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Postdiagnosis Smoking Cessation and Reduced Risk for Lung Cancer Progression and Mortality

A Prospective Cohort Study

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Background: Lung cancer is the leading cause of cancer death worldwide, and about one half of patients with lung cancer are active smokers at diagnosis.

Objective: To determine whether quitting smoking after diagnosis of lung cancer affects the risk for disease progression and mortality.

Design: Prospective study of patients with non–small cell lung cancer (NSCLC) who were recruited between 2007 and 2016 and followed annually through 2020.

Setting: N.N. Blokhin National Medical Research Center of Oncology and City Clinical Oncological Hospital No. 1, Moscow, Russia.

Patients: 517 current smokers who were diagnosed with early-stage (IA-IIIA) NSCLC.

Measurements: Probabilities of overall survival, progression-free survival, and lung cancer–specific mortality and hazard ratios (HRs) for all-cause and cancer-specific mortality.

Results: During an average of 7 years of follow-up, 327 (63.2%) deaths, 273 (52.8%) cancer-specific deaths, and 172 (33.7%) cases of tumor progression (local recurrence or metastasis) were recorded. The adjusted median overall survival time was 21.6 months higher among patients who had quit smoking than those who continued smoking (6.6 vs. 4.8 years, respectively; $P = 0.001$). Higher 5-year overall survival (60.6% vs. 48.6%; $P = 0.001$) and progression-free survival (54.4% vs. 43.8%; $P = 0.004$) were observed among patients who quit than those who continued smoking. After adjustments, smoking cessation remained associated with decreased risk for all-cause mortality (HR, 0.67 [95% CI, 0.53 to 0.85]), cancer-specific mortality (HR, 0.75 [CI, 0.58 to 0.98]), and disease progression (HR, 0.70 [CI, 0.56 to 0.89]). Similar effects were observed among mild to moderate and heavy smokers and patients with earlier and later cancer stages.

Limitation: Exposure measurements were based on self-reported questionnaires.

Conclusion: Smoking cessation after diagnosis materially improved overall and progression-free survival among current smokers with early-stage lung cancer.

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In 2018, an estimated 2.09 million people worldwide were diagnosed with lung cancer and 1.76 million died of this disease, making it the leading cause of cancer death worldwide (1). Non–small cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases, with cigarette smoking being the major risk factor (2). Since the successful implementation of tobacco control policies over the past decades, the incidence of lung cancer has been declining (3). However, lung cancer survival rates have improved only slightly and 5-year survival remains poor, even in patients with early-stage disease (4–8).

More than 80% of patients with NSCLC have a history of smoking, and around 40% to 50% are current smokers at the time of diagnosis (9, 10). Evidence that smoking cessation after diagnosis might improve the survival of patients with cancer is limited and mainly originates from retrospective studies that measured smoking status at the time of diagnosis or treatment without follow-up (10–12), or from a few prospective studies with a limited number of smokers and short follow-up (1 year) (13, 14). Furthermore, it is not clear whether any effects of smoking cessation differ between mild to moderate smokers and heavy smokers or among those with earlier- versus later-stage tumors.

We performed a large prospective study with multiple repeat interviews to investigate changes in smoking behavior after a diagnosis of lung cancer among current smokers to evaluate whether smoking cessation affected overall and progression-free survival and the risk for all-cause and lung cancer–specific mortality among these patients.

Methods

Study Sample and Design

This study included patients with newly diagnosed early-stage (I, II, or IIIA) NSCLC, coded as C34 (site code) and primary invasive (morphology code 3) according to the third edition of the International Classification of Diseases for Oncology (15) who were originally recruited to a large multicentric prospective cohort study of lung cancer survival in Russia. Participants were recruited between May 2007 and July 2016 from the departments of thoracic surgery at N.N. Blokhin National Medical Research Center of Oncology and City Clinical Oncological Hospital No. 1, Moscow, Russia, after receiving a histologic diagnosis of NSCLC and before receiving any local or systematic treatment of their current

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tumor. Participants who were current smokers at the time of diagnosis and had been actively followed to collect data on changes in smoking behavior and disease status were considered eligible for our study (Figure 1). Current smokers were defined as individuals who had been smoking at least 1 cigarette per day for more than 1 year before the time of diagnosis. At enrollment, informed written consent was obtained from all participants. This study was approved by the ethical committees of the International Agency for Research on Cancer and N.N. Blokhin National Medical Research Center of Oncology before data collection.

Questionnaires and Enrollment Data

At enrollment, all participants had a personal interview during which a structured questionnaire was completed to gather information on demographic characteristics, family and medical histories, and various exposures and lifestyle habits. Anthropometric measurements were also obtained. Body mass index was categorized as underweight (<18.5 kg/m^2), normal (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), or obese (≥30 kg/m^2).

Participants were asked whether they had been diagnosed with any chronic health conditions, including diabetes mellitus, hypertension, stroke, and cardiovascular disease. They were also asked about their lifetime history of cigarette smoking, including the frequency of smoking and the average number of cigarettes smoked each day. We calculated the cumulative cigarettes smoked in pack-years (based on a pack of 20 cigarettes) by multiplying the number of cigarette packs smoked per day by the number of years the participant had smoked. The participants were also asked about their lifetime history of regularly drinking alcoholic beverages. Regular drinking was defined as drinking alcoholic beverages at least once per week for 1 year.

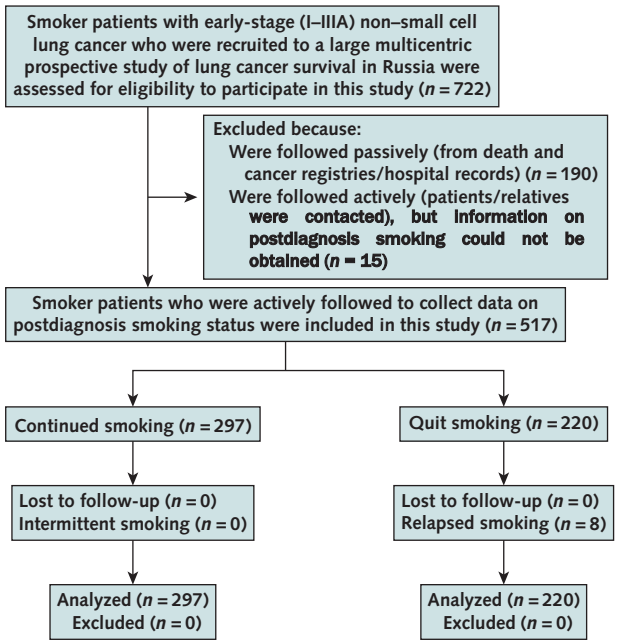
All relevant medical, imaging, and pathology documents were reviewed by an expert local team to complete a questionnaire that included necessary information on the histopathologic features of the tumor and current illness. The completed questionnaires and data underwent a quality control and quality assurance process by a central team at the International Agency for Research on Cancer. We categorized the participants on the basis of their tumor histology as having squamous cell carcinoma, adenocarcinoma, and neuroendocrine tumors. Tumor stage was classified at diagnosis and before any treatment was given for the current tumor, according to the seventh edition of the TNM classification system from the American Joint Commission on Cancer (16). For participants whose disease was diagnosed before 2010, tumor stage was based on the sixth edition of the TNM classification system, which we converted to the seventh edition classification by using the guidelines of both editions (Appendix Tables 1 and 2, available at Annals.org).

Follow-up and Data Collection

Participants were followed annually to determine their vital status, tumor progression, events occurring after diagnosis (including recurrence and metastasis), and therapeutic procedures that they had received during each follow-up period. Active follow-up was performed by contacting the patients and their families and reviewing their medical records. When necessary, responsible physicians were also contacted. The cohort data were linked to the national cancer and death registries, to avoid misclassification and to record the primary and secondary cause of death and the occurrence of second primary cancers on the basis of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (17).

During each annual follow-up, the participants were asked about stopping smoking and, if applicable, the time of smoking cessation. Participants were categorized as "quit smoking" if they reported to have quit smoking completely during the follow-up time. Otherwise, participants were categorized as "continued smoking." Eight patients who had quit smoking were reported to have relapsed smoking in subsequent follow-up periods (Figure 1).

Figure 1. Study flow diagram.



Statistical Analysis

Failure time regression models with time-dependent covariates (18, 19) were used to analyze overall survival, progression-free survival, and lung cancer–specific survival. In this method, a time-dependent variable for "quit smoking" is used to define patients who quit smoking and those who continued smoking. For patients who quit smoking, the value of the time-dependent variable is 0 before the time of quitting smoking and changes to 1 when they quit smoking and onward. For the continuing smokers, the value remains as 0 in the follow-up. For patients who quit smoking and then relapsed smoking, the value of the time-dependent variable is 0 before the time of quitting smoking and after the time of relapsing smoking (18, 19).

Table 1. Baseline Demographic and Clinical Characteristics and Postenrollment Treatments

Characteristic	All Patients	Patients Who Continued Smoking	Patients Who Quit Smoking
Participants, *n (%)*	517 (100.0)	297 (57.4)	220 (42.5)
Mean age (SD), *y*	61.3 (7.9)	60.9 (7.5)	61.9 (8.4)
Gender, *n (%)*			
Male	458 (88.5)	264 (88.8)	194 (88.1)
Female	59 (11.4)	33 (11.1)	26 (11.8)
Education, *n (%)*			
University education	174 (33.6)	97 (32.6)	77 (35.0)
School education	343 (66.3)	200 (67.3)	143 (65.0)
Median BMI (IQR), *kg/m²*	24.9 (22.5–28.0)	24.4 (22.2–27.9)	25.8 (23.1–28.3)
Chronic diseases, *n (%)**			
No	343 (66.3)	194 (65.3)	149 (67.7)
Yes	174 (33.6)	103 (34.6)	71 (32.2)
Regular alcohol drinking, *n (%)*			
Never	143 (27.6)	86 (28.9)	57 (25.9)
Former	102 (19.7)	46 (15.4)	56 (25.4)
Current	272 (52.6)	165 (55.5)	107 (48.6)
Median cumulative cigarettes smoked (IQR), *pack-years*	46.9 (36.0–57.1)	47.0 (36.0–57.2)	46.0 (35.7–57.0)
Histology, *n (%)*			
Squamous cell carcinoma	307 (59.3)	177 (59.6)	130 (59.0)
Adenocarcinoma	172 (33.2)	99 (33.3)	73 (33.1)
Neuroendocrine tumors	38 (7.3)	21 (7.0)	17 (7.7)
Tumor stage, *n (%)*			
IA	139 (26.8)	75 (25.2)	64 (29.0)
IB	152 (29.4)	91 (30.6)	61 (27.7)
IIA	63 (12.1)	40 (13.4)	23 (10.4)
IIB	49 (9.4)	26 (8.7)	23 (10.4)
IIIA	114 (22.0)	65 (21.8)	49 (22.2)
Surgery, *n (%)*			
No	60 (11.6)	39 (13.1)	21 (9.5)
Yes	457 (88.3)	258 (86.8)	199 (90.4)
Chemotherapy, *n (%)*			
No	401 (77.5)	231 (77.7)	170 (77.2)
Yes	116 (22.4)	66 (22.2)	50 (22.7)
Radiation therapy, *n (%)*			
No	404 (78.1)	234 (78.7)	170 (77.2)
Yes	113 (21.8)	63 (21.2)	50 (22.7)

BMI = body mass index; IQR = interquartile range.
* Hypertension, diabetes mellitus, stroke, and cardiovascular diseases.

Cox proportional hazards regression models were used to assess the probability of overall and progression-free survival among participants who quit versus continued smoking. Fine–Gray competing-risks regression models, accounting for death from other causes as the competing event, were used to assess the cumulative incidence of lung cancer–specific death among participants who quit versus those who continued smoking.

In all models, the entry time was defined as the date at which the participant was diagnosed with NSCLC. To assess the probability of overall survival and hazards of all-cause mortality, date of death from any cause was set as the end of follow-up time, whereas date of the last contact was set as the censoring date for patients who were alive at the last contact (through 7 June 2020). To assess the probability of progression-free survival, date of death from any cause or date of tumor progression, whichever occurred first, was set as the end of follow-up time, whereas date of the last contact was set as the censoring date for patients who were alive and did not have any documented tumor progression at the last contact. To assess the probability of lung cancer–specific mortality and its hazards, date of death from lung cancer was set as the end of follow-up time for the event of interest, date of death from any other cause was set as the end of follow-up time for the competing event, and date of last contact was set as the censoring date for patients who were alive at the last contact. Appendix Table 3

Table 2. Estimates of Survival Rates Among Patients With Early-Stage Non–Small Cell Lung Cancer Who Quit Smoking Versus Those Who Continued Smoking After Diagnosis

Variable	Patients Who Continued Smoking	Patients Who Quit Smoking	*P* Value
Patients, *n* (%)	297 (57.4)	220 (42.5)	
Adjusted estimates of overall survival*			0.001
Median survival time, *y*	4.8	6.6	
Probability of survival at 3 y (95% CI), %	66.2 (62.3–70.8)	74.5 (69.1–79.3)	
Probability of survival at 5 y (95% CI), %	48.6 (44.3–55.2)	60.6 (53.6–67.1)	
Adjusted estimates of progression-free survival*			0.004
Median progression-free survival, *y*	3.9	5.7	
Probability of progression-free survival at 3 y (95% CI), %	58.3 (53.7–63.5)	67.2 (60.9–72.7)	
Probability of progression-free survival at 5 y (95% CI), %	43.8 (38.1–48.9)	54.4 (46.7–61.5)	
Adjusted estimates of lung cancer–specific mortality*†			0.040
Median time to lung cancer–specific mortality, *y*	6.0	7.9	
Probability of lung cancer–specific mortality at 3 y (95% CI), %	30.1 (25.1–34.4)	23.7 (17.2–27.1)	
Probability of lung cancer–specific mortality at 5 y (95% CI), %	43.5 (38.5–50.0)	35.0 (27.3–41.7)	

* Estimates are derived from adjusted time-dependent models, where quitting smoking was defined as a time-dependent variable. These models are adjusted for year of diagnosis, age at diagnosis, sex, education, body mass index, history of chronic diseases, cumulative cigarettes smoked, alcohol drinking status, tumor histology, tumor stage, surgical resection of the tumor, receipt of chemotherapy, and receipt of radiation therapy.
† In this model, death from any cause other than lung cancer was set as a competing event.

(available at Annals.org) summarizes the statistical models and the time points and definitions of events of interest, competing events, and censoring, as well as the Stata commands that we used to analyze the data.

The multivariate models were adjusted for year of diagnosis (2007–2010, 2011–2013, or 2013–2016), age at diagnosis (continuous), sex, education (school level or university level), body mass index at diagnosis (underweight, normal, overweight, or obese), history of chronic diseases (no or yes), cumulative cigarettes smoked at diagnosis (continuous pack-years), alcohol drinking status at diagnosis (never, former, or current drinker), tumor histology (squamous cell carcinoma, adenocarcinoma, or neuroendocrine tumor), tumor stage at diagnosis (IA, IB, IIA, IIB, or IIIA), surgical resection of the tumor (yes or no), chemotherapy (yes or no), and radiation therapy (yes or no). The model covariates were selected a priori on the basis of the available literature to include the suspected prognostic factors for NSCLC survival and also the variables that might influence the assessed exposure. None of the participants had missing data for the predictor or outcome variables. The proportional hazard assumption was tested by using the Schoenfeld global test, which was met for all variables in the multivariable models except for tumor stage, chemotherapy, and radiation therapy; these variables showed time-varying effects and were therefore treated as time-varying covariates, allowing for time-by-treatment interaction (20).

We repeated the analyses across the strata of mild to moderate smokers versus heavy smokers, patients with earlier- versus later-stage tumors, patients who did versus those who did not receive chemotherapy, and patients who did versus those who did not receive radiation therapy, and we performed an interaction test to assess whether the differences across the strata were statically significant. We performed a sensitivity analysis by exclusively assessing the effects of early smoking cessation on the outcomes of interest, where we selected an arbitrary period of 3 months postdiagnosis and classified those who quit smoking within this period as "smoking quitters" and those who quit after 3 months as "continuing smokers."

Type 1 error was set at 5%. All statistical analyses were 2-sided and were performed by using Stata statistical software, version 15.1.

Role of the Funding Source

This study was funded by the International Agency for Research on Cancer. The funder had no role in the design, conduct, or reporting of the study.

RESULTS

Five hundred seventeen current smokers with early-stage NSCLC were recruited to this study and were prospectively followed for an average of 7.0 years (SD, 2.5 years) (**Figure 1**); 220 participants (42.5%) reported that they had quit smoking, of whom 8 relapsed smoking during follow-up (**Appendix Table 4**, available at Annals.org), and 297 participants (57.4%) reported that they continued smoking after their diagnosis. These groups were similar across a range of demographic, lifestyle, and clinical variables (**Table 1**). Of the 220 patients who quit smoking, 157 (71.3%) quit shortly after diagnosis and before the time of receiving the first treatment, and a further 33 (15%) quit after treatment initiation but during the first year of diagnosis. Thirty patients (13.6%) quit after the first year of diagnosis (**Appendix Figure**, available at Annals.org).

The median overall survival time was 5.2 years, and the 3- and 5-year overall survival rates were 65.1% and 50.9%, respectively. The adjusted median overall survival time was 21.6 months higher (6.6 vs. 4.8 years; $P = 0.001$) among patients who quit smoking than among continuing smokers (**Table 2**). Similarly, patients who quit smoking had 21.6 months longer progression-free survival

(5.7 vs. 3.9 years; $P = 0.004$) than continuing smokers (Table 2). The adjusted proportion of patients still alive was 8.3 percentage points (95% CI, 1.0 to 16.3 percentage points) higher at 3 years and 12 percentage points (CI, 1.4 percentage points to 21.5 percentage points) higher at 5 years among patients who quit smoking than continuing smokers (Table 2). In addition to having higher probability of overall and progression-free survival, participants who quit smoking had a lower cumulative incidence of dying of lung cancer ($P = 0.040$) (Figure 2). The adjusted median time from diagnosis to lung cancer–specific mortality was 22.8 months lower (7.9 vs. 6.0 years; $P = 0.040$) among continuing smokers than among patients who quit smoking (Table 2).

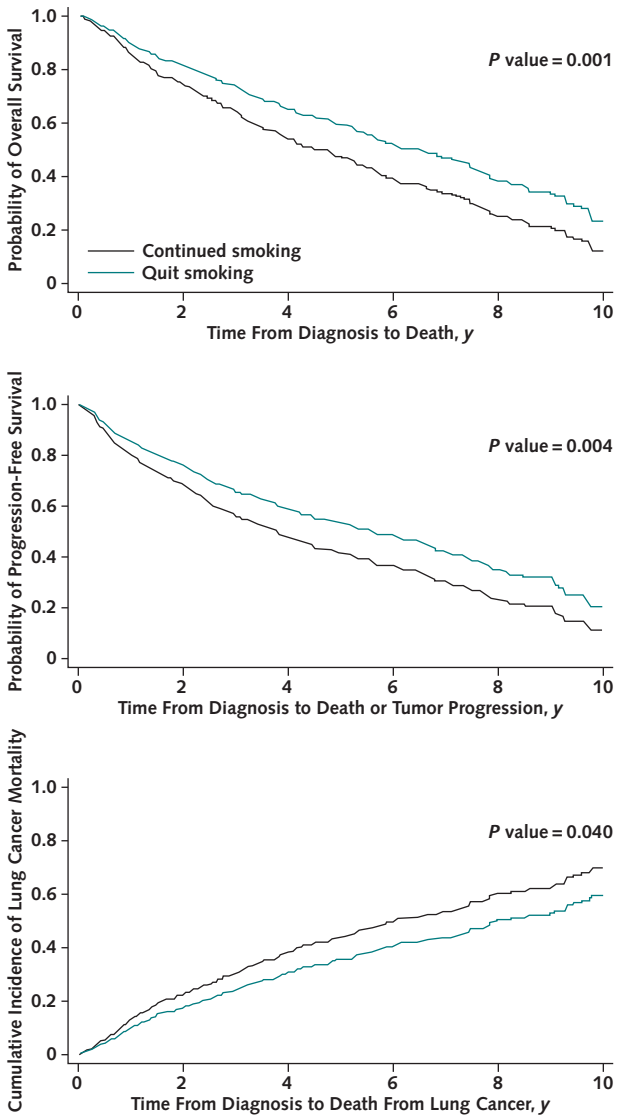
After adjustment for potential confounders and risk factors, quitting smoking postdiagnosis was associated with decreased risk for all-cause mortality (hazard ratio [HR], 0.67 [CI, 0.53 to 0.85]), disease progression (tumor recurrence or death) (HR, 0.70 [CI, 0.56 to 0.89]), and lung cancer–specific mortality (HR, 0.75 [CI, 0.58 to 0.98]) (Table 3). The protective effects of smoking cessation were similar among patients with earlier- and later-stage tumors (Appendix Table 5, available at Annals.org), mild to moderate and heavy cigarette smokers (Appendix Table 6, available at Annals.org), and patients who received and those who did not receive chemotherapy or radiation therapy (Appendix Tables 7 and 8, available at Annals.org). In the sensitivity analysis, where we defined "patients who quit smoking" as those who quit smoking exclusively within the first 3 months after diagnosis, similar results were obtained showing decreased risk for all-cause mortality (HR, 0.68 [CI, 0.53 to 0.87]), disease progression (HR, 0.72 [CI, 0.56 to 0.92]), and lung cancer–specific mortality (HR, 0.77 [CI, 0.59 to 1.02]) among these patients compared with continuing smokers (Appendix Table 9, available at Annals.org).

Discussion

This prospective study of 517 current smokers with early-stage NSCLC who were followed for an average of 7 years shows that quitting smoking after diagnosis improved overall and progression-free survival and decreased the risks for overall mortality and lung cancer–specific mortality in these patients. We observed the protective effects of quitting smoking across all subgroups, including mild to moderate and heavy smokers, patients with earlier and later tumor stages, and patients who received and those who did not receive chemotherapy or radiation therapy.

This study enrolled a large number of patients with early-stage NSCLC and actively followed them for more than 7 years to record possible smoking cessation during the follow-up period and to investigate whether quitting smoking postdiagnosis affected survival and disease progression in these patients. We found quitting smoking after diagnosis to be an important predictor of overall and progression-free survival in patients with early-stage NSCLC. Compared with patients who continued smoking in the follow-up period, those who quit smoking had 33% decreased risk for overall mortality and 25% decreased risk for cancer-specific mortality. Furthermore, the median survival time was 21.6 months longer among those who quit smoking than those who continued smoking. Almost 60% of this cohort of patients did not quit smoking, resulting in a substantial number of excess deaths and disease progression events among this group. These results also show that the beneficial effects of quitting smoking on the survival of patients with NSCLC may be similar or even superior to those reported for the new and emerging

Figure 2. Association between quitting smoking postdiagnosis and probability of overall survival (*top*) and progression-free survival (*middle*) and the cumulative incidence of lung cancer–specific mortality (*bottom*).



Survival probabilities are based on adjusted estimates obtained from time-dependent Cox models, and cumulative incidence of lung cancer–specific mortality was derived from a competing risk model in which death from non-lung cancer causes was considered the competing event. Data are adjusted for year of diagnosis, age at diagnosis, sex, education, body mass index, history of chronic diseases, cumulative cigarettes smoked, alcohol drinking status, tumor histology, tumor stage, surgical resection of the tumor, receipt of chemotherapy, and receipt of radiation therapy.

Table 3. Association Between Quitting Smoking Postdiagnosis and Outcomes Among Patients With Early-Stage Non–Small Cell Lung Cancer

Variable	Patients Who Continued Smoking	Patients Who Quit Smoking	*P* Value
Patients, *n* (%)	297 (57.4)	220 (42.5)	
All-cause mortality*			
Cases (total deaths), *n (%)*	204 (62.3)	123 (37.6)	
Adjusted hazard ratio (95% CI)	1.00 (reference)	0.67 (0.53–0.85)	0.001
Disease progression (tumor recurrence or death)*			
Cases (total deaths), *n (%)*	216 (63.1)	126 (36.8)	
Adjusted hazard ratio (95% CI)	1.00 (reference)	0.70 (0.56–0.89)	0.004
Lung cancer–specific mortality*†			
Cases (total deaths), *n (%)*	171 (62.6)	102 (37.3)	
Adjusted cause-specific hazard ratio (95% CI)	1.00 (reference)	0.75 (0.58–0.98)	0.040

* Estimates are derived from adjusted time-dependent models, where quitting smoking was defined as a time-dependent variable. These models are adjusted for year of diagnosis, age at diagnosis, sex, education, body mass index, history of chronic diseases, cumulative cigarettes smoked, alcohol drinking status, tumor histology, tumor stage, surgical resection of the tumor, receipt of chemotherapy, and receipt of radiation therapy.
† In this model, death from any cause other than lung cancer was set as a competing event.

targeted and immunotherapy therapeutics, which might not be accessible for all patients and require specialized settings (21, 22). In 2010, a meta-analysis of 9 observational and interventional studies that included 1295 patients with early-stage lung cancer (499 with NSCLC and 796 with SCLC) showed an almost 3-fold increase in risk for all-cause mortality and a 2-fold increase in risk for disease recurrence among continuing smokers compared with patients who quit smoking (10). However, most studies in this meta-analysis had measured exposure to smoking retrospectively and lacked clear definitions of smoking status (10). The few available studies that collected smoking information in a prospective manner were too small to provide reliable results (13, 14).

The protective effects of smoking cessation was observed among all subgroups of patients with lung cancer, including those with earlier and later tumor stage, mild to moderate and heavy smokers, and those who received and those who did not receive chemotherapy or radiation therapy. At the time of lung cancer diagnosis, patients may feel fatalistic and not recognize the beneficial effects of quitting smoking postdiagnosis. Furthermore, only a subset of patients with cancer who smoke are recommended to quit smoking by their physicians (23, 24). Our results strongly suggest that patients with lung cancer who smoke should be encouraged to stop smoking at any time and at each visit after diagnosis, regardless of their history of cumulative cigarettes smoked, tumor stage, and treatment status. There have been some recent efforts in the Unites States to promote smoking treatment adoption in cancer care settings, but more efforts are needed to strengthen the implementation of these programs (23, 24).

A recent review by Gemine and Lewis (25) identified different mechanisms that could underlie the negative effects of smoking continuation on lung cancer survival. These include the effect of tobacco smoke and its carcinogenic compounds on the promotion of tumor growth, cellular damage, genetic mutations, immunosuppression, increasing resistance to and complications from the available treatments, and enhancing tumor recurrence and other comorbid conditions that can potentially increase the risk for mortality in patients with lung cancer.

Strengths of our study include providing prospective evidence on the protective effects of smoking cessation on a wide range of outcomes in patients with early-stage NSCLC who smoked, obtaining repeated interviews during which smoking status questions were asked on each occasion, and using stringent analytic methods to maximize controlling for potential biases. Inclusion of a large number of patients who smoked and a long follow-up period provided the opportunity to assess the effects of smoking cessation across different subgroups, population strata, and follow-up periods.

Our study has limitations. First, the study was observational. We did not intervene in the management and treatment of patients and collected the available outcome data through active and passive follow-up. Some outcome data, including causes of death and tumor progression information, were collected by using death certificates and hospital records that were determined by different physicians. The accuracy of these outcomes might differ on the basis of the physicians' work-up and the patients' adherence to follow-up visits. Therefore, some misclassification of primary cause of death and tumor progression status is inevitable, and caution is required when interpreting the results for these outcomes. However, these outcomes are usually used as a surrogate for overall survival in oncology trials to speed up getting results, and overall survival remains the definitive metric for assessing the effects of different interventions among patients, which is likely to have a very low level of misclassification (26, 27). The long follow-up period allowed us to obtain reliable results on the protective effects of quitting smoking on overall survival that remained constant across all stratified and sensitivity analyses.

Second, exposure measurements were based on self-report, and therefore we cannot rule out the possibility of measurement errors. However, owing to the

prospective nature of this study, any errors in measuring the exposures are likely to be nondifferential with respect to outcome.

Finally, although we used sophisticated statistical approaches to control for potential biases, smoking cessation might still be associated with unmeasured confounders of improved lung cancer outcomes. More studies are required to confirm these findings.

In summary, our prospective study provides extensive evidence that quitting smoking after a diagnosis of early-stage NSCLC can have an important effect on subsequent mortality and progression-free survival. Given that at least 50% of active smokers with NSCLC are thought to continue smoking after diagnosis (28), this provides an important opportunity to substantially improve overall and progression-free survival in this type of cancer.

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References

1. **Bray F, Ferlay J, Soerjomataram I, et al.** Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424. [PMID: 30207593] doi:10.3322/caac.21492

2. **Duma N, Santana-Davila R, Molina JR.** Non-small cell lung cancer: epidemiology, screening, diagnosis, and treatment. Mayo Clin Proc. 2019;94:1623-1640. [PMID: 31378236] doi:10.1016/j.mayocp.2019.01.013

3. **Wild CP, Weiderpass E, Stewart BW, eds.** World Cancer Report: Cancer Research for Cancer Prevention. International Agency for Research on Cancer, World Health Organization. Accessed at https://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-Cancer-Research-For-Cancer-Prevention-2020 on 21 April 2021.

4. **Lu T, Yang X, Huang Y, et al.** Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. Cancer Manag Res. 2019;11:943-953. [PMID: 30718965] doi:10.2147/CMAR.S187317

5. **Debieuvre D, Locher C, Asselain B, et al.** Evidence of slight improvement in five-year survival in non-small-cell lung cancer over the last 10 years: results of the French KBP-CPHG real-world studies. Bull Cancer. 2019;106:283-292. [PMID: 30803715] doi:10.1016/j.bulcan.2019.01.010

6. **Chi A, Fang W, Sun Y, et al.** Comparison of long-term survival of patients with early-stage non-small cell lung cancer after surgery vs stereotactic body radiotherapy. JAMA Netw Open. 2019;2:e1915724. [PMID: 31747032] doi:10.1001/jamanetworkopen.2019.15724

7. **Liang Y, Wakelee HA.** Adjuvant chemotherapy of completely resected early stage non-small cell lung cancer (NSCLC). Transl Lung Cancer Res. 2013;2:403-10. [PMID: 25806259] doi:10.3978/j.issn.2218-6751.2013.07.01

8. **Shin JY, Yoon JK, Marwaha G.** Progress in the treatment and outcomes for early-stage non-small cell lung cancer. Lung. 2018;196:351-358. [PMID: 29550987] doi:10.1007/s00408-018-0110-1

9. **Fares AF, Jiang M, Yang P, et al.** Smoking cessation (SC) and lung cancer (LC) outcomes: a survival benefit for recent-quitters? A pooled analysis of 34,649 International Lung Cancer Consortium (ILCCO) patients [Abstract]. J Clin Oncol. 2020;38(15_suppl):1512.

10. **Parsons A, Daley A, Begh R, et al.** Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. BMJ. 2010;340:b5569. [PMID: 20093278] doi:10.1136/bmj.b5569

11. **Jassem J.** Tobacco smoking after diagnosis of cancer: clinical aspects. Transl Lung Cancer Res. 2019;8:S50-S58. [PMID: 31211105] doi:10.21037/tlcr.2019.04.01

12. **Roach MC, Rehman S, DeWees TA, et al.** It's never too late: smoking cessation after stereotactic body radiation therapy for non-small cell lung carcinoma improves overall survival. Pract Radiat Oncol. 2016 Jan-Feb;6:12-8. [PMID: 26598909] doi:10.1016/j.prro.2015.09.005

13. **Gemine RE, Ghosal R, Collier G, et al; LungCast Investigators.** Longitudinal study to assess impact of smoking at diagnosis and quitting on 1-year survival for people with non-small cell lung cancer. Lung Cancer. 2019;129:1-7. [PMID: 30797485] doi:10.1016/j.lungcan.2018.12.028

14. **Tao L, Wang R, Gao YT, et al.** Impact of postdiagnosis smoking on long-term survival of cancer patients: the Shanghai cohort study. Cancer Epidemiol Biomarkers Prev. 2013;22:2404-11. [PMID: 24319070] doi:10.1158/1055-9965.EPI-13-0805-T

15. **Fritz A, Percy C, Jack A, et al, eds.** International Classification Of Diseases for Oncology. World Health Organization. 2000. Accessed at https://apps.who.int/iris/handle/10665/42344 on 16 April 2020.

16. **Edge SB, Compton CC.** The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM [Editorial]. Ann Surg Oncol. 2010;17:1471-4. [PMID: 20180029] doi:10.1245/s10434-010-0985-4

17. **World Health Organization.** International Classification of Diseases, 10th Revision (ICD-10). 2016. Accessed at https://icd.who.int/browse10/2016/en on 9 August 2018.

18. **Shintani AK, Girard TD, Eden SK, et al.** Immortal time bias in critical care research: application of time-varying Cox regression for observational cohort studies. Crit Care Med. 2009;37:2939-45. [PMID: 19770737] doi:10.1097/CCM.0b013e3181b7fbbb

19. **Zhou Z, Rahme E, Abrahamowicz M, et al.** Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. Am J Epidemiol. 2005;162:1016-23. [PMID: 16192344]

20. **Bellera CA, MacGrogan G, Debled M, et al.** Variables with time-varying effects and the Cox model: some statistical concepts illustrated with a prognostic factor study in breast cancer. BMC Med Res Methodol. 2010; 10:20. [PMID: 20233435] doi:10.1186/1471-2288-10-20
21. **Nagasaka M, Gadgeel SM.** Role of chemotherapy and targeted therapy in early-stage non-small cell lung cancer. Expert Rev Anticancer Ther. 2018;18:63-70. [PMID: 29168933] doi:10.1080/14737140.2018.1409624
22. **Owen D, Chaft JE.** Immunotherapy in surgically resectable non-small cell lung cancer. J Thorac Dis. 2018;10:S404-S411. [PMID: 29593886] doi:10.21037/jtd.2017.12.93
23. **D'Angelo H, Rolland B, Adsit R, et al.** Tobacco treatment program implementation at NCI cancer centers: progress of the NCI Cancer Moonshot-funded Cancer Center Cessation Initiative. Cancer Prev Res (Phila). 2019;12:735-740. [PMID: 31481540] doi:10.1158/1940-6207.CAPR-19-0182
24. **Fiore MC, D'Angelo H, Baker T.** Effective cessation treatment for patients with cancer who smoke-the fourth pillar of cancer care. JAMA Netw Open. 2019;2:e1912264. [PMID: 31560380] doi:10.1001/jamanetworkopen.2019.12264
25. **Gemine R, Lewis K.** Smoking cessation with lung cancer: not too little, never too late! European Medical Journal. 20 October 2016. Accessed at www.emjreviews.com/respiratory/article/smoking-cessation-with-lung-cancer-not-too-little-never-too-late on 31 August 2020.
26. **Perrone F.** Don't forget survival, please [Letter]. Lancet Oncol. 2006;7:703-4. [PMID: 16945763]
27. **Venook AP, Tabernero J.** Progression-free survival: helpful biomarker or clinically meaningless end point? [Editorial]. J Clin Oncol. 2015;33:4-6. [PMID: 25366687] doi:10.1200/JCO.2014.57.9557
28. **Baser S, Shannon VR, Eapen GA, et al.** Smoking cessation after diagnosis of lung cancer is associated with a beneficial effect on performance status. Chest. 2006;130:1784-90. [PMID: 17166997]

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Appendix Table 1. Differences Between the Sixth and Seventh Editions of the AJCC TNM Staging System for Lung Cancer*

AJCC Cancer Staging Manual, Seventh Edition (2010)	AJCC Cancer Staging Manual, Sixth Edition (2002)
TX: Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy	TX: Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0: No evidence of primary tumor	T0: No evidence of primary tumor
Tis: Carcinoma in situ	Tis: Carcinoma in situ
T1: Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)	T1: Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1a: Tumor ≤2 cm in greatest dimension	–
T1b: Tumor >2 cm but ≤3 cm in greatest dimension	–
T2: Tumor >3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤5 cm): Involves main bronchus, ≥2 cm distal to the carina Invades visceral pleura (PL1 or PL2) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung	T2: Tumor with any of the following features of size or extent: >3 cm in greatest dimension Involves main bronchus, ≥2 cm distal to the carina Invades the visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a: Tumor >3 cm but ≤5 cm in greatest dimension	
T2b: Tumor >5 cm but ≤7 cm in greatest dimension	
T3: Tumor >7 cm or one that directly invades any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (<2 cm distal to the carina but without involvement of the carina); or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe	T3: Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus <2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
T4: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, **separate tumor nodule(s) in a different ipsilateral lobe**	T4: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodule(s) in the same lobe; or tumor with malignant pleural effusion
NX: Regional lymph nodes cannot be assessed	NX: Regional lymph nodes cannot be assessed
N0: No regional node metastases	N0: No regional node metastases
N1: Metastases to ipsilateral peribronchial and/or ipsilateral hilar node(s) and intrapulmonary nodes, including involvement by direct extension	N1: Metastases to ipsilateral peribronchial and/or ipsilateral hilar node(s) and intrapulmonary nodes, including involvement by direct extension of the primary tumor
N2: Metastases to ipsilateral mediastinal and/or subcarinal lymph node(s)	N2: Metastases to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3: Metastases in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular node(s)	N3: Metastases in contralateral mediastinal, contralateral hilar, ipsilateral contralateral scalene, or supraclavicular node(s)
–	MX: Distant metastasis cannot be assessed
M0: No distant metastasis	M0: No distant metastasis
M1: Distant metastasis	M1: Distant metastasis present (M1 includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral)
M1a: Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion	–
M1b: Distant metastasis (in extrathoracic organs)	–

AJCC = American Joint Committee on Cancer.
* Differences between the editions are indicated in boldface.

Appendix Table 2. Differences Between the Sixth and Seventh Editions of the AJCC TNM Staging System for Lung Cancer, by TNM Methods*

AJCC Cancer Staging Manual, Seventh Edition (2010)				AJCC Cancer Staging Manual, Sixth Edition (2002)			
Stage	**T**	**N**	**M**	**Stage**	**T**	**N**	**M**
Occult carcinoma	TX	N0	M0	Occult carcinoma	TX	N0	M0
0	Tis	N0	M0	0	Tis	N0	M0
IA	**T1a, T1b**	N0	M0	IA	T1	N0	M0
IB	**T2a**	N0	M0	IB	T2	N0	M0
IIA	**T2b**	N0	M0	IIA	T1	N1	M0
	T1a, T1b	N1	M0				
	T2a	N1	M0				
IIB	T2b	N1	M0	IIB	T2	N1	M0
	T3	N0	M0		T3	N0	M0
IIIA	T1a, T1b, T2a, T2b	N2	M0	IIIA	T1	N2	M0
	T3	N1, N2	M0		T2	N2	M0
	T4	**N0, N1**	**M0**		T3	N1, N2	M0
IIIB	Any T	N3	M0	IIIB	Any T	N3	M0
	T4	**N2**	**M0**		T4	Any N	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

AJCC = American Joint Committee on Cancer.

* Differences between the editions are indicated in boldface. An overview on how the 7th edition of AJCC methods of assigning TNM and staging for non–small cell lung cancer map to the current 8th edition of AJCC staging system is found at https://radiologyassistant.nl/chest/lung-cancer/tnm-classification-8th-edition.

Appendix Table 3. Statistical Methods and Software Commands Used to Analyze the Data

Outcome	Statistical Method	Stata Commands	Event of Interest	Competing Event	Censoring Event
Adjusted time-dependent models					
Hazards of all-cause mortality/probability of overall survival*	Time-dependent Cox regression	stsplit, stcox (after using stsplit), scurve_tvc (for creating the adjusted curves), bsurvci (for creating 95% CIs for the estimates)	Date of death due to any cause	Not applicable	Date of last contact for patients alive at last contact
Probability of progression-free survival	Time-dependent Cox regression	stsplit, stcox (after using stsplit), scurve_tvc (for creating the adjusted curves), bsurvci (for creating 95% CIs for the estimates)	Date of death due to any cause or date of tumor progression, whichever occurred first	Not applicable	Date of last contact for patients alive with no tumor progression at last contact
Hazards of lung cancer–specific mortality/cumulative incidence of lung cancer mortality	Time-dependent Fine-Gray competing risk regression	stsplit, stcrreg (after using stsplit), stcurve (postestimation), stpm2cif (for creating 95% CIs for the estimates)	Date of death due to lung cancer	Date of death due to any cause other than lung cancer	Date of last contact for patients alive at last contact
Adjusted fixed-time models (for sensitivity analysis)					
Hazards of all-cause mortality	Cox regression	stcox	Date of death due to any cause	Not applicable	Date of last contact for patients alive at last contact
Hazards of disease progression	Cox regression	stcox	Date of death due to any cause or date of tumor progression, whichever occurred first	Not applicable	Date of last contact for patients alive with no tumor progression at last contact
Hazards of lung cancer–specific mortality	Fine-Gray competing risk regression	stcrreg	Date of death due to lung cancer	Date of death due to any cause other than lung cancer	Date of last contact for patients alive at last contact

* The estimates from this model were used to calculate the adjusted differences in the proportion of patients alive at different time points. For more information on the calculation of the CIs for these differences, see https://online.stat.psu.edu/stat100/lesson/9/9.3.

Appendix Table 4. Time of Quitting and Relapsing Smoking Among Patients Who Quit and Then Relapsed

Patient	Time of Quitting Smoking After Diagnosis, *mo*	Time of Relapsing Smoking After Diagnosis, *mo*
1	<1	60
2	2	3
3	24	66
4	<1	48
5	<1	2
6	11	39
7	24	36
8	<1	30

Appendix Table 5. Association Between Quitting Smoking Postdiagnosis and Outcomes Among Patients With Early-Stage Non–Small Cell Lung Cancer Who Smoked, by Tumor Stage at Diagnosis

Variable	Diagnosis at Earlier Tumor Stage (IA, IB, IIA)		Diagnosis at Later Tumor Stage (IIB, IIIA)		*P* Value for Interaction
	Continued Smoking	Quit Smoking	Continued Smoking	Quit Smoking	
Participants (total participants in stratum), *n (%)*	206 (58.1)	148 (41.8)	91 (55.8)	72 (44.1)	
All-cause mortality*					0.77
Cases (total deaths in stratum), *n (%)*	129 (64.1)	72 (45.8)	75 (59.5)	51 (40.4)	
Adjusted hazard ratio (95% CI)	1.00 (reference)	0.68 (0.50–0.93)	1.00 (reference)	0.63 (0.43–0.94)	
Lung cancer–specific mortality*†					0.61
Cases (total lung cancer–specific deaths in stratum), *n (%)*	105 (66.4)	53 (33.5)	66 (57.3)	49 (42.6)	
Adjusted cause-specific hazard ratio (95% CI)	1.00 (reference)	0.70 (0.49–1.00)	1.00 (reference)	0.73 (0.48–1.11)	

* Estimates are derived from adjusted time-dependent models, where quitting smoking was defined as a time-dependent variable. These models are adjusted for year of diagnosis, age at diagnosis, sex, education, body mass index, history of chronic diseases, cumulative cigarettes smoked, alcohol drinking status, tumor histology, surgical resection of the tumor, receipt of chemotherapy, and receipt of radiation therapy.
† In this model, death from any cause other than lung cancer was set as a competing event.

Appendix Table 6. Association Between Quitting Smoking Postdiagnosis and Outcomes Among Patients With Early-Stage Non–Small Cell Lung Cancer Who Smoked, by Pack-Years of Smoked Cigarettes at Diagnosis

Variable	Mild to Moderate Smokers (≤40 Pack-Years)		Heavy Smokers (>40 Pack-Years)		*P* Value for Interaction
	Continued Smoking	Quit Smoking	Continued Smoking	Quit Smoking	
Participants (total participants in stratum), *n (%)*	104 (56.5)	80 (43.4)	193 (57.9)	140 (42.0)	
All-cause mortality*					0.22
Cases (total deaths in stratum), *n (%)*	68 (64.7)	37 (35.2)	136 (61.2)	86 (38.7)	
Adjusted hazard ratio (95% CI)	1.00 (reference)	0.59 (0.37–0.92)	1.00 (reference)	0.75 (0.56–0.99)	
Lung cancer–specific mortality*†					0.58
Cases (total lung cancer–specific deaths in stratum), *n (%)*	57 (64.0)	32 (35.9)	114 (61.9)	70 (38.0)	
Adjusted cause-specific hazard ratio (95% CI)	1.00 (reference)	0.68 (0.40–1.16)	1.00 (reference)	0.78 (0.57–1.06)	

* Estimates are derived from adjusted time-dependent models, where quitting smoking was defined as a time-dependent variable. These models are adjusted for year of diagnosis, age at diagnosis, sex, education, body mass index, history of chronic diseases, cumulative cigarettes smoked, alcohol drinking status, tumor histology, surgical resection of the tumor, receipt of chemotherapy, and receipt of radiation therapy.
† In this model, death from any cause other than lung cancer was set as a competing event.

Appendix Table 7. Association Between Quitting Smoking Postdiagnosis and Outcomes Among Patients With Early-Stage Non–Small Cell Lung Cancer Who Smoked, by Receipt of Chemotherapy

Variable	Did Not Receive Chemotherapy		Received Chemotherapy		*P* Value for Interaction
	Continued Smoking	Quit Smoking	Continued Smoking	Quit Smoking	
Participants (total participants in stratum), *n (%)*	231 (57.6)	170 (42.3)	66 (56.9)	50 (43.1)	
All-cause mortality*					0.74
Cases (total deaths in stratum), *n (%)*	147 (63.0)	86 (36.9)	57 (60.6)	37 (39.3)	
Adjusted hazard ratio (95% CI)	1.00 (reference)	0.74 (0.55–0.98)	1.00 (reference)	0.56 (0.34–0.92)	
Lung cancer–specific mortality*†					0.86
Cases (total lung cancer–specific deaths in stratum), *n (%)*	120 (63.4)	69 (36.5)	51 (60.7)	33 (39.2)	
Adjusted cause-specific hazard ratio (95% CI)	1.00 (reference)	0.81 (0.59–1.12)	1.00 (reference)	0.62 (0.37–1.03)	

* Estimates are derived from adjusted time-dependent models, where quitting smoking was defined as a time-dependent variable. These models are adjusted for year of diagnosis, age at diagnosis, sex, education, body mass index, history of chronic diseases, cumulative cigarettes smoked, alcohol drinking status, tumor histology, surgical resection of the tumor, receipt of chemotherapy, and receipt of radiation therapy.
† In this model, death from any cause other than lung cancer was set as a competing event.

Appendix Table 8. Association Between Quitting Smoking Postdiagnosis and Outcomes Among Patients With Early-Stage Non–Small Cell Lung Cancer Who Smoked, by Receipt of Radiation Therapy

Variable	Did Not Receive Radiation Therapy		Received Radiation Therapy		*P* Value for Interaction
	Continued Smoking	Quit Smoking	Continued Smoking	Quit Smoking	
Participants (total participants in stratum), *n (%)*	234 (57.9)	170 (42.0)	63 (55.7)	50 (44.2)	
All-cause mortality*					0.71
Cases (total deaths), *n (%)*	149 (63.6)	85 (36.3)	55 (59.1)	38 (40.8)	
Adjusted hazard ratio (95% CI)	1.00 (reference)	0.65 (0.49–0.87)	1.00 (reference)	0.69 (0.42–1.13)	
Lung cancer–specific mortality*†					0.26
Cases (total lung cancer–specific deaths in stratum), *n (%)*	126 (64.6)	69 (35.3)	45 (57.6)	33 (42.3)	
Adjusted cause-specific hazard ratio (95% CI)	1.00 (reference)	0.68 (0.49–0.95)	1.00 (reference)	0.89 (0.54–1.47)	

* Estimates are derived from adjusted time-dependent models, where quitting smoking was defined as a time-dependent variable. These models are adjusted for year of diagnosis, age at diagnosis, sex, education, body mass index, history of chronic diseases, cumulative cigarettes smoked, alcohol drinking status, tumor histology, surgical resection of the tumor, receipt of chemotherapy, and receipt of radiation therapy.
† In this model, death from any cause other than lung cancer was set as a competing event.

Appendix Table 9. Association Between Quitting Smoking Within 3 Months of Diagnosis and Death or Disease Progression Among Patients With Early-Stage Non–Small Cell Lung Cancer Who Smoked

Variable	Continued Smoking or Quit ≥3 mo After Diagnosis	Quit Smoking <3 mo After Diagnosis	*P* Value
Participants (total participants in stratum), *n (%)*	342 (66.1)	175 (33.8)	
All-cause mortality*			
Cases (total deaths in stratum), *n (%)*	227 (69.4)	100 (30.5)	
Adjusted hazard ratio (95% CI)	1.00 (reference)	0.68 (0.53–0.87)	0.002
Disease progression (tumor recurrence or death)*			
Cases (total cases with disease progression), *n (%)*	235 (68.7)	107 (31.2)	
Adjusted cause-specific hazard ratio (95% CI)	1.00 (reference)	0.72 (0.56–0.92)	0.009
Lung cancer–specific mortality*†			
Cases (total lung cancer–specific deaths), *n (%)*	188 (68.8)	85 (31.1)	
Adjusted cause-specific hazard ratio (95% CI)	1.00 (reference)	0.77 (0.59–1.02)	0.077

* Estimates are derived from fixed-time models, where all participants who quit smoking during the first 3 mo after diagnosis were categorized as "smoking quitters" at baseline in the models. These models are adjusted for year of diagnosis, age at diagnosis, sex, education, body mass index, history of chronic diseases, cumulative cigarettes smoked, alcohol drinking status, tumor histology, surgical resection of the tumor, receipt of chemotherapy, and receipt of radiation therapy.
† In this model, death from any cause other than lung cancer was set as a competing event.

Appendix Figure. Frequency of quitting smoking at different time points after diagnosis among patients with early-stage lung cancer who smoked.