deliberated on making such a recommendation.
  + Recommendations are phrased to match the strength of recommendation.
    - **Strong recommendations** use "should do" phrasing, or phrasing implying an expectation to perform the recommended action for most patients.
    - **Conditional recommendations** use "consider" or "suggested" phrasing.
  + Recommendations are verified by ≥ 1 editor with methodological expertise, not involved in recommendation drafting or development, with explicit confirmation that Strong recommendations are adequately supported.
  + Recommendations are published only after consensus is established with agreement in phrasing and strength of recommendation by all editors.
  + If recommendations are questioned during peer review or post publication by a qualified individual, or reevaluation is warranted based on new information detected through systematic literature surveillance, the recommendation is subject to additional internal review.

### **DynaMed Editorial Process**

* DynaMed topics are created and maintained by the [DynaMed Editorial Team](https://www.ebsco.com/clinical-decisions/dynamed-solutions/about/meet-our-experts" \t "_blank) and adhere to [evidence-based methodology](https://www.ebsco.com/clinical-decisions/dynamed-solutions/about/evidence-based-process/methodology) and [inclusive language standards](https://www.ebsco.com/clinical-decisions/dynamed-solutions/about/health-equity-inclusive-language).
* All editorial team members and reviewers have declared that they have no financial or other competing interests related to this topic, unless otherwise indicated.
* DynaMed content includes Practice-Changing Updates, with support from our partner, McMaster University.