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Lung Cancer in Nonsmoking Individuals
A Review

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IMPORTANCE Lung cancer in nonsmoking individuals (defined as people who have smoked fewer than 100 cigarettes in their lifetime) accounts for 15% to 20% of all lung cancer cases worldwide. In the US, the annual incidence of lung cancer in nonsmoking individuals is 14.4 to 20.8 per 100 000 person-years in females and 4.8 to 12.7 per 100 000 person-years in males.

OBSERVATIONS Most lung cancers in nonsmoking individuals are histologically adenocarcinomas (60%-80%) with the remainder being squamous or adenosquamous (10%-20%) and rarely small cell lung cancer (<10%). Risk factors include exposure to passive smoking, radon exposure, air pollution, asbestos, and history of lung cancer in a first-degree family member. Therapeutically targetable genomic variants, such as *EGFR* mutations or *ALK* gene rearrangements, are more common in tumors from nonsmoking individuals compared with those with a smoking history (defined as people who currently or formerly smoked) (43% vs 11% for *EGFR* and 12% vs 2% for *ALK*). In contrast, tumor mutation burden, the number of somatic mutations in a tumor cell, is lower in lung cancer among nonsmoking individuals (0-3 mutations/megabase [Mb] vs 0-30 mutations/Mb). Similar to individuals with a history of smoking, nonsmoking individuals with lung cancer may present with wheeze, chest pain, dyspnea, hemoptysis, or symptoms attributable to metastatic disease (eg, bone pain and headache) or be diagnosed with incidentally detected disease.
The US Preventive Services Task Force does not currently recommend lung cancer screening with low-dose computed tomographic scans for nonsmoking individuals, although screening guidelines vary globally. Treatment typically involves a combination of surgery, radiotherapy, and systemic therapies depending on stage, performance status, and molecular features of the tumor. Comprehensive next-generation sequencing should be performed on stage Ib to IIIa lung cancer tumor tissue from nonsmoking individuals because actionable genomic alterations, such as *EGFR* mutations or *ALK* gene rearrangements, are treated with targeted therapy such as the tyrosine kinase inhibitors osimertinib or lorlatinib, respectively. Median survival among nonsmoking individuals with advanced non–small cell lung cancer (stage IIIb or higher) and actionable genomic alterations can exceed 3 to 5 years, while survival without these genomic alterations is similar to lung cancer in people with a history of smoking (1-2 years).

CONCLUSIONS Lung cancer in nonsmoking individuals accounts for 15% to 20% of lung cancer cases worldwide. Among patients with lung cancer, nonsmoking individuals are more likely to have genomic alterations such as *EGFR* mutations or *ALK* gene rearrangements, and these patients have improved survival when treated with tyrosine kinase inhibitors compared with chemotherapy.

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Lung cancer is the leading cause of cancer-related mortality worldwide, causing approximately 1.8 million deaths in 2022.[1] Although tobacco smoking is the predominant risk factor for lung cancer, present in 80% to 85% of cases, smoking rates are declining in the US and in many other parts of the world. In parallel with a decrease in adult US smoking rates (23.3% in 2000 vs 11.5% in 2021[2]), lung cancer incidence in the US declined from 68 per 100 000 in 2000 to 47 per 100 000 in 2021.[3]

Lung cancer among nonsmoking individuals (those who have smoked fewer than 100 cigarettes in their lifetime) accounts for 15% to 20% of all lung cancer cases[4,5] and may be related to factors including age, air pollution, passive smoking, radon exposure, asbestos exposure, and germline genetic risk (**Box**).[6-8] The misperception that lung cancer is almost invariably caused by smoking may delay assessment and diagnosis.[9,10] This review discusses the epidemiology, risk factors, screening, clinical presentation, assessment, diagnosis, treatment, and prognosis of lung cancer in nonsmoking individuals.

Methods

A PubMed search for English-language articles describing studies on lung cancer in nonsmoking individuals was conducted from January 1, 2005, to August 1, 2025. In total, 902 studies were retrieved from this search and 92 were included in this review, consisting of 6 meta-analyses or systematic reviews, 16 randomized clinical trials, 8 prospective cohort studies, 7 retrospective cohort studies, 3 cross-sectional studies, 4 observational or case-control studies, 13 genomic or molecular studies, 11 narrative reviews, 10 statistical or surveillance reports, 11 guidelines or recommendation statements, 2 registry or database studies, and 1 preclinical or experimental study.

Epidemiology and Screening

Most lung cancers in nonsmoking individuals are adenocarcinomas (60%-80%), and are diagnosed at a median age of 67 years compared with age 70 years in people with a history of smoking (defined as people who currently or formerly smoked) (**Figure**).[4-6,11-13] The absolute incidence of lung cancer in nonsmoking individuals in the US and worldwide is increasing. A retrospective study of 10 000 cases from 3 US hospital networks reported that the proportion of lung cancer among nonsmoking individuals increased from 8% to 14.9% from 1990 to 2013.[4] A pooled analysis of 7 Finnish cohorts reported an absolute increase in lung cancer among nonsmoking individuals from 6.9 per 100 000 person-years in 1972 to 12.9 per 100 000 person-years in 2015.[14] Lung cancer is the third most diagnosed cancer worldwide, and if lung cancer in nonsmoking individuals were classified as a distinct entity, it would be the seventh most common cancer.[15]

There are substantial ethnic, racial, and geographic differences in the incidence of lung cancer in nonsmoking individuals. The age-adjusted incidence rate of lung cancer in nonsmoking individuals who were Asian females in the US between 2000 and 2013 was 17.5 per 100 000 individuals (95% CI, 15.0-20.2) compared with 10.1 per 100 000 (95% CI, 9.0-11.3) for non-Hispanic White females.[16]

Box. Frequently Asked Questions About Lung Cancer in Nonsmoking Individuals[a]

How common is lung cancer in nonsmoking individuals and what are known risk factors?

Worldwide, lung cancer in nonsmoking individuals accounts for 15% to 20% of all lung cancers. Exposure to passive smoking, radon, air pollution, and asbestos and having a first-degree relative with lung cancer are common risk factors for lung cancer in nonsmoking individuals.

Among patients with lung cancer, which genetic variants are more common among nonsmoking individuals compared with people with a history of smoking?

Nonsmoking individuals with lung cancer have higher rates of genomic alterations such as *EGFR* mutations or *ALK* gene rearrangements that directly contribute to carcinogenesis and represent potential molecular targets. Among patients with these genetic alterations, use of tyrosine kinase inhibitors (osimertinib and lorlatinib) is associated with improved survival.

What are the recommendations about screening for lung cancer in nonsmoking individuals?

The US Preventive Services Task Force does not recommend screening nonsmoking individuals for lung cancer with low-dose computed tomographic scans. In contrast, Taiwan initiated a national lung cancer early detection program in 2022 that offers biennial low-dose computed tomographic scans to nonsmoking individuals with a family history of lung cancer.

[a] Nonsmoking individuals are defined as people who have smoked fewer than 100 cigarettes in their lifetime. People with a history of smoking are defined as people who currently or formerly smoked.

The incidence of lung cancer in nonsmoking individuals worldwide is higher among women than men; however, this may be confounded by the difference in the population at risk.[17,18] In Taiwan, up to 83% of lung cancer cases among nonsmoking individuals occur in women.[5,19,20] Smoking has historically been higher among males than females and there are concerns about the accuracy of data on smoking status.[20] For example, a study of electronic health care records of 16 874 individuals in the US reported 80% had inaccuracies in their smoking history.[21] In addition, the US Surveillance, Epidemiology, and End Results program, which aggregates survival data from lung cancers registered in the US, does not record smoking status.[22]

A pooled analysis of 7 Finnish cohorts demonstrated an age-standardized increase in lung cancer among female nonsmoking individuals (0.4 per 100 000 person-years in 1972 vs 6.2 per 100 000 person-years in 2015) compared with a stable rate of lung cancer among male nonsmoking individuals (6.5 per 100 000 person-years in 1972 vs 6.7 per 100 000 person-years in 2015).[14] A study that included 6 population-based cohorts (n = 1 364 658 individuals, n = 5379 incident lung cancer cases) reported that the age-adjusted incident rate ranged from 14.4 to 20.8 per 100 000 person-years in nonsmoking females and 4.8 to 12.7 per 100 000 person-years in nonsmoking males.[11]

Environmental Risk Factors

Several environmental exposures are associated with an increased risk of lung cancer in nonsmoking individuals (Figure). Radon, a colorless gas that arises from the radioactive decay of uranium found

Figure. Principal Differences Between Lung Cancer in Nonsmoking Individuals and Lung Cancer in People With a History of Smoking

	Lung cancer in **Nonsmoking individuals** (have smoked fewer than 100 cigarettes in their lifetime)	Lung cancer in **People with a history of smoking** (people who currently or formerly smoked)
Proportion of new lung cancer diagnoses worldwide	15%-20%[4,6]	80%-85%[4,6]
Absolute incidence	**0.16** per 1000 person-years[12]	**2.99** per 1000 person-years[12]
Median age at diagnosis	**67** years[11]	**70** years[11]
Sex difference	**19%** of females with lung cancer **9%** of males with lung cancer[11]	**81%** of females with lung cancer **91%** of males with lung cancer[11]
Histology	Lung adenocarcinoma, **60%-80%** Squamous cell, **17%** Small cell, **8%**[13]	Squamous cell, **41%** Lung adenocarcinoma, **24%** Small cell, **17%**[13]
Lung adenocarcinoma risk factors	Secondhand smoke Occupational exposures (eg, asbestos, silica) Radon Outdoor air pollution (particularly $PM_{2.5}$) Household air pollution (eg, fumes from cooking and heating) Prior radiotherapy Family history Asian ancestry Germline variants	Smoking Secondhand smoke Occupational exposures (eg, asbestos, silica) Radon Outdoor air pollution Prior radiotherapy Germline variants *Risk factor effects may be additive with smoking*
Lung adenocarcinoma frequency of oncogenic drivers (see Table 1)	**78%-92%**[38]	**49.5%**[40]
Tumor mutation burden	**0-3** Mutations/Mb[41]	**0-30** Mutations/Mb[41]
Genomic signature	None	Smoking signature (SBS4)[42]
Screening recommendations	No national screening programs other than Taiwan[53]	In the US: Annual low-dose computed tomography screen for those aged 50-80 years with ≥20 pack-year history and smoked within last 15 years[49]
Survival benefit with immunotherapy	Hazard ratio, **0.87** (95% CI, 0.74-1.74)[81]	Hazard ratio, **0.74** (95% CI, 0.69-0.81)[17]

Mb indicates megabase; $PM_{2.5}$, particulate matter with a diameter of less than 2.5 μm; and SBS4, Catalogue of Somatic Mutations in Cancer (COSMIC) variation profile associated with smoking, characterized by a transcriptional bias for C>A variations.

in rocks and soil, is classified as a class I carcinogen by the International Agency for Research on Cancer.[23] Up to 21 000 cases of lung cancer–related deaths in the US annually are due to radon, leading the US Centers for Disease Control and Prevention to recommend that all homes be tested for radon, but radon testing is not federally mandated as a requirement for a home sale.[24] A meta-analysis containing estimates from 4 pooled studies (incorporating data from 24 individual case-control studies), 1 case-control study, and 1 cohort study reported an adjusted excess relative risk of lung cancer of 0.15 (95% CI, 0.06-0.25) per 100 Bq/m^3 increase in radon.[25] For homes that have radon levels at or above 4 pCi/L, or 150 Bq/m^3, the Environmental Protection Agency recommends reducing radon levels using measures such as active soil depressurization and improved ventilation. Because no level of radon exposure is considered safe, the Environmental Protection Agency also advises homeowners to consider mitigation for levels between 2 and 4 pCi/L (75-150 Bq/m^3).[26]

In 2022, worldwide, approximately 200 000 cases of lung adenocarcinoma, the predominant histologic subtype of lung cancer, were attributed to ambient air pollution, estimated using a population-attributable fraction model.[8] Specifically, particulate matter with a diameter of less than 2.5 μm ($PM_{2.5}$), found in diesel exhaust or smoke from indoor cooking, can penetrate the alveoli and enter the bloodstream after inhalation. $PM_{2.5}$, a known cause of lung cancer, promotes tumorigenesis via an influx of macrophages and release of interleukin-1β.[27] Approximately 99% of people worldwide live in areas that exceed World Health Organization guidelines on $PM_{2.5}$ (<5 μg/m^3 annually). A recent multicountry study (6799 lung cancer cases, including 3615 lung cancer cases in nonsmoking individuals and 26 807 controls without lung cancer) reported an association between $PM_{2.5}$ levels and *EGFR*-driven lung cancer incidence, with the relative incidence rates increasing by 0.63 to 1.82 (per 100 000 population), per 1 μg/m^3 increase of $PM_{2.5}$.[28]

Other environmental particulates associated with lung cancer in nonsmoking individuals include asbestos and silica, which are considered group 1 carcinogens by the International Agency for Research on Cancer.[29] Secondhand smoke exposure is also associated with an increased risk of lung cancer among nonsmoking individuals. A systematic review of a retrospective observational cohort and 5 case-control studies that included 622 469 individuals reported a hazard ratio (HR) of 1.28 (95% CI, 1.10-1.48) for lung cancer in nonsmoking individuals.[30] A secondary analysis of the Global Burden of Disease Study data reported that secondhand smoke was responsible for nearly 100 000 deaths worldwide in 2021.[31] Prior radiotherapy to the chest is another risk factor for lung cancer; a retrospective observational study that found 1.74% of 613 746 patients (smoking status unavailable) who received radiotherapy during breast cancer treatment subsequently developed lung cancer.[32]

Familial and Genetic Risk

Data from a case-control study of 24 380 individuals with lung cancer and 23 399 controls indicated that individuals with a first-degree relative with lung cancer had an odds ratio of 1.51 (95% CI, 1.39-1.63) for developing lung cancer compared with those without this family history.[33]

Large-scale genome-wide association studies have identified a pattern of low penetrance germline variants in regions such as 5p15.33 and 3q28 associated with increased risk of lung cancer in nonsmoking individuals. These variants involve multiple genes associated with cell cycle regulation, DNA damage, immune response, and genomic stability.[34] Singular, highly penetrant germline variants in genes such as *EGFR* and *YAP1* are rare, but have been reported in familial lung cancers from Western and Asian populations, respectively.[35,36] Clonal hematopoiesis, the age-related expansion of a subpopulation of hematopoietic cells with acquired somatic mutations, has been associated with the incidence of many diseases, including lung cancer. In a clonal hematopoiesis case-control study of 104 cases of incident lung cancers and 343 age-, smoking status–, and sex-matched controls, the odds ratio for risk of incident lung cancer was 1.43 (95% CI, 1.06-1.94). Although limited by the relatively small number of nonsmoking individuals (11 cases and 35 controls) included in the analysis, this effect may be independent of smoking history.[37]

Compared with people with a history of smoking and lung cancer, nonsmoking individuals with lung cancer have higher rates of somatic variants and gene rearrangements that activate genes that directly contribute to carcinogenesis and represent potential molecular targets.[38-42] For example, in a study of 17 712 patients with lung cancer, somatic mutations in the *EGFR* gene were identified in 40% to 60% of lung cancer tumor tissue in nonsmoking individuals compared with approximately 10% of people with a history of smoking and lung cancer.[43] A study of 121 patients with lung cancer younger than age 40 years (73% nonsmoking individuals) indicated that 84% carried an actionable oncogenic variant[44] (**Table 1**). Rearrangements in the *ALK* and *ROS1* genes are found in 5% to 14% and 1% to 2% of tumors, respectively, of patients with lung cancer,[45] but with higher rates in nonsmoking individuals (odds ratio, 3.57 [95% CI, 2.04-6.25] for *RET* fusions in nonsmoking individuals compared with people with a history of smoking).[46] Other actionable genomic alterations found more frequently in lung cancer biopsy specimens from nonsmoking individuals compared with people with a history of smoking include somatic variants in *ERBB2* (formerly *HER2*), and gene fusions or rearrangements in *RET, NTRK1/2/3*, and *NRG1*.[46,47] A study of nonsmoking patients with lung adenocarcinomas (n = 160) reported 78% to 92% had clinically actionable driver variations compared with 49.5% in people who had ever smoked (n = 299).[38] A study of 188 lung adenocarcinomas that included 20 nonsmoking individuals found that nonsmoking individuals had a 10-fold lower tumor mutational burden, defined as the total number of DNA mutations in cancer cells, than tumors from people with a history of smoking.[48]

Screening

To reduce lung cancer mortality, the US Preventive Services Task Force (USPSTF) guidelines recommend low-dose computed tomographic (CT) scanning for individuals aged 50 to 80 years with a 20 or more pack-year history of smoking who currently smoke or quit within the past 15 years.[49-52] However, the USPSTF does not currently recommend screening for lung cancer in nonsmoking individuals.[53,54] In contrast, Taiwan initiated a national lung cancer early detection program in 2022, offering biennial low-dose CT scans to nonsmoking individuals (aged 45-74 years for females and 50-74 years for males) with a family history of lung cancer.[55] This screening program was based on results from a study that performed CT screening for 12 011 asymptomatic Taiwanese nonsmoking individuals aged 55 to 75 years with risk factors such as having a first-degree relative with lung cancer, passive smoking exposure, or cooking without ventilation. This study reported that 2.7% with a family history of lung cancer were diagnosed with incident lung cancer, in contrast to 1.6% without a family history ($P < .0001$), and 77.4% of lung cancers were diagnosed at stage I.[55]

Clinical Presentation

Among individuals diagnosed with lung cancer, nonsmoking individuals have a similar clinical presentation as individuals with a history of tobacco consumption.[38] In a registry of 9876 patients diagnosed with lung cancer in Spain, 1177 (11.9%) were nonsmoking individuals. Among nonsmoking individuals, the most common symptoms at diagnosis were cough (34%), dyspnea (29%), pain (28%), and weight loss (19%). The percentage who were asymptomatic (31.5% of all patients) did not differ when stratified by smoking status.[56] In a retrospective series of 539 patients who underwent surgical resection for primary lung cancer at the University of California, Los Angeles, 345 (64%) were asymptomatic and had their tumors discovered incidentally on CT imaging and 143 (41%) were people who had never smoked.[57]

Assessment and Diagnosis

Imaging

The recommended imaging study for patients with chest symptoms concerning for lung cancer or with an abnormality detected on chest radiograph is a contrast-enhanced chest CT to evaluate the primary lesion and assess for nodal involvement and metastases.

Brain imaging, preferably magnetic resonance imaging, should be performed in all patients diagnosed with lung cancer, as 10% to 25% have brain metastases at diagnosis.[58] This rate may be higher in patients with genomic alterations such as *EGFR* mutations and *ALK* or *RET* fusions with 52% of 50 patients presenting with brain metastases having an *EGFR* variation in 1 study.[58] Fluorodeoxyglucose positron emission tomography–CT should be performed for patients being considered for potentially curative local therapy (such as radiotherapy or surgery) to determine extent of nodal involvement and to exclude metastatic disease.[59]

Patients with indeterminate pulmonary nodules (a focal distinct radiographic density surrounded by lung tissue) should undergo follow-up imaging based on the Fleischner Society guidelines (eTable in the Supplement). More than 95% of indeterminate pulmonary nodules are benign and the probability of malignancy is less than 1% for all nodules smaller than 6 mm (eTable in the Supplement).[60]

Tissue Diagnosis and Molecular Testing

Biopsy of tumor tissue in the lung and/or lymph nodes performed with percutaneous biopsy or bronchoscopic biopsy, often guided by endobronchial ultrasound, confirms the diagnosis and may be useful

Table 1. Driver Variation Frequency and Current Availability of Targeted FDA-Approved Drugs[a,b]

Oncogene	Variation frequency in nonsmoking individuals, %	Variation frequency in people with a history of smoking, %[c]	Targetable alteration	FDA-approved drugs (target alteration)	Year of first approval	Median overall survival, mo	Median progression-free survival, mo	Delivery route
EGFR	43	11	(1) Exon 19 deletion or exon 21 L858R	Afatinib (1,2)	2018	27.9	11	Oral
				Amivantamab (3)	2024	NR	11.4	Intravenous
				Dacomitinib (1,2)	2018	34.1	14.7	Oral
				Erlotinib (1,2)	2016	84.2	10	Oral
				Gefitinib (1,2)	2003	27	9.2	Oral
			(2) S768I, L861Q, and/or G719X	Osimertinib (1,2)	2015	38.6	18.9	Oral
			(3) Exon 20 insertion variation	Amivantamab + chemotherapy	2024	38.9	20.6	Oral
ALK	12	2	Rearrangement	Alectinib	2015	NR	34.8	Oral
				Brigatinib	2017	NR	16.7	Oral
				Ceritinib	2014	51.3	16.6	Oral
				Crizotinib	2015	NR	10.9	Oral
				Ensartinib	2024	NR	25.8	Oral
				Lorlatinib	2018	NR	NR	Oral
KRAS	9.10	29	G12C	Adagrasib	2022	NR	7.4	Oral
				Sotorasib	2021	12.5	6.3	Oral
ROS1	3.22	1.11	Rearrangement	Entrectinib	2019	47.8	15.7	Oral
				Crizotinib	2011	NR	10.9	Oral
				Repotrectinib	2023	NR	35.7	Oral
				Taletrectinib	2025	NR	45.6	Oral
ERBB2 (formerly *HER2*)	2.22	1.34	Variation	Fam-trastuzumab deruxtecan	2022	17.8	8.2	Intravenous
RET	2	0.5	Rearrangement	Pralsetinib	2022	21.2	10.7	Oral
				Selpercatinib	2022	NR	24.8	Oral
BRAF	1.83	4.12	V600E	Encorafenib/binimetinib	2018	33.6	14.9	Oral
				Dabrafenib/trametinib	2013	25.9	11.1	Oral
MET	1.5	2.1	Exon 14 skipping	Capmatinib	2020	20.8	10.8	Oral
				Tepotinib	2021	29.7	15.9	Oral
NRG1	0.18	0.08	Gene fusion	Zenocutuzumab	2024	Not reported	6.8	Intravenous
NTRK	~ 0.17[d]		Gene fusion	Entrectinib	2019	41.5	28	Oral
				Repotrectinib	2024	NR	NR	Oral

Abbreviations: FDA, Food and Drug Administration; NR, not reached (meaning data were too immature to calculate data).

[a] Frequency data from whole-exome sequencing profiling of 160 people with lung cancer.

[b] Nonsmoking individuals are defined as people who have smoked fewer than 100 cigarettes in their lifetime. People with a history of smoking are defined as people who currently or formerly smoked.

[c] Smoking values are weighted averages among the people with a history of smoking categories.[38]

[d] Reliable data by smoking status not available.

for staging. Molecular testing should be performed for all nonsmoking individuals with lung cancer to aid decision-making about use of targeted therapy and immunotherapy.[61] High-throughput next-generation sequencing with DNA and RNA panels is currently recommended to identify genetic variants or rearrangements in genes including *EGFR*, *ALK*, *ROS1*, and *RET* for consideration of targeted therapies.[61] Characterization of circulating tumor DNA (ctDNA) or liquid biopsy is emerging as a test for detecting actionable genomic variants in plasma and may be particularly useful if limited tissue is available for molecular analyses. A study of 171 individuals with lung cancer reported that compared with patients with ctDNA–high status (n = 38), those with a preoperative ctDNA–negative status (n = 18) had improved 5-year overall survival (100% [95% CI, 100%-100%] vs 48.8% [95% CI, 34.7%-68.7%]; *P* = .0024).[62] Among patients who develop resistance to treatment, rebiopsy of lung cancer or liquid biopsy can reveal mechanisms of resistance such as alterations in genes encoding components of the PI3K/AKT/mTOR pathway and alterations in RAS, which can guide subsequent treatment strategies.[63]

Staging

Most nonsmoking individuals with lung cancer are diagnosed at an advanced stage, typically with unresectable locally advanced disease (stage III) or distant metastases (stage IV). In a retrospective cohort study of 254 nonsmoking patients with lung cancer, 62.9% were diagnosed with stage III or IV disease.[64] In another retrospective cohort study of 795 nonsmoking patients, 43.4% were diagnosed with stage IIIB to IV cancer.[64] Early detection of lung cancer

in nonsmoking individuals may be difficult due to absence of routine screening in this population and the often nonspecific symptoms such as cough and fatigue. However, staging at diagnosis can vary significantly by geography and by use of CT screening. For example, in the targeted low-dose CT screening trial for high-risk people who had never smoked in Taiwan, 246 of 257 (95.7%) were diagnosed with stage IA or IB lung cancer, demonstrating the potential effect of screening in shifting diagnosis toward earlier stages.[55]

Treatment

Treatment for lung cancer is guided by the stage, histology, and molecular status of the tumor; patient performance status, comorbidities, and preferences; and does not differ by smoking status. Treatment options primarily include surgery, radiation therapy, and systemic therapy often given in combination depending on disease stage and often involving multidisciplinary assessment and treatment by surgeons, medical and radiation oncologists, radiologists, pathologists, and nurses to deliver personalized treatment recommendations.

Early-Stage and Locally Advanced Lung Cancer

Surgical resection is the preferred treatment for patients with anatomically resectable lung cancer (stage I-III) who are medically eligible for surgery, with follow-up CT screening recommended every 6 months for 2 to 3 years and then annually. For patients with stage IB-IIIA and resected *EGFR* mutation positive or *ALK* rearranged non–small cell lung cancer (NSCLC), targeted therapies are effective in both nonsmoking individuals and people with a history of smoking. A phase 3 trial of 682 patients with stage IB-IIIA completely resected *EGFR*-mutation NSCLC reported that among patients with stage II to IIIA disease randomized to 3 years of treatment with the EGFR tyrosine kinase inhibitor (TKI) osimertinib 80 mg once daily or placebo, 4-year disease-free survival was 70% in the osimertinib group vs 29% in the placebo group, with a disease-free survival HR of 0.23 (95% CI, 0.18-0.30) at a median follow-up of 44.2 months (osimertinib) and 19.6 months (placebo).[65] The HR for death or recurrence at 2 years was 0.23 (95% CI, 0.15-0.34) in nonsmoking individuals (n = 488) and 0.10 (95% CI, 0.04-0.22) in those who had smoked (n = 194).[66] A follow-up study of this cohort of patients with stage IB to IIIA disease reported a 5-year overall survival of 85% in the osimertinib group vs 73% in the placebo group (overall HR for death, 0.49 [95% CI, 0.33-0.73]; $P < .001$).[67] In a trial of 257 patients with stage IB, II, or III resected *ALK* rearrangement–positive NSCLC, after 2 years of adjuvant TKI (alectinib) or platinum-based chemotherapy among patients with stage II or IIIA lung cancer, disease-free survival at 2 years was 93.8% in the alectinib group and 63.0% in the chemotherapy group (HR for disease recurrence or death, 0.24 [95% CI, 0.13-0.45]; $P < .001$).[68]

A trial that included 216 patients with unresectable *EGFR*-mutated stage III NSCLC without progression during or after chemoradiotherapy reported improved median progression-free survival (PFS) with adjuvant osimertinib vs placebo (39.1 months vs 5.6 months), with an HR for disease progression or death of 0.22 (95% CI, 0.14-0.34) in nonsmoking individuals (n = 102) and 0.26 (95% CI, 0.14-0.48) in people with a history of smoking (n = 41).[69]

Immunotherapy with programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors are commonly prescribed neoadjuvant or adjuvant treatments for patients with early-stage lung cancer. However, their role for treating nonsmoking individuals with lung cancer is less clear due to a lower likelihood of response to immunotherapy, particularly in the context of *EGFR* gene mutations or *ALK* gene rearrangements. A pooled analysis of 3 randomized trials that included treating individuals with nivolumab (n = 292), pembrolizumab (n = 691), or atezolizumab (n = 144) vs docetaxel (n = 776) reported that single-agent immunotherapy did not improve overall survival in *EGFR*-mutation NSCLC, regardless of smoking status (HR, 1.05 [95% CI, 0.70-1.55]).[70] Additionally, patients with *EGFR* gene mutations and *ALK* gene rearrangements have often been excluded from perioperative and adjuvant studies of immunotherapy for patients with lung cancer; few nonsmoking individuals have therefore been included in these studies.[71,72] In one trial, 797 patients with stage II, IIIA, or IIIB NSCLC were randomized to the PD-1 inhibitor pembrolizumab 200 mg (n = 397) or placebo (n = 400) given with chemotherapy prior to surgery and for 12 months after surgery vs preoperative chemotherapy alone.[73] Overall survival in all patients at 36 months was 71% (95% CI, 66%-76%) in the pembrolizumab group and 64% (95% CI, 58%-69%) in the placebo group (HR, 0.72 [95% CI, 0.56-0.93]).[73] The greatest benefit for perioperative pembrolizumab was seen in those who currently smoked (HR for OS, 0.59 [95% CI, 0.38-0.93]), with less benefit seen in nonsmoking individuals (HR, 1.00 [95% CI, 0.41-2.46]).[74]

Unresectable Locally Advanced or Metastatic Lung Cancer

For patients with advanced-stage lung cancer, treatment typically consists of a combination of chemotherapy, immunotherapy, or targeted therapies. Treatment with targeted agents have shown benefits over chemotherapy for individuals who have *EGFR* mutations, *ALK* rearrangements, and *RET* rearrangements. A trial that randomized 556 patients with advanced-stage *EGFR* mutation lung cancer reported the HR for disease progression or death was significantly lower among patients randomized to osimertinib vs first-generation oral EGFR-TKI, with an HR of 0.48 (95% CI, 0.34-0.68) for those who smoked (n = 199) and 0.45 (95% CI, 0.34-0.59) for nonsmoking individuals (n = 357).[74] Overall survival was also improved with osimertinib vs first-generation oral EGFR-TKI (38.6 months vs 31.8 months; HR, 0.80).[75] A post hoc analysis of 5-year outcomes of the CROWN study, in which 296 patients with advanced *ALK*-positive NSCLC were randomized to lorlatinib (an ALK inhibitor) or crizotinib (a TKI), reported improved outcomes with lorlatinib.[76] In the lorlatinib group, median PFS was not reached (NR [95% CI, 64.3-NR]) vs 9.1 months (95% CI, 7.4-10.9) in the crizotinib group (HR, 0.19 [95% CI, 0.13-0.27]); 5-year PFS was 60% (95% CI, 51%-68%) in the lorlatinib group vs 8% (95% CI, 3%-14%) in the crizotinib group.[76] Other Food and Drug Administration–approved oncogene-driven therapies, such as repotrectinib or taletrectinib for *ROS1*-positive tumors, have demonstrated higher response rates and durations of response than seen historically with chemotherapy in both people with a history of smoking and nonsmoking individuals with objective response rates, defined as the percentage of patients with a partial or complete response to therapy, seen in 89% of individuals (n = 152) for taletrectinib and 79% of individuals with repotrectinib (n = 71)[77,78] (Table 1).

For lung cancers without actionable genomic alterations that can be treated with targeted therapy, chemotherapy combined with immunotherapy can be considered.[79,80] However, single-agent

immunotherapy with inhibitors of PD-1 or PD-L1, such as pembrolizumab, have limited efficacy in nonsmoking individuals,[81] particularly with *EGFR* or *ALK* alterations, and should not be used for nonsmoking patients with these variants and unresectable locally advanced or metastatic lung cancer.[81]

Local therapy, such as radiotherapy or surgery, may be used to treat sites of metastatic disease. For brain metastases, stereotactic radiosurgery can be used in preference to whole-brain radiotherapy to minimize central nervous system toxicity including cognitive effects.[82] TKIs with excellent central nervous system penetration, such as the *EGFR* inhibitor osimertinib or the ALK inhibitor lorlatinib, may be used instead of radiotherapy for brain metastasis in many patients.[69] Stereotactic ablative radiotherapy (SABR) is recommended for oligometastatic disease in conjunction with systemic treatment due to its ability to deliver more targeted radiotherapy to a region.[83] In an open-label phase 2 trial of 99 patients with a controlled primary tumor and 1 to 5 metastases, median overall survival was 41 months (95% CI, 26-NR) in patients randomized to SABR vs 28 months (95% CI, 19-33) with standard care.[84] However, adverse events (grade 2 or higher) occurred in 19 of 66 patients (29%) in the SABR group vs 3 (9%) of 33 in the standard care group (P = .026), and treatment-related deaths occurred in 3 of 66 patients (4.5%) after SABR compared with 0 in the standard care group.[84]

Prognosis

Lung cancer survival primarily depends on stage at diagnosis (5-year survival rate of 65% for stage I vs <10% for stage IV), performance status, and presence of actionable genetic alterations for treatment.[85] A prospective cohort study of 5594 patients with NSCLC (61.8% lung adenocarcinoma) reported a median overall survival of 58.9 months (95% CI, 51.9-67.4) for 795 nonsmoking individuals (55.8% stage 1A-IIIA, 43.4% stage IIIB-IV), a median overall survival of 51.2 months (95% CI, 47.7-54.6) for 3308 people who had previously smoked (68.9% stage 1A-IIIA, 30.1% stage IIIB-IV), and a median overall survival of 34 months (95% CI, 29.1-42.3) for 1491 people who currently smoked (63.6% stage 1A-IIIA, 35.9% stage IIIB-IV).[64]

Significant improvements in PFS and overall survival among patients with lung cancer have occurred with use of targeted therapies directed at oncogenic drivers.[59,86,87] A population-based study using the Surveillance, Epidemiology, and End Results data reported that 2-year lung cancer–specific survival improved from 26% for patients diagnosed in 2001 to 35% in 2014, a change largely attributable to the advent of targeted therapies. A French study reported that median overall survival among patients diagnosed with lung adenocarcinoma increased from 8.5 months in 2000 (n = 1684) to 20.7 months in 2020 (n = 5015), although no information on smoking status was provided.[88] The median overall survival for advanced *EGFR* mutation–positive lung cancer treated with EGFR inhibitors is currently 38.6 months and the median overall survival for patients with advanced *ALK*-positive NSCLC treated with ALK inhibitors exceeds 5 years among people with a history of smoking and nonsmoking individuals (Table 1).[75,89]

Practical Considerations

Individuals with lung cancer may face stigma due to the disease's association with smoking, which can lead to feelings of isolation.[81]

Table 2. Lung Cancer Support Groups Available to Patients, Clinicians, and Scientists for Advocacy, Support, and Funding

Support group	Role/focus
ALK Positive	Support and advocacy for patients with *ALK*-positive lung cancer, focusing on research and education
BRAF Bombers	Dedicated to supporting and educating patients with *BRAF*-mutated lung cancer
EGFR Resisters	Support and advocacy group for patients with *EGFR*-mutated lung cancer, focusing on treatment resistance
Exon 20 Group	Specializes in supporting patients with *EGFR* exon 20 insertion variations, advocating for research and treatments
KRAS Kickers	Supports patients with *KRAS*-mutated lung cancer, promoting research and sharing treatment information
LUNGevity Foundation	Offers support, education, and funding for lung cancer research, focusing on early detection and treatment
MET Crusaders	Advocacy for those affected by lung cancer with a *MET* variation
RETpositive	Supports patient with forms of *RET*-positive cancers
ROS1ders	Seeks to improve outcomes for those with *ROS1*-positive cancers

Patient education and psychosocial support for nonsmoking individuals with lung cancer enhances well-being and may improve outcomes through greater adherence to treatment as found in a systematic review of 18 cohorts.[80] A trial of 151 patients with metastatic lung cancer randomized to early palliative care (n = 77 with 18 nonsmoking individuals) vs standard of care (n = 74 with 16 nonsmoking individuals) found that early palliative care led to significant improvement in quality of life, reduced depressive symptoms, and improved median survival (11.6 months vs 8. 9 months, P = .02).[90] Many support and advocacy groups exist, including those focusing on specific molecular subtypes of lung cancer (**Table 2**). Proactive follow-up of respiratory symptoms with CT imaging, regardless of a patient's smoking history, could lead to earlier-stage lung cancer diagnosis, a message echoed by awareness campaigns such as See Through the Symptoms[10] and All You Need Is Lungs.[9]

Future Directions

Ongoing trials, such as the Female Asian Nonsmoker Screening Study (FANSS), in the US are evaluating potential benefits of screening for lung cancer among high-risk groups of nonsmoking individuals.[91] In addition, studies of biomarker-based early detection approaches in blood (such as multicancer early detection tests and proteomic approaches) are in progress to determine whether lung cancers can be detected at an early and more curable stage.

Limitations

This review has several limitations. First, smoking history is often not included in many databases, cancer registries, and clinical trials, making it difficult to accurately determine the incidence and prevalence of lung cancer in nonsmoking individuals and to evaluate treatment outcomes based on smoking status. Second, accurate quantification of environmental exposures, such as air pollution, is challenging. Third, the quality of the evidence was not formally evaluated. Fourth, some articles may have been missed.

Conclusions

Lung cancer in nonsmoking individuals accounts for 15% to 20% of the lung cancer cases worldwide. Among patients with lung cancer, nonsmoking individuals are more likely to have genomic alterations, such as *EGFR* mutations or *ALK* gene rearrangements, and these patients have improved survival when treated with TKIs compared with chemotherapy.

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