**Duration of smoking abstinence before non-small cell lung cancer (NSCLC) diagnosis, overall and NSCLC-specific survival: A pooled, retrospective cohort study**

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**RESEARCH IN CONTEXT**

**Evidence before this study:** We searched PubMed for all relevant studies published in English between January 1, 2000 and September 1, 2022, with the terms “smoking” OR “smoking cessation” OR “smoking abstinence” AND “lung cancer” OR “cancer”. There is a large amount of evidence associating smoking and lung cancer risk, as well as studies evaluating lung cancer survival by smoking status at diagnosis. Nevertheless, few studies evaluated the benefits of smoking cessation prior to diagnosis and lung cancer survival: we identified two studies that assessed the benefit of smoking cessation prior to cancer diagnosis, one of them indicating a statistically significant survival benefit for recent quitters and the other lacking survival significance, possibly due to limited sample size. There were no previous large-scale studies addressing the benefits of smoking cessation on lung cancer survival in a geographically diverse population.

**Added value of this study:** To our knowledge, this is the first large-scale study to show that, in lung cancer, smoking abstinence for a duration as short as one year prior to diagnosis is associated with improved overall survival, compared to individuals who are current smokers at diagnosis. This finding was consistent across all stages, histologies, sexes, and different cumulative smoking history, from a geographically diverse, large sample pooled analysis.

**Implications of all the available evidence:** Smoking abstinence as short as one year, even after a lifetime of smoking, improves lung cancer overall survival and might influence positively smokers’ decisions to quit smoking.

**ABSTRACT**

**BACKGROUND**: The association between the duration of smoking abstinence prior to lung cancer diagnosis and subsequent survival can influence public health messaging in the era of lung cancer screening.

**METHODS**: We utilized the COS-ILCCO database to determine if the duration of abstinence duration prior to non-small cell lung cancer (NSCLC) diagnosis is associated with improved overall (OS) and NSCLC cancer-specific survival (CSS). Kaplan-Meier and multivariable Cox models (adjusted Hazard Ratios/aHR) were generated using individual, harmonized patient data across 26 studies (North America, Europe, and Asia) for OS, and for 13 studies (with data) for CSS.

**FINDINGS**: When compared to current-smokers (n=15,036), former-smokers (n=14,845) who had abstained from smoking for 1-3 years prior to NSCLC diagnosis had an OS aHR=0.92 (95%CI:0.87-0.97); in patients who had quit 3-5 years, OS aHR=0.90 (95%CI:0.83-0.97); and in patients who had abstained for >5 years, OS aHR=0.90 (95%CI:0.87-0.93). Improved CSS (n=9,727) was observed in patients who had quit cigarette smoking with progressively longer time periods and became significant at abstinence durations >5 years (aHR=0.87; 95%CI:0.81-0.93). Results were consistent across age, sex, histology, and stage distributions.

**INTERPRETATION**: In this large, geographically diverse, international study, mortality was reduced in NSCLC patients whose duration of smoking abstinence prior to NSCLC diagnosis was as short as one-year prior; thus, quitting smoking now can improve overall survival even if lung cancer is diagnosed at the next annual (or longer) lung cancer screening visit. Longer durations of abstinence also reduced the risk of death specifically from lung cancer.

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**Introduction**

With 1.3 billion current smokers worldwide, cigarette smoking remains the greatest, single modifiable risk factor for all-cause mortality1, 2. With its accompanying >70 carcinogens, cigarette smoking is associated with the development of many cancers but is most closely linked with lung cancer3, where the population-attributable risk is large4.

Lung cancer is the leading cause of cancer death worldwide5. Non-small cell lung cancer (NSCLC) comprises >80% of all lung cancers6, with an overall five-year survival rate under a quarter7. Smoking also affects lung cancer prognosis8, and former smokers have intermediate survival outcomes between lifetime never-smokers and current smokers9, 10. Thus, smoking cessation has been championed as an important behavioral change by primary health professionals. Smoking abstinence reduces the risk of cardiovascular and respiratory diseases events, reduces risks of a dozen cancer types over time, and improves reproductive health. In the general population, lung cancer risk is reduced by half after 5-10 years of smoking abstinence.8, 11-13

With the rise of lung cancer screening using low-dose computed tomography (LDCT)14, 15 health professionals are leading screening programs with embedded smoking cessation components16-19. A teachable moment occurs shortly after lung cancer screening and the receipt of the results when there is improved readiness and motivation to quit smoking20. All benefits of smoking cessation should be explicitly clarified to smokers during this teachable moment, thus improving the chances of successfully achieving smoking abstinence21.

In contrast to the well-known effects on cancer prevention by smoking cessation11, the prognostic association of improved outcomes with smoking cessation for patients who eventually develop lung cancer remains under-recognized by some individuals8, 12, 22. For instance, continuing to smoke after lung cancer diagnosis negatively impacts treatment efficacy, by increasing the clearance of systemic therapies and limiting radiation efficacy23. However, some current smokers not only do not recognize the benefits of smoking cessation but instead believe that lung screening could be an adequate replacement for smoking cessation24.

The primary aim of this COS-ILCCO (Clinical Outcomes Studies of the International Lung Cancer Consortium) analysis is to determine the shortest duration of smoking abstinence prior to a diagnosis of NSCLC that is associated with improvement in survival. We aim to provide evidence supporting the multi-faceted benefits of smoking cessation, which may strengthen patient motivation and provider delivery of smoking cessation messaging.

A secondary aim was to assess the association of smoking abstinence and NSCLC-specific survival, as the motivation to quit may be improved if there is a direct link between smoking abstinence and dying *specifically* from lung cancer.

**Methods**

**Study Population**

Individual-level data was pooled from NSCLC patients across 26 studies participating in COS-ILCCO (http://ilcco.iarc.fr). Eligible patients had smoking data (before lung cancer diagnosis), epidemiological data at diagnosis (age, sex, ethnicity, education), and clinical information (histology, date of diagnosis, stage at diagnosis, vital status at last follow up, date of last follow up or death). Data across studies were checked for inconsistency, inadmissible values, and outliers before harmonizing and coding variables uniformly into a common dataset25, 26. Written informed consent was obtained from all study participants; each study was approved by local institutional research ethics boards.

**Variables**

Covariates considered in this study (age at diagnosis, sex, ethnicity, cumulative smoking measured in pack-years, educational level, disease stage at diagnosis, histology, and year of diagnosis) were available in the consortium database and have been identified as being important prognostically. The year of diagnosis served as a surrogate measure of global overall improvement in clinical management and survival of patients over time.

Self-reported smoking behavior at lung cancer diagnosis was collected across all studies, except two cohort studies that collected smoking information before the lung cancer diagnosis date (n=1,819) and two studies lacked pack-years information (n=1,029). The final analysis included all studies, but we performed a sensitivity analysis excluding studies that lacked either pack-years or smoking information at the time of diagnosis (baseline). Smoking status was classified as: never-smokers, who had smoked fewer than 100 cigarettes in their lifetime; current-smokers, who smoked cigarettes within one year of the diagnosis date; and former-smokers, who had quit for at least one year prior to diagnosis. Most consortium studies were originally epidemiological case-control studies that had utilized one-year before the date of diagnosis as a cut-off to define current- *versus* former-smokers; we kept the same definition for our prognostic analyses. For former smokers, we included only cases where a date of last cigarette was reported, or a time interval from the date of quitting smoking until the date of lung cancer diagnosis was provided; these data were used to calculate abstinence duration.

**Statistical Analysis**

Descriptive statistics included frequencies and percentages for categorical variables and medians and IQR for continuous variables. Chi-square and Kruskal-Wallis tests were used to compare categorical and continuous variables, respectively.

The primary outcome was overall survival (OS) for all causes, measured in years from diagnosis date until the date of the last follow-up or death due to any cause. We generated unadjusted and adjusted OS curves using the method of Kaplan-Meier and log-rank tests, to confirm previously known relationships of smoking status and survival27, and to evaluate survival effects by smoking status and/or time of abstinence. Cox proportional hazards regression models28 were adjusted for clinico-epidemiological factors identified in a baseline clinical multivariable model. Among ever-smokers, we used current-smokers as the reference group for analyses evaluating unadjusted hazard ratios (HRs) and adjusted hazard ratios (aHRs) of former-smokers for associations with duration of abstinence before NSCLC diagnosis (primary analysis).

 Because the primary analysis had grouped together all patients with long-term abstinence of >5 years prior to NSCLC diagnosis, we also sought to explore the association between various durations of long-term abstinence and NSCLC survival. To address this, we generated adjusted penalized spline smoothing curves of ever-smokers to visually compare the overall survival aHR of long-term abstinence (plotted as a continuous variable) prior to NSCLC diagnosis, when compared to current smokers. Penalized curves described the aHR relationships of former- *versus* current-smokers (y-axis) compared to long-term durations of abstinence and NSCLC diagnosis date (x-axis). Exploratory analyses also evaluated subgroups of patients by clinico-demographic variables and reported through Forest plots. We also assessed a secondary endpoint, NSCLC-specific mortality, using a proportional hazards model for the sub-distribution of a competing risk of death29.

To provide examples of absolute risk benefit, we generated 5- and 10-year OS estimates by smoking status and duration of abstinence for a prototypical white male under the age of 65 years, with under 40 pack-years of smoking history and Stage I lung adenocarcinoma, being treated at the Mayo clinic (the study site with the largest patient cohort). We also generated cumulative incidence estimates of NSCLC-specific mortality at 5- and 10-year for the same prototypical male, treated at the Princess Margaret Cancer Center, Toronto (Mayo cohort lacks NSCLC-specific mortality).

Sensitivity analyses were performed to determine the robustness of our results. These sensitivity analyses are described in detail in the Supplementary Methods and in Supplementary Tables.

All analyses were conducted using R software Version 4.2.2 (http://CRAN.R-project.org, R Foundation, Vienna, Austria) and SAS Version 9.4. All P values were based on two-sided tests. The primary analysis was considered statistically significant at P<0.05.

A STROBE checklist is attached as an Appendix.

**Role of the funding source**

The funders of this study had no role in study design, data collection, data analysis, data interpretation, writing of the report or in the decision to submit.

**Results**

**Baseline population characteristics**

There were 16 North American studies, six from Europe, three from Asia and one from South America (**Supplementary Table 1**; supplementary data available online). Of 42,087 NSCLC patients in the full database, we excluded 4,474 patients with missing information on smoking, key covariates, or outcome. We analyzed 37,613 NSCLC patients: 7,732 (20.5%) never-smokers, 15,036 (39.9%) current-smokers and 14,845 (39.4%) former-smokers (**CONSORT diagram**). **Supplementary Table 2** compares the clinico-demographics of individuals who were analyzed *versus* the full dataset. **Supplementary** **Table 3** shows clinico-demographic information by smoking status of the analyzed dataset. Relative to current- or former-smokers, never-smokers were more likely to be female, Asian, and be diagnosed with adenocarcinomas (p<0.0001, each comparison), all expected findings. As most Asian studies did not collect education data (**Supplementary Table 4**), missing education data was also associated with being a never-smoker. Compared to current-smokers, former-smokers were more likely to be older, have adenocarcinomas, have Stage I *versus* Stage IV NSCLC, and have lower cumulative smoking exposure (p<0.0001, each comparison).

**Smoking status and overall survival**

Unadjusted (**Figure 1A-1B**) and adjusted survival curves **Figure 1C-1D)**, confirmed known relationships of smoking status and OS. Compared to current-smokers, never-smokers had longer survival, while the OS of former-smokers was intermediate between never- and current-smokers (**Supplementary Table 5**; all comparisons by smoking status, p<0.0001). Estimates for the probability of being alive and the cumulative incidence of death specifically from NSCLC at 5 and 10 years for our prototypical white male Stage I patient under the age of 65 years, by smoking status, are presented in **Supplementary Table 6 (top)**. For this prototypical patient, the probability of being alive in 5 and 10 years after a NSCLC diagnosis are respectively of 53% and 35% if a current smoker; 57% and 40%, respectively, if a former smoker; and 63% and 46%, respectively, if a never smoker. In terms of NSCLC cumulative incidence of death at 5 and 10 years, this prototypical patient had estimates of 21% and 26%, respectively, if he were a current smoker; 19% and 23%, respectively, if a former smoker; and 17% and 21%, respectively, if a never smoker.

**Duration of abstinence and overall survival among ever-smokers**

In the primary analysis of the association of duration of abstinence and OS among ever-smokers, we first created clinical prognostic univariable and multivariable Cox proportional hazard models that did not include duration of abstinence, and with or without smoking status (current, former), which served as the backbone for all subsequent multivariable analyses (**Supplementary Table 7)**. In these models, patients who were older, male, white, who had less education, more advanced stage, non-adenocarcinoma subtype lung cancers, and greater cumulative smoking exposure were individually associated with significantly worse OS. For our primary analysis, we then added the duration of abstinence into these models, which replaced smoking status (**Table 1**). Compared to current smokers (never quit or quit within the past year prior to NSCLC diagnosis), patient with 1 to 3 years of abstinence had an OS aHR of 0.92 (95% CI: 0.87-0.97); when the abstinence duration that was between 3 and 5 years prior to NSCLC diagnosis, the aHR was 0.90 (95% CI: 0.83-0.97); and after over 5 years of abstinence prior to the diagnosis of NSCLC, the aHR was 0.90 (95% CI: 0.87-0.93).

In subgroup analyses of clinico-demographic factors (Forest plots, **Figure 2 (left side)**), though there was variability in the magnitude of association in various subgroups, all subgroups demonstrated some degree of improved OS after one or more years of abstinence prior to NSCLC diagnosis, when compared to patients who had not quit or who had under a year of abstinence prior to NSCLC diagnosis (current smoker). Results of the sensitivity analyses demonstrated similar associations to the primary analysis (**Supplementary Tables 8 - 11**).

From the penalized spline curves (**Figure 3A**), aHRs remained consistently and significantly lower than unity at time intervals ranging from 5 years to as long as 25 years of abstinence prior to NSCLC diagnosis.

**Supplementary Table 6 (bottom)** provides estimates for OS comparing current smokers to various abstinence durations in our prototypical white male Stage I patient under the age of 65 years. For this prototypical patient, the probability of being alive at 5 and 10 years was 54% and 36% respectively if a current smoker. In contrast, the probabilities were 57% and 40%, respectively, for a patient with > 5 years of abstinence prior to diagnosis.

**Abstinence Duration and NSCLC Cause-Specific Survival (CSS) Sensitivity Analysis**

In 9,727 ever-smoking patients of 13 studies with available cause of death data, OS in this patient subgroup was similar to the entire cohort of 26 studies. In **Table 2**, CSS was significantly improved for former-smokers (*versus* current-smokers) when the abstinence period was >5 year: the aHR was 0.87 (95%CI: 0.81-0.93). With abstinence between 1 and 3 years, the aHR was 0.94 (95%CI: 0.87-1.02), and with abstinence between 3 and 5 years, the aHR was 0.91 (95%CI: 0.79-1.05). In **Figure 2 (right side)**, the direction of NSCLC CSS was improved across all clinico-demographic subgroups when the abstinence prior to NSCLC diagnosis was at least 1 year. Spline curve analyses also demonstrated a consistent improvement in CSS when long-term abstinence prior to NSCLC diagnosis was between 5 and 25 years (**Figure 3B**). **Supplementary Table 6 (bottom)** presents cumulative incidence estimates of NSCLC-specific mortality at 5- and 10-year for our prototypical male, for different abstinence durations. As an example from this table, if our prototypical male was a current smokers at the time of NSCLC diagnosis, the cumulative incidence of death from NSCLC would be 27% at 5 years and 34% at 10 years. In contrast, if the prototypical patient were abstinent > 5 years prior to diagnosis, this cumulative incidence of death from NSCLC would have been 24% and 30% at 5 and 10 years, respectively.

**Additional, stratified survival analyses**

 Subgroup analysis by cumulative smoking (pack-years) is shown in **Supplementary Figures 1 (OS) and 2 (CSS)**. Regardless of how the patients were dichotomized by different pack-year cut points, there was a consistent directional pattern of improved OS/CSS across different abstinence durations in former-smokers when compared to current-smokers.

In **Supplementary Figure 3**, we performed stratified analyses by decade of diagnosis. There was a trend to larger benefit of smoking abstinence in the more recent decades. Specifically, in patients diagnosed in the 2010’s (most recent decade with data), the OS aHR was 0.87 (95% CI: 0.80-0.94) for smoking abstinence of at least a year prior to diagnosis, compared to current smokers and the aHR for CSS was 0.79 (95% CI: 0.65-0.96). Similarly, we evaluated heterogeneity by study site for both OS and CSS (**Supplementary Figures 4 and 5**, respectively); the meta-analytic hazard ratios, using random effects models, were very similar to the overall adjusted hazard ratios for both OS/CSS.

**Discussion**

This large, international pooled analysis examined the association of duration of smoking abstinence prior to NSCLC diagnosis and subsequent survival after diagnosis. Smoking abstinence for a duration as short as one year prior to NSCLC diagnosis was associated with improved OS, when compared to individuals who continued to smoke until lung cancer diagnosis. These findings were consistent across all age distributions, both sexes, lung cancer stages at diagnosis and main histological subtypes of NSCLC, thus allowing a generalized statement that quitting smoking *today* can improve lung cancer outcomes *later* (if “later” were defined as being at least a one-year interval).

Smaller studies that assessed various durations of abstinence in former smokers *versus* smokers have found either borderline or non-significant aHRs for OS of approximately 0.90 and are consistent with our strongly significant COS-ILCCO results (**Figure 2**). Other studies30, 31 have data that has been included in the present pooled analysis. The strength of our analysis is due to the large numbers of patients across multiple continents, with exploratory analyses that show that the directions of these associations are consistent across multiple demographic patient subgroups and clinical conditions at diagnosis.

The relative improvement in OS and CSS differences as a result abstinence prior to lung cancer diagnosis, reported as adjusted HRs of 0.90, are comparable to receiving three or four months of adjuvant chemotherapy in early-stage resected NSCLC, which has a meta-analytic HR of 0.8932. Abstinence appears to have similar relative survival benefits and should be strongly encouraged alongside adjuvant treatments.

Determining the absolute benefit for abstinence depends on a range of other clinico-demographic prognostic variables. When considering a prototypical patient, we had estimated the absolute survival benefit to range from 3-5% at 5-10 years (**Supplementary Table 6**). Furthermore, recently diagnosed NSCLC patients appear to have a greater magnitude of improved survival from abstinence (**Supplementary Figure 3**), which may be attributable to improved treatments for both lung cancer and non-lung cancer (i.e. cardiovascular and respiratory) conditions. In contrast, the absolute 5-year OS benefit of adjuvant chemotherapy based on different randomized clinical trials ranges from 4-15%32; in this context, abstinence prior to diagnosis reaches the lower end of benefit of adjuvant chemotherapy. In aggregate, these results provide compelling evidence that the prognostic improvement in survival associated with abstinence meets the standard to be an integral component of the lung cancer treatment arsenal to improve lung cancer survival outcomes, in parallel with other established therapies.

Our results also provide new evidence that the association of abstinence with improved OS is not simply due to reduced mortality from non-lung cancer causes, but that with increasing abstinence durations (particularly 5+ years), there is significant improvement in NSCLC-specific survival. This pattern of results of early OS improvement due to abstinence from non-lung cancer causes with later improvement in OS associated with decreased lung cancer mortality itself has been well described in the general population; the early improvement in survival outcome is derived from non-cancer causes, such as reduced heart attacks, while the later survival improvements are partially derived from lung cancer13. However, the potential mechanisms by which smoking cessation improves lung cancer-specific survival will be different than for the general population, and include: (i) improved tolerance to initial or subsequent treatment, leading to subtle differences in disease control that may take several years to become clinically evident33, 34; (ii) improved treatment response rates, which is a short-term surrogate marker of delayed disease relapse or absence of disease progression; the ultimate result will be longer long-term survival23, 35, 36;, and (iii) early data suggesting that nicotine may drive cancer progression through the nicotinic acetylcholine receptor23. The NSCLC-specific survival improvement sends the message that becoming abstinent *now* can lead to a lower chance of dying from *lung cancer* *itself*, if one were to be diagnosed with lung cancer *at a later date*. Nonetheless for the pragmatic patient, dying from lung cancer *versus* non-lung cancer causes may be less important, and benefits to OS should remain the primary public health message.

Combining lung cancer screening with smoking cessation counseling is effective37. In the US National Lung Screening Trial15, there was a 20% reduction in lung cancer mortality in the control (chest radiograph) arm after seven years of abstinence; in the LDCT arm (reflecting the combined benefit of LDCT screening and smoking abstinence), this mortality reduction was even greater, at 30%38. To mimic a LDCT screening cohort, we performed subgroup analyses whereby we restricted our COS-ILCCO dataset to patients with different pack-year histories (**Supplementary Figures 1 and 2**); we found improved survival with abstinence durations of at least a year, in the heavy smokers, similar to our primary OS and secondary CSS analyses. However, unlike prior analyses of screening populations, our COS-ILCCO dataset contained a wider distribution of smokers by cumulative smoking exposure, with patients included from multiple continents who were neither restricted by age nor to being asymptomatic at the time of lung cancer diagnosis (eligibility criteria typically used for entry into screening programs). Thus, our findings are generalizable to a broader range of patients, which is useful for smoking cessation counseling outside of the LDCT screening context.

A recent meta-analysis reported adherence to lung cancer screening (i.e., having participants in a screening program return for subsequent screening) of only 55%39. Furthermore, smoking relapses occur often in screening participants even in motivated participants, as evidenced by patients enrolled in the NLST screening trial40. In the future, it may be worthwhile to study whether reinforcement messaging of the benefits of abstinence and other interventions on lung cancer survival at each and subsequent screen may motivate patients both to adhere to the screening schedule better and to remain abstinent.

Limitations of this study include: (i) that all smoking data were self-reported; biochemical validation data was unavailable. However, in clinical practice and screening, self-reporting is the norm; (ii) the COS-ILCCO database does not have information on smoking cessation after lung cancer diagnosis, limited treatment, comorbidity data, and socioeconomic status data (other than education level), and no other genetic or environmental factors41. As an example, ability to stop smoking may be associated with adherence to treatment regimens and healthier lifestyles, both of which may serve as confounders to any relationship with OS. The prognostic impact of these factors relative to smoking abstinence is unclear. **Supplementary Figure 6** outlines how it may be inappropriate to adjust for comorbidities anyway, as it may be both a confounder and a collider variable. Nonetheless, our results should be best described as clinically important associations, but would fall short of being labelled causal; (iii) 10.6% of the original dataset was excluded from analysis due to missing data on key primary, covariate and outcome variables; however, there were no substantial differences in clinico-demographic data between the patients analyzed and the original dataset; (iv) though the COS-ILCCO database lacked information on molecular testing results and targeted therapy, this likely had minimal effects on our results as the most common drug-targetable molecular alterations in NSCLC (*EGFR* mutations and *ALK* rearrangements) are primarily found in never-smokers, with targeted therapy generally restricted to Stage IV patients only42, 43,; and (v) there was not enough data to analyze small cell lung cancer in the same manner; nonetheless, NSCLC represents the vast majority of all lung cancers diagnosed globally.

In summary, we found improved overall survival with adjusted hazard ratios of approximately 0.9 in NSCLC cancer patients who had quit smoking for at least a year prior to their lung cancer diagnosis when compared to current smokers. Results were consistent from one year of smoking abstinence to more than two decades of smoking abstinence prior to NSCLC diagnosis. These associations were consistent, independent of age, sex, disease stage, and histological subtype. Such findings have the potential to be beneficial to all forms of smoking cessation counselling, including during lung cancer screening. Results from this study can be incorporated into smoking cessation tools, in a multi-pronged approach that includes personalized risk assessment tools, pharmacotherapy, and tobacco-control policies. Our results provide evidence that *it is never too late to quit smoking*.

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**Contributors statement**

AFF, WX and GL conceived the study. AFF, WX and GL contributed to the interpretation of the results. YL, MJ and MCB harmonized the data. ACLL and RA conducted the literature review. YL, MJ and WX did the statistical analyses. AFF, WX and GL drafted the first version of the manuscript. NBL, FAS, ZW, ND, ASW, JX, TK, NEC, CH, HM, MJB, LFL, GFT, MPR, MPAD, FT, BS, PB, DZ, IH, JL, BS, DM, MS, HB, AA, AC, JKF, ARR, SSS, AT, YW, LLM, RMR, MBS, CC, HS, BMR, MTL, KS, JZ, AGS, MST, DCC, PY, RJH, WX, GL contributed to critical review of the manuscript. AFF, YL, MJ, MCB, WX and GL directly accessed and verified the underlying data. All authors accept responsibility for the decision to submit for publication. AFF, WX and GL attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Declaration of Interests**

All authors declare that they have no conflict of interest.

**Data sharing**

The dataset from our study is held securely in coded form at the Princess Margaret Cancer

Center, Toronto, Ontario, although ownership of data shared within ILCCO remains with the

original investigator/studies. Data sharing agreements prohibit making the dataset publicly

available, but data will be made available upon approval by the ILCCO Executive Committee and individual study principal investigators with mechanisms published on its website

www.ilcco.iarc.fr. The same committee and mechanism approved the present analysis. Relevant ethical and data-sharing approval must be obtained as per ILCCO policy. The underlying analysis plan and analytic code are available from the authors upon request.

**Figure Legends**

**Figure 1.** Overall Survival curves among subsets of non-small cell lung cancer (NSCLC) patients, by smoking status (**Panels A and B**), and by duration of abstinence among ever-smokers (**Panels C and D**). Both unadjusted Kaplan-Meier curve (**Panels A and C**) and fully adjusted survival curves estimated by Cox proportional hazards model (**Panels B and D**) are presented. **Panels B** and **D** were adjusted by age, sex, ethnicity, educational status, clinical stage at diagnosis, study site, year of diagnosis, and histology; **Panel D** was further adjusted by pack-years. Number of individuals at-risk are provided for the unadjusted survival curves. The p-values of **Panel A** (p<0.0001) and **Panel C** (p<0.0001) are based on the log-rank tests; the p-values of **Panel B** (p<0.0001) and **Panel D** (p<0.0001) are based on the likelihood ratio tests.

**Figure 2.** Forest plots of adjusted overall survival hazard ratio (left side) and adjusted subdistribution hazard ratio (SHR) of former-smokers (for NSCLC cancer-specific survival, right side) with more than one-year duration of abstinence prior to NSCLC diagnosis *versus* (vs.) current-smokers (with < 1 year of abstinence). Subgroups are defined by clinic-demographic variables: age, sex, ethnicity, education, histology, and disease stage at diagnosis.

**Figure 3.** Association of log-term abstinence (from 5 to 25 years) before a diagnosis of non-small cell lung cancer (NSCLC) and overall survival (OS) or NSCLC cancer-specific survival (CSS). Penalized smoothing spline curves showing the hazard ratios of OS (Panel A) or CSS (**Panel B**) comparing former- *versus* current-smokers (y-axis), which are plotted against the duration of abstinence (in years; x-axis).

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