



Lung cancer trends and tumor characteristic changes over 20 years (2000–2020): Results of three French consecutive nationwide prospective cohorts' studies

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Summary

Background Long-term changes in lung cancer (LC) patients are difficult to evaluate. We report results from the French KBP-2020 real-life cohort.

Methods KBP-2020 was a prospective cohort that included all patients diagnosed with LC in 2020, in nonacademic public hospital in France. Patient and tumour characteristics were described and compared with similarly designed cohorts in 2000 and 2010.

Findings In 2020, 82 centers included 8,999 patients diagnosed with LC. The proportion of women increased: 34.6% (3114/8999) compared to, 24.3% (1711/7051) and 16.0% (904/5667) in 2010 and 2000 ($p < 0.0001$). The proportion of non-smokers was higher in 2020 (12.6%, 1129/8983) than in previous cohorts (10.9% (762/7008) in 2010; 7.2% (402/5586) in 2000, $p < 0.0001$). In 2020, at diagnosis, 57.6% (4405/7648) of patients had a metastatic/disseminated stage non-small-cell lung cancer (NSCLC) (58.3% (3522/6046) in 2010; 42.6% (1879/4411) in 2000, $p < 0.0001$). Compared with 2000 and 2010 data, early survival improved slightly. In 2020, 3-month mortality of NSCLC varied from 3.0% [2.2 – 3.8] for localized to 9.6% [8.1 – 11.0] for locally advanced to 29.2% [27.8 – 30.6] for metastatic and was 24.8% [22.3 – 27.3] for SCLC.

Interpretation To our knowledge KBP cohorts have been the largest, prospective, real-world cohort studies involving LC patients conducted in worldwide. The trend found in our study shows an increase in LC in women and still a large proportion of patients diagnosed at metastatic or disseminated stage.

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Abbreviations: LC, Lung Cancer; NSCLC, Non-small-cell lung cancer; CPHG, French College of General Hospital Pulmonologists; NPH, Nonacademic public hospitals; TMB, Tumour molecular burden; SCLC, Small-cell lung cancer; PS, Performance status

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Research in context

Evidence before this study

Lung cancer (LC) is the leading cause of cancer death worldwide, and the most common cancer and leading cause of cancer death among men. The two previous epidemiological studies, KBP-2000 and KBP-2010, conducted in France at a ten-year interval, enabled the description of lung cancer characteristics and its changes: more women, more never-smokers, and more adenocarcinomas. In addition, one-year mortality rate significantly decreased from 2000 to 2010 in non-small-cell lung cancer. The KBP-2020 was performed similarly, to the two previous KBP-studies to compare and capture trends in lung cancer patient and tumor characteristics over the last 20 years.

Added value of this study

These prospective studies conducted every 10 years since 2000 demonstrated relevant changes in tumor and patient characteristics. Compared with previous cohorts, in 2020, the proportion of women had increased; non-smokers were more common than beforehand, the proportion of <50-year-olds with LC had decreased. Adenocarcinoma incidence was on the rise. Early mortality slightly improved.

Implications of all the available evidence

Real-life data and randomized control trial data are considered mutually complementary. Our real-life studies provide insight into the epidemiology and practical LC management in French NPHs. KBP studies, consecutive nationwide prospective cohorts, by their size and composition allow a description and representative comparison of LC.

Introduction

Lung cancer (LC) is the leading cause of cancer death in France and worldwide.^{1,2} LC is also one of the most common cancer and leading cause of cancer death among men, with approximately 1.37 million new cases in 2018 worldwide. Among women, incidence rates were generally lower than in men, with approximately

770 828 new cases in 2020.³ Nonetheless, geographic variations in incidence rates differed between women and men, which was attributed to historical gender differences in cigarette smoking.¹

In France, LC was revealed to be the second most common cancer in men, whilst being the third most common one in women.⁴ The last decades have witnessed profound changes concerning LC. First, incidence rates have remained almost stable in men, whereas they have substantially increased in women. Smoking rates have significantly decreased in France, owing to the implementation of national anti-smoking plans.⁵ Second, progress in the therapeutic decision-making and patient care has been largely promoted over the last decades in several fields, including radiology, pathology, molecular profiling of lung cancers, surgery, radiation therapy, as well as improvement in systemic therapy with the advent of targeted therapies and immunotherapy.

In France, lung cancers are managed in different health care structures, such as academic hospitals ($N=32$), nonacademic public hospitals ($N=296$), private hospitals or practices ($N=170$), and Cancer Centers ($N=20$). Interestingly, the network of nonacademic public hospitals was revealed to take care of close to 50% of newly diagnosed LCs.⁶ The French College of General Hospital Pulmonologists (CPHG) is a network coordinating teaching and research actions in lung diseases for nonacademic public hospitals.

In order to capture the consequences of this changing social and health context, we have conducted recurrent observational prospective studies every 10 years, including all consecutive LC patients diagnosed in participating nonacademic public hospitals (NPH), referred to as the KBP-2000/2010/2020-CPHG studies.^{7–9} The objectives were to describe the baseline characteristics of all new cases of primary lung cancer diagnosed in NPHs in 2000, 2010, and 2020 and to evaluate 5-year survival. We previously reported in 2010 vs. 2000 an increasing number and percentage of women and non-smokers among patients diagnosed with Stage IV, as well as a very large increase in the number and percentage of adenocarcinomas regardless of age, gender, or smoking status. The smoking status of men had significantly changed, involving twice as many non-

smokers ($p < 0.0001$). The 5-year overall survival was slightly improved, due to the increased non-small-cell lung cancer (NSCLC) survival (11.4% in 2000 vs. 13.8% in 2010; $p < 0.001$).¹⁰ Here, we report the main baseline results from the KBP-2020-CPHG study and compare them to those from the previous cohorts for the LC patient and tumour characteristics. Early mortality (1 and 3 months) has also been reported.

Methods

KBP-CPHG studies

KBP-2020-CPHG is a multicenter, observational, prospective study conducted in France, whose main objective was to estimate mortality rates at 1 and 5 years in patients diagnosed with primary LC. Patients were included from January 1 to December 31, 2020.

Similarly, to the two previous KBP-studies performed in 2000 and 2010, the KBP-2020-CPHG was a large observational study focused on incident LC cases diagnosed in French NPHs (pneumology or oncology departments) over a one-year period. The vital status was collected at different follow-up times (1–3 months; 1–2 and 5 years).

The study was promoted by the CPHG. All pulmonologists or thoracic oncologists practicing in NPHs (pneumology or oncology departments) were invited either by mail or by e-mail to participate to the study, with overall 219 pneumology departments contacted.

Since 2000, all KBP-CPHG studies have been conducted using a similar methodology including the same study design, involving similar participating centers, and using comparable patient recruitment methods, with similar inclusion and exclusion criteria, as well as numerous common items among the three questionnaires, which rendered it possible to compare the respective datasets. Continuity was ensured for implementing and monitoring of the three studies, with a partial replacement of the Scientific Committee between 2000, 2010, and 2020. This guarantees homogeneity in method and data collection. Methodology and results from 2000's and 2010's studies were previously published.^{8–10}

Inclusion and exclusion criteria

All patients newly diagnosed with LC between January 1 and December 31, 2020, in one of the participating centers were eligible for participating to the study, diagnosed either cytologically or histologically. Patients were to be over 18 years old, and they all were duly informed about the study. The date of diagnosis was considered to be the sampling date of the first biopsy confirming the pathological diagnosis.

Exclusion criteria were secondary LC assessed by the investigator as being a recurrence of primary LC based

on several criteria (histology, clinical and imaging characteristics, as well as delay from previous LC), patients having previously participated to the study, in addition to those either deprived of liberty following a judicial or administrative decision or unable to provide consent.

Data collection

The investigators were requested to exhaustively include all consecutive new LC cases, while completing patient electronic case report forms in terms of patient and tumour characteristics, and first treatment applied. COVID-19 data collection was added during 2020 (date; hospitalization). Detailed patient information was collected, including age, gender, height, weight loss percentage, smoking habits, cannabis use, as well as performance status (PS). Mode of discovery, date of first specialist contact, and date of tissue sampling were also collected.

Collected tumour data comprised histological tumour type, stage according to the 8th TNM classification, metastasis (number and localization), biomarker screening, PDL-1 status, and if available tumour molecular burden (TMB). Follow-up was planned to assess overall survival until 5 years. Vital status and date of death were obtained from the investigator or town council of the patients' birthplace at least 5 years after the first inclusion. In the 2020 KBP cohort, and in comparison, with the 2000 and 2010 results, we have reported herein the data on 1–3 month mortality.

Data quality control

The Scientific Committee assessed the study completeness and exhaustiveness throughout the year. Several controls and procedures were set up to ensure high-quality and reproducible data sets. All data were quality checked for inadmissible values, inconsistencies, and missing data. The Committee investigated the consistency of investigators' recruitment and its regularity to identify non-exhaustive inclusions. The investigators were contacted (i) when they included less patients during the second part of the year compared to the first; (ii) when the number of included patients varied drastically between 2020 as compared with both previous studies (2000 and 2010); (iii) to verify if they had omitted to include patients diagnosed during 2020 Christmas holidays. During the monitoring period, five centers were visited by an independent clinical research associate (C. R.A.) who helped investigators verify if their recruitment was appropriate. Overall, 10 centers whose recruitment was not exhaustive were excluded from the analyzed database to avoid biases.

All investigators (or authorized person) had to check their inclusions with hospital medicalized information system program, conclusions of the oncology multidisciplinary team meetings, or the anatomopathological

register of each center and return a signed document attesting this verification. Only six of the 82 centers omitted to return this document. Data-related issues were resolved by the Scientific Committee. Major deviations comprised questionnaires in duplicate, no histological or cytological sample, and sampling date outside of the recommended window.

Definitions

We used the 8th TNM edition in 2020,¹¹ 7th edition in 2010,¹² and 6th edition in 2000.¹³ Given the difficulty of correspondence among those, we mainly classified tumour stages into localized including Stages I and II, locally advanced comprising Stage III, and metastatic/disseminated encompassing Stage IV diseases.

Tobacco smokers were defined as subjects who reported having smoked at least 100 cigarettes in their lifetime, and former tobacco smokers as those who declared smoking cessation for at least 1 year prior to diagnosis. Inversely, never-smokers were defined as those having smoked less than 100 cigarettes in their lifetime. Smoking duration, average number of cigarettes smoked per day, and/or pack-years were systematically retrieved.

Disease discovery patterns were notified as symptomatic, fortuitous, or opportunistic individual screening. Symptomatic disease discovery was notified when diagnosed upon an examination carried out at the patient's or doctor's request for LC-related symptoms. Fortuitous disease discovery was when diagnosis was either made upon an examination for another symptomatic condition or follow-up for another disease (e.g., coronary heart disease). Opportunistic individual screening was notified as LC detection in asymptomatic patients following high suspicion of lung cancer (e.g., for current smokers or for asbestos exposure).

Statistical analysis

The data were expressed as frequency and percentage for categorical variables, and by mean and standard deviation (SD) for continuous variables. Confidence intervals (CI) for proportions were derived at the 95% level using the exact method. KBP-2020-CPHG, KBP-2010-CPHG, and KBP-2000-CPHG data were compared using the Student's t-test (to compare 2010 and 2020 when data from 2000 were not available) or ANOVA test (to compare the three instances) for quantitative variables and Chi-squared testing for qualitative variables. Alternative non parametric tests were conducted as appropriate. The Cochran-Armitage trend test was applied to test significant trends over the years.

Univariate and multivariable logistic regression models were applied to estimate odds ratios (ORs) and 95% CIs. Analyses were adjusted for age (continuous variable), gender (qualitative variable), and smoking

habits (categorical variable). All statistical analyses were performed using R Version 4.0.0 (2020-04-24). All p-values were two-sided, and p-value ≤ 0.05 was considered statistically significant.

Mortality rates at 1 and 3 months with 95% confidence intervals were estimated with the Kaplan-Meier method in each cohort. Estimations were stratified on stage (localized, locally advanced or metastatic/disseminated) in NSCLC and calculated overall in SCLC.

Ethics approval and consent to participate

According to French regulation, the patients provided oral informed consent and non-opposition to participating in this study. To protect personal data confidentiality in line with legal requirements, data hosting and security was provided by ClinInfo Company. Name specific data were provided by an approved health data host, Avenir Télématique. Personal data were stored separately from the remaining data and encrypted with exclusive access given to investigators.

The KBP-2020-CPHG protocol was approved by independent ethics committees: *Comité de Protection des Personnes (CPP) Sud méditerranée VI*, (on May 3, 2019; July 19, 2019 [amendement on July 19, 2019, and October 11, 2020]); and by French National Drug Authority (*Agence Nationale de Sécurité des Médicaments [ANSM]*) under the ID RCB: 2019-A00943-54. The study protocols were approved by French data protection commission (CNIL) on November 19, 2019 (ID #919267). The ClinicalTrials.gov Identifier is NCT04402099.

Role of the funding source

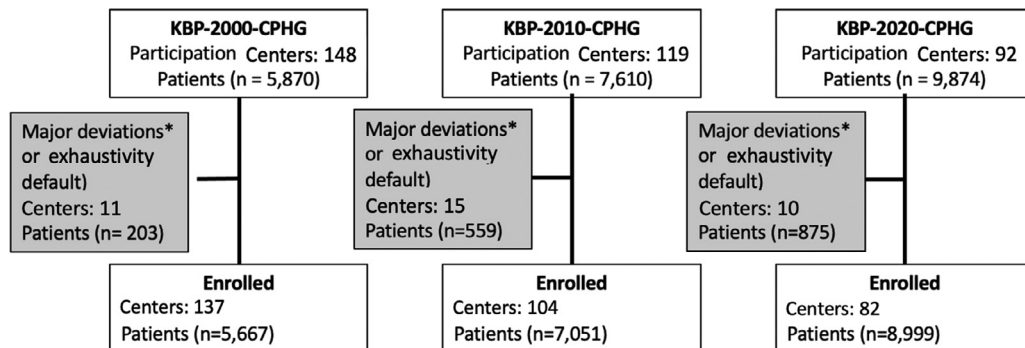
The funders of the study had no roles in the study design, data collection, data analysis, data interpretation, writing or reading of the report.

Results

Patients' demographic and tumour characteristics - KBP-2020

In 2020, 98 centers accepted to participate, but finally 6 didn't participate. Thus, 92 centers actually agreed to participate in the study and 9,874 patients were included. Ten centers (875 patients) were either excluded for exhaustivity default or for major deviations. Therefore, the analysis included 82 centers and 8,999 patients (Figure 1).

On average (mean \pm SD), 109 \pm 60 LC patients were included by each center in 2020 (min: 28 patients and max: 330 patients). Overall, 42 centers were previously investigator centers for both 2000 and 2010 KBP studies. Patient and tumour characteristics are summarized in Table 1. Among the 8,999 patients, mean age at diagnosis was 67.8 \pm 10.3 years, i.e., older at diagnosis compared to 2010 (65.5 \pm 11.3 years) and 2000 (64.6 \pm 11.5



*Major deviations were questionnaires in duplicate, no histological or cytological samples, sampling dates outside of the recommended window

Figure 1. Flowchart of study populations.

years), and 3114 (34.6% - 3114/8999) were women. The proportion of active smokers, former smokers, and never-smokers was 52.9%, 34.6%, and 12.6% (4748, 3106, 1129/8983), respectively. PS was mainly PSo (2754/8812; 31.3%) or PSI (3820/8812; 43.3%). Disease discovery was mainly symptomatic (6452/8995; 72.7%), it was fortuitous in 2182/8995 (24.3%); LC detection in asymptomatic patients following high LC suspicion (opportunistic individual screening) allowed for LC diagnosis in 361/8995 (4.0%) patients, with no difference observed between men and women. The distribution between SCLC and NSCLC is respectively 12.6% (1137/8999) and 86.9% (7820/8999) of LC. Adenocarcinoma was the most common histological type (4667/8999, 51.9%), found in 47.3% of men (2781/5885) and in 60.6% (1886/3114) of women (Table 2). Concerning 7648 NSCLC patients, localized LC was identified in 21.5% (1648) of cases, locally advanced LC in 20.9% (1595), and metastatic/disseminated LC in 57.6% (4405).

Gender

The women represented 34.6% (3114/8999) of our cohort. They were younger at diagnosis than men (mean±SD, 66.9±10.8 vs. 68.3±10.1). Among the youngest patients (≤50 years), the proportion of women was 41.1% (176/428). Comparison with 2010 and 2000 cohorts revealed a significant increase in the proportion of women (34.6% (3114/8999) vs. 24.3% (1711/7051) in 2010 and 16.0% (904/5667) in 2000, $p < 0.0001$). The results highlight a lesser proportion of patients under 60 years in 2020 than in previous KBP study. For men, this decrease concerns both percentages and absolute numbers. For women under 50 years, we notice a decrease in percentage and absolute number and between 51 and 60 years, only a decrease in percentage (Figures 2 and 3).

In 2020, the frequency of localized LC (Stages I & II, 24.9% (660/2709), 95% CI [22.8%–26.0%]) was

higher among women than among men (19.8% (992/5153), 95% CI [18.2%–20.4%]).

Smoking status

The rate of active smokers was roughly comparable among the three study populations (52.9% (4748/8983), 49.2% (3451/7008), and 52.5% (2931/5586) in 2020, 2010, and 2000, respectively), as shown in Table 1. The proportion of never-smokers among men was significantly higher in 2020 compared to 2010 and 2000 (6.3% (371/5872) in 2020, 4.3% (230/5303) in 2010, and 2.4% (115/4698) in 2000, $p < 0.0001$). Inversely, the proportion of never-smokers among women progressively decreased over the decades (24.4% (758/3111) in 2020, 31.2% (532/1705) in 2010, and 32.3% (287/888) in 2000, $p < 0.0001$). A trend towards an increase in active smokers was seen only in women upon the last decade (52.7% (1639/3111) vs. 47.3% (807/1705) respectively). Conversely, an increase in never-smokers was particularly marked among men under 50 years old, and a similar trend was observed among men over 70 years old in 2020.

However, in 2020, the proportion of never-smokers among women was still higher than among men (24.4% (758/3111) vs. 6.3% (371/5872)).

Evolution of histological types over two decades

Based on our data, a significant increase in the occurrence of adenocarcinoma among NSCLC patients was observed across the studies, and this significant trend ($p < 0.0001$) persisted after adjusting for age, gender, and smoking status (OR=2.1 [1.9–2.2], $p < 0.0001$ in 2010; OR=2.7 [2.5–3.0], $p < 0.0001$ in 2020) (Table 3). Notably, this increased proportion of adenocarcinoma was observed both among men and women (OR=2.8 [2.6–3.1], $p < 0.0001$ in men in 2020 vs. OR=2.5 [2.1–2.9], $p < 0.0001$ in women). Unlike the adenocarcinoma type, the proportion of other subtypes like small-cell lung cancer (SCLC) (16.5% (930/5660) /13.5% (950/7051) /12.6% (1137/8999) in 2000, 2010, and 2020, respectively), as well as squamous cell and large-cell

	KBP-2000						KBP-2010						KBP-2020																	
	Total		Men		Women		Total		Men		Women		Total		Men		Women													
	n (%)	95%CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI												
Age (years)	5667		4763		84.0 [83.1-85.0]		904		16.0 [15.0-16.9]		7051		5340		75.7 [74.7-76.7]		1711		24.3 [23.3-25.3]		8999		5885		65.4 [64.4-66.4]		3114		34.6 [33.6-35.6]	
<i>Mean +/- SD [Median ; Q1-Q3]</i>	64.6±11.5 [65.4 ; 56.0-73.3]		64.6±11.1 [65.4 ; 56.3-73.0]		64.1±13.3 [65.9 ; 53.3-74.6]		65.5±11.3 [65 ; 57-75]		65.8±10.8 [65 ; 58 - 74]		64.8±12.8 [64 ; 55-76]		67.8±10.3 [68.0 ; 61.3-74.6]		68.3±10.1 [68.6 ; 62.1-74.8]		66.9±10.8 [66.8 ; 59.7-74.1]													
	n=5664		n=4760		n=904		n=7051		n=5340		n=1711		n=8999		n=5885		n=3114													
≤ 50	698 (12.3)	[11.5 - 13.2]	529 (11.1)	[10.2 - 12.1]	169 (18.7)	[16.1 - 21.3]	615 (8.7)	[8.1 - 9.4]	385 (7.2)	[6.5 - 7.9]	230 (13.4)	[11.9 - 15.2]	428 (4.8)	[4.3 - 5.2]	252 (4.3)	[3.8 - 4.8]	176 (5.7)	[4.9 - 6.5]												
51-60	1235 (21.8)	[20.8 - 22.9]	1078 (22.6)	[21.5 - 23.9]	157 (17.4)	[15.0 - 20.0]	1899 (26.9)	[25.9 - 28.0]	1431 (26.8)	[25.6 - 28.0]	468 (27.4)	[25.3 - 29.5]	1491 (16.6)	[15.8 - 17.4]	862 (14.6)	[13.8 - 15.6]	629 (20.2)	[18.8 - 21.7]												
61-70	1714 (30.3)	[29.1 - 31.5]	1487 (31.2)	[29.9 - 32.6]	227 (25.1)	[22.4 - 28.2]	2066 (29.3)	[28.2 - 30.4]	1655 (31.0)	[29.8 - 32.3]	411 (24.0)	[22.0 - 26.1]	3297 (36.6)	[35.6 - 37.6]	2177 (37.0)	[35.8 - 38.2]	1120 (36.0)	[34.3 - 37.7]												
71-80	1594 (28.1)	[27.0 - 29.3]	1331 (28.0)	[26.7 - 29.3]	263 (29.1)	[26.2 - 32.2]	1732 (24.6)	[23.6 - 25.6]	1355 (25.4)	[24.2 - 26.6]	377 (22.0)	[20.1 - 24.1]	2651 (29.5)	[28.5 - 30.4]	1837 (31.2)	[30.0 - 32.4]	814 (26.1)	[24.6 - 27.7]												
>80	423 (7.5)	[6.8 - 8.2]	335 (7.0)	[6.3 - 7.8]	88 (9.7)	[7.9 - 11.9]	739 (10.5)	[9.8 - 11.2]	514 (9.6)	[8.9 - 10.5]	225 (13.2)	[11.6 - 14.9]	1132 (12.6)	[11.9 - 13.3]	757 (12.9)	[12.0 - 13.8]	375 (12.0)	[10.9 - 13.2]												
Smoking	n=5586		n=4698		n=888		n=7008		n=5303		n=1705		n=8983		n=5872		n=3111													
<i>Never smoker</i>	402 (7.2)	[6.5 - 7.9]	115 (2.4)	[2.0 - 2.9]	287 (32.3)	[29.3 - 35.5]	762 (10.9)	[10.2 - 11.6]	230 (4.3)	[3.8 - 4.9]	532 (31.2)	[29.0 - 33.5]	1129 (12.6)	[11.9 - 13.3]	371 (6.3)	[5.7 - 7.0]	758 (24.4)	[22.9 - 25.9]												
<i>Former smoker</i>	2253 (40.3)	[39.0 - 41.6]	2083 (44.3)	[42.9 - 45.8]	170 (19.1)	[16.6 - 21.9]	2795 (39.9)	[38.7 - 41.0]	2644 (49.9)	[48.5 - 51.2]	366 (21.5)	[19.6 - 23.5]	3106 (34.6)	[33.6 - 35.6]	2392 (40.7)	[39.5 - 42.0]	714 (23.0)	[21.5 - 24.5]												
<i>Active smoker</i>	2931 (52.5)	[51.2 - 53.8]	2500 (53.2)	[51.8 - 54.6]	431 (48.5)	[45.2 - 51.9]	3451 (49.2)	[48.1 - 50.4]	2644 (49.9)	[48.5 - 51.2]	807 (47.3)	[44.9 - 49.7]	4748 (52.9)	[51.8 - 53.9]	3109 (52.9)	[51.7 - 54.2]	1639 (52.7)	[50.9 - 54.5]												
Among current and former smokers	n=5112		n=4526		n=586		n=5945		n=4832		n=1113		n=7362		n=5153		n=2209													
<i>Number of pack-years</i>	44.4±21.4 [40 ; 30 - 52]		45.2±21.5 [40 ; 30-55]		38.5±20.4 [38 ; 25-50]		43.0±21.4 [40 ; 30-50]		44.1±21.7 [40 ; 30-52]		38.3±19.4 [37 ; 26-50]		42.5±23.0 [40 ; 30-50]		43.8±23.6 [40 ; 30-51]		39.3±21.2 [40 ; 25-50]													
<i>Duration of smoking (years)</i>	n=4926		n=4361		n=565		n=5268		n=4272		n=996		n=4943		n=3435		n=1508													
<i>Mean +/- SD [Median ; Q1-Q3]</i>	37.3±11.5 [40 ; 30 - 45]		37.6±11.3 [40 ; 30-45]		34.9±12.6 [33 ; 27-42]		37.5±11.6 [40 ; 30-45]		37.9±11.5 [40 ; 30-45]		35.7±12.1 [35.5 ; 30-42]		40.0±12.3 [41 ; 32-49]		40.0±12.8 [40 ; 31-50]		39.9±11.3 [41 ; 33-48]													
<i>Smoking cessation/LC time</i>	n=2177		n=2013		n=164		n=2647		n=2308		n=339		n=3106		n=2392		n=714													
<i>Mean +/- SD [Median ; Q1-Q3]</i>	11.3±9.8 [9 ; 3-17]		11.4±9.7 [10 ; 3-17]		10.7±11.5 [6 ; 2-15]		14.8±11.7 [12 ; 5-22]		15.2±11.6 [12 ; 5-22]		12.5±11.4 [10 ; 4-20]		16.5±12.6 [14 ; 5-24]		17.4±12.9 [15 ; 6-26]		13.4±11.2 [11 ; 4-19]													
PS at diagnosis	n=5656		n=4754		n=902		n=6976		n=5288		n=1688		n=8812		n=5760		n=3052													
<i>PS0</i>	1518 (26.8)	[25.7 - 28.0]	1254 (26.4)	[25.1 - 27.7]	264 (29.3)	[26.3 - 32.4]	1902 (27.3)	[26.2 - 28.3]	1427 (27.0)	[25.8 - 28.2]	475 (28.1)	[26.0 - 30.4]	2754 (31.3)	[30.3 - 32.2]	1718 (29.8)	[28.7 - 31.0]	1036 (33.9)	[32.3 - 35.7]												
<i>PS1</i>	2131 (37.7)	[36.4 - 39.0]	1804 (37.9)	[36.6 - 39.3]	327 (36.3)	[33.1 - 39.5]	2904 (41.6)	[40.5 - 42.8]	2204 (41.7)	[40.3 - 43.0]	700 (41.5)	[39.1 - 43.9]	3820 (43.3)	[42.3 - 44.4]	2532 (44.0)	[42.7 - 45.3]	1288 (42.2)	[40.4 - 44.0]												
<i>PS2</i>	1004 (17.8)	[16.8 - 18.8]	856 (18.0)	[16.9 - 19.1]	148 (16.4)	[14.1 - 19.0]	1284 (18.4)	[17.5 - 19.3]	987 (18.7)	[17.6 - 19.7]	297 (17.6)	[15.8 - 19.5]	1492 (16.9)	[16.2 - 17.7]	996 (17.3)	[16.3 - 18.3]	496 (16.3)	[15.0 - 17.6]												
<i>PS3</i>	817 (14.4)	[13.5 - 15.4]	686 (14.4)	[13.4 - 15.5]	131 (14.5)	[12.3 - 17.0]	693 (9.9)	[9.2 - 10.7]	521 (9.9)	[9.1 - 10.7]	172 (10.2)	[8.8 - 11.8]	581 (6.6)	[6.1 - 7.1]	411 (7.1)	[6.5 - 7.8]	170 (5.6)	[4.8 - 6.5]												
<i>PS4</i>	186 (3.3)	[2.8 - 3.8]	154 (3.2)	[2.8 - 3.8]	32 (3.5)	[2.5 - 5.0]	193 (2.8)	[2.4 - 3.2]	149 (2.8)	[2.4 - 3.3]	44 (2.6)	[1.9 - 3.5]	165 (1.9)	[1.6 - 2.2]	103 (1.8)	[1.5 - 2.2]	62 (2.0)	[1.6 - 2.6]												

Table 1: Univariate comparison of main patient characteristics.

¹Never smokers were subjects who had smoked less than 100 cigarettes in their lifetime.

PS, performance status; PY, pack-year; SD, standard deviation.

All comparisons for the overall population over time were statistically significant.

Histology	Former classification	KBP-2000						KBP-2010						KBP-2020					
		Men		Women		Men		Women		Men		Women		Men		Women			
		n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI		
	<i>New classification</i>	<i>n=5650*</i>		<i>n=4753</i>	<i>84.0</i>	<i>n=897</i>	<i>16.0</i>	<i>n=7051</i>		<i>n=5340</i>	<i>75.7</i>	<i>n=1711</i>	<i>24.3</i>	<i>n=8999</i>		<i>n=5885</i>	<i>65.4</i>	<i>n=3114</i>	<i>34.6</i>
<i>Small cell lung cancer</i>	<i>Small cell lung cancer</i>	930 (16.5)	[15.5 - 17.5]	786 (16.5)	[15.5 - 17.6]	144 (16.1)	[13.7 - 18.7]	950 (13.5)	[12.7 - 14.3]	725 (13.6)	[12.7 - 14.5]	225 (13.2)	[11.6 - 14.9]	1137 (12.6)	[12.0 - 13.3]	732 (12.4)	[11.6 - 13.3]	405 (13.0)	[11.9 - 14.2]
<i>Squamous cell carcinoma</i>	<i>Squamous cell carcinoma</i>	2193 (38.8)	[37.5 - 40.1]	1989 (41.8)	[40.4 - 43.3]	204 (22.7)	[20.1 - 25.7]	1852 (26.3)	[25.2 - 27.3]	1604 (30.0)	[28.8 - 31.3]	248 (14.5)	[12.9 - 16.3]	1993 (22.1)	[21.3 - 23.0]	1584 (26.9)	[25.8 - 28.1]	409 (13.1)	[12.0 - 14.4]
<i>Adenocarcinoma</i>	<i>Non-lobular adenocarcinoma</i>	1640 (29.0)	[27.8 - 30.2]	1244 (26.2)	[24.9 - 27.5]	396 (44.1)	[40.9 - 47.5]	3199 (45.4)	[44.2 - 46.5]	2239 (41.9)	[40.6 - 43.3]	960 (56.1)	[53.7 - 58.5]	4667 (51.9)	[50.8 - 52.9]	2781 (47.3)	[46.0 - 48.5]	1886 (60.6)	[58.8 - 62.3]
<i>Large cell carcinoma</i>	<i>Large cell carcinoma, not otherwise specified</i>	667 (11.8)	[11.0 - 12.7]	569 (12.0)	[11.1 - 12.9]	98 (10.9)	[9.0 - 13.2]	754 (10.7)	[10.0 - 11.4]	563 (10.5)	[9.7 - 11.4]	191 (11.2)	[9.7 - 12.8]	504 (5.6)	[5.1 - 6.1]	377 (6.4)	[5.8 - 7.1]	127 (4.1)	[3.4 - 4.8]
<i>Bronchio-alveolar</i>	<i>Lepidic adenocarcinoma</i>	44 (0.8)	[0.6 - 1.1]	28 (0.6)	[0.4 - 0.9]	16 (1.8)	[1.1 - 2.9]	59 (0.8)	[0.6 - 1.1]	37 (0.7)	[0.5 - 1.0]	22 (1.3)	[0.8 - 2.0]	383 (4.3)	[3.9 - 4.7]	229 (3.9)	[3.4 - 4.4]	154 (4.9)	[4.2 - 5.8]
<i>Other subtypes</i>	<i>Sarcomatoid carcinoma</i>	88 (1.6)	[1.3 - 1.9]	62 (1.3)	[1.0 - 1.7]	26 (2.9)	[1.9 - 4.3]	148 (2.1)	[1.8 - 2.5]	103 (1.9)	[1.6 - 2.3]	45 (2.6)	[1.9 - 3.5]	273 (3.0)	[2.7 - 3.4]	154 (2.6)	[2.2 - 3.1]	119 (3.8)	[3.2 - 4.6]
	<i>Large cell neuroendocrine carcinoma</i>													65 (0.7)	[0.6 - 0.9]				
	<i>Carcinoid tumors</i>													112 (1.2)	[1.0 - 1.5]				
	<i>Others subtypes</i>													80 (0.9)	[0.7 - 1.1]				
	<i>Combination of several subtypes</i>													16 (0.2)	[0.1 - 0.3]				
<i>Combination of several subtypes</i>	<i>Combination of several subtypes</i>	88 (1.6)	[1.3 - 1.9]	75 (1.6)	[1.3 - 2.0]	13 (1.4)	[0.8 - 2.5]	89 (1.3)	[1.0 - 1.6]	69 (1.3)	[1.0 - 1.6]	20 (1.2)	[0.7 - 1.8]	42 (0.5)	[0.3 - 0.6]	28 (0.5)	[0.3 - 0.7]	14 (0.4)	[0.3 - 0.8]

Table 2: Tumour characteristics.

* 17 missing data in 2000.

p-value <0.0001 for all comparisons.

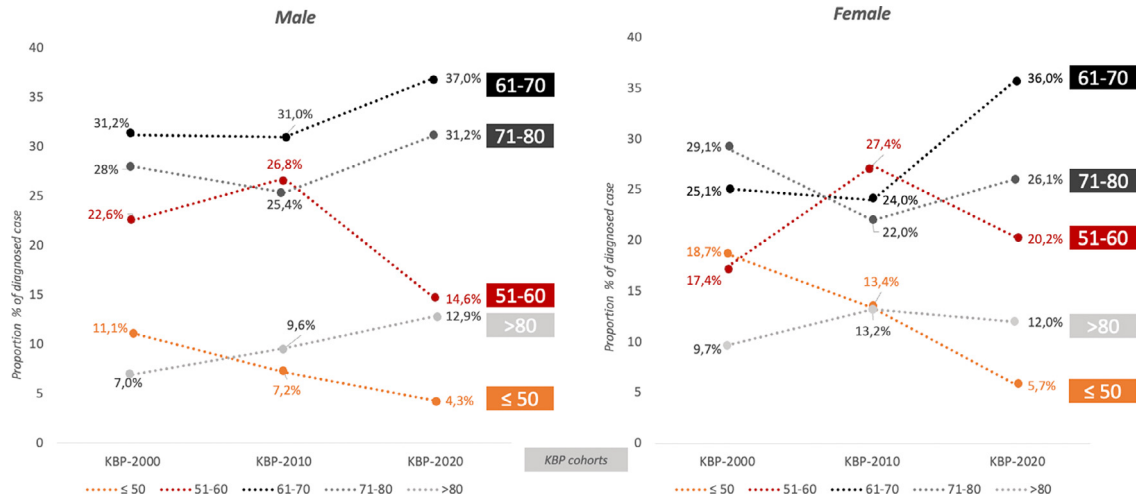


Figure 2. Lung cancer cases distribution according to age in males and females in KBP-cohorts.

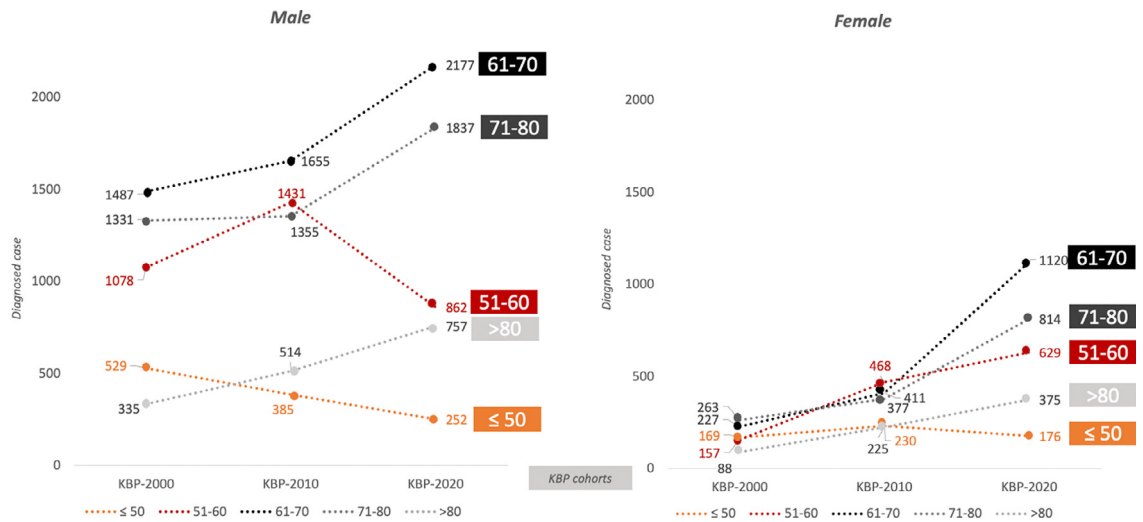


Figure 3. Absolute numbers of lung cancer cases according to age in males and females in KBP-cohorts.

carcinomas significantly decreased over the two decades ($p < 0.0001$ for each histological type, p trends < 0.0001).

Evolution of lung cancer staging over two decades

In 2020, NSCLCs tended to be less localized and more disseminated or metastatic than in 2000, with LC being more frequently diagnosed at an advanced stage (metastatic/disseminated), 57.6% (4405/7648) vs. 42.6% (1879/4411). This proportion of Stage IV amongst non-lepidic adenocarcinoma at diagnosis was 63.4% (2905/4579). However, compared to 2010, the breakdown of stages (localized - locally advanced - metastatic/disseminated) at NSCLC diagnosis was quite similar.

Early (1 and 3 months) mortality

Early mortality, measured at 1-month, 3-month for NSCLC according to stage, and for SCLC, in the three KBP cohorts (2020, 2010, and 2000) have been summarized in Table 4. In 2020, only 3.0% [95% CI: 2.1 - 3.8] of localized and 9.6% [8.2 - 11.1] of locally advanced NSCLC (vs respectively 6.6% [5.1 - 8.1] and 13.8% [12.0 - 15.6] in 2010 or 8.3% [6.6 - 10.0] and 20.2% [18.2 - 22.3] in 2000) but 29.1% [27.7 - 30.4] of patients with metastatic/disseminated NSCLC died within 3 months of diagnosis (vs respectively 31.9% [30.3 - 33.4] in 2010 and 33.7% [31.5 - 35.8] in 2000). Compared with 2000 and 2010, early survival was shown to improve slightly, especially in localized and locally advanced stage.

	Adenocarcinoma in NSCLC			Adenocarcinoma in NSCLC - Men			Adenocarcinoma in NSCLC - Women		
	n/N	%		n/N	%		n/N	%	
KBP-2000	1627/4660	34.9		1234/3915	31.5		393/745	52.8	
KBP-2010	3199/6083	52.6		2239/4597	48.7		960/1486	64.6	
KBP-2020	4667/7847	59.5		2781/5143	54.1		1886/2704	69.7	
	OR ¹	95% CI	p-value	OR ²	95% CI	p-value	OR ²	95% CI	p-value
Univariate model									
KBP-2000	1	Reference		1	Reference		1	Reference	
KBP-2010	2.1	[1.9-2.2]	<0.0001	2.1	[1.9-2.3]	<0.0001	1.6	[1.4-2.0]	<0.0001
KBP-2020	2.7	[2.5-3.0]	<0.0001	2.6	[2.4-2.8]	<0.0001	2.1	[1.8-2.4]	<0.0001
Multivariate model¹									
KBP-2000	1	Reference		1	Reference ²		1	Reference ²	
KBP-2010	2.0	[1.9-2.2]	<0.0001	2.1	[1.9-2.3]	<0.0001	1.7	[1.5-2.1]	<0.0001
KBP-2020	2.7	[2.5-3.0]	<0.0001	2.8	[2.6-3.1]	<0.0001	2.5	[2.1-2.9]	<0.0001

Table 3: Proportion of adenocarcinomas in patients with non-small cell lung cancer.

NSCLC, non-small-cell lung cancer, CI, confidence interval; OR, odds ratio.

¹ OR adjusted for age at diagnosis, sex, and smoking status.

² OR adjusted for age at diagnosis and smoking status.

	2000		2010		2020	
	1 Month % [95% CI]	3 Months % [95% CI]	1 Month % [95% CI]	3 Months % [95% CI]	1 Month % [95% CI]	3 Months % [95% CI]
NSCLC						
Localized	1.9 [1.1-2.8]	8.3 [6.6-10.0]	2.6 [1.6-3.5]	6.6 [5.1-8.1]	0.9 [0.5-1.4]	3.0 [2.1-3.8]
Locally advanced	7.0 [5.7-8.3]	20.2 [18.2-22.3]	5.3 [4.1-6.5]	13.8 [12.0-15.6]	3.0 [2.2-3.9]	9.6 [8.2-11.1]
Metastatic/disseminated	13.5 [11.9-15.0]	33.7 [31.5-35.8]	12.7 [11.6-13.8]	31.9 [30.3-33.4]	11.0 [10.0-11.9]	29.1 [27.7-30.4]
SCLC						
All stages	15.9 [13.5-18.2]	27.1 [24.1-29.9]	14.0 [11.8-16.2]	24.9 [22.1-27.6]	15.0 [12.8-17.0]	24.6 [22.0-27.0]

Table 4: Early mortality in lung cancer, non-small-cell lung cancer according to stage and small cell lung cancer.

^aMortality (%), with 95% CI.

^bNSCLC, non-small-cell lung cancer. SCLC, small-cell lung cancer. CI, confidence interval.

Discussion

To our knowledge, the KBP studies are the largest real-life prospective nationwide studies focused on LC in Europe or in the world. The originality of our project lies in the constitution of three consecutive cohorts using a similar methodology (employed similar centers, study designs, and recruitment methods) and conducted at 10-year intervals with a barometer effect. Forty-two centers participated in the three studies, and 57 participated in two studies (Figure 4). This provides particular strength when comparing data over time upon two decades, while investigating trends in patient and tumour characteristics. In addition, to compare the three cohorts in a multivariate manner, an ordinal regression was performed. This analysis can be found in the Supplementary Material.

A total of 8,999 patients were included in 2020, representing around 20% of LCs diagnosed in France according to the data provided in 2018 by INCa (Institut national du cancer - national cancer institute or French NCI) issued from the national network of French registers.¹⁴ The increased since 2000 in our cohort proved to be consistent with French registers, as published and reported between 1990 and 2018. Our data are closed to those observed in this registry: male/female ratio (31,231 male vs. 15,132 female); age (median: 67 for male and 65 for female); distribution of histological types: 11.3% small cell lung cancer – 26.7% squamous carcinoma – 42.1% adenocarcinoma.¹⁵

The most striking trend was the increasing proportion of women (34.6%) within the LC population in 2020. This trend could possibly be attributed to

changing smoking habits over time, as previously reported.¹⁶ In a nationwide registry of cancer patients that is still ongoing in Spain and involving 13,590 participants, Ruano-Ravina et al. reported a proportion of 25.6% women.¹⁷ In the UK, a serial, cross-sectional, observational study derived from the National Cancer Registration and Analysis Service (NCRAS) and based on 27,795 patients suffering from LC reported a 44.4% percentage of women with a mean age of 72 years.¹⁸ In a systematic review pertaining to gender-associated differences in fatal and non-fatal LC risk, O’Keefe and colleagues were, however, unable to identify any evidence-based difference in smoking-related LC risk among men and women.¹⁹ Recent reports have suggested that sex hormones may likely play a crucial role in chronic respiratory diseases.^{20,21} These between-gender differences in LC features have led some researchers to consider LC in women to be a distinct biological entity.²²

An increasing proportion of never-smokers was recorded across the successive KBP cohorts, though most LC patients were still shown to be smokers in France (87.6%). There is a clear difference in smoking rates between France and other countries in Europe. While smoking was shown in France to be still increasing between 2000 and 2020 in women (29.8% vs. 31.9%, respectively), and slowly declining in men (38.5% vs 34.9%, respectively), it was shown to be declining both in men and women in Europe, especially in the UK, Germany, and Spain.²³ Whereas the proportion of never-smokers was still highest in women as compared to men, this gender difference tended to decrease across time.

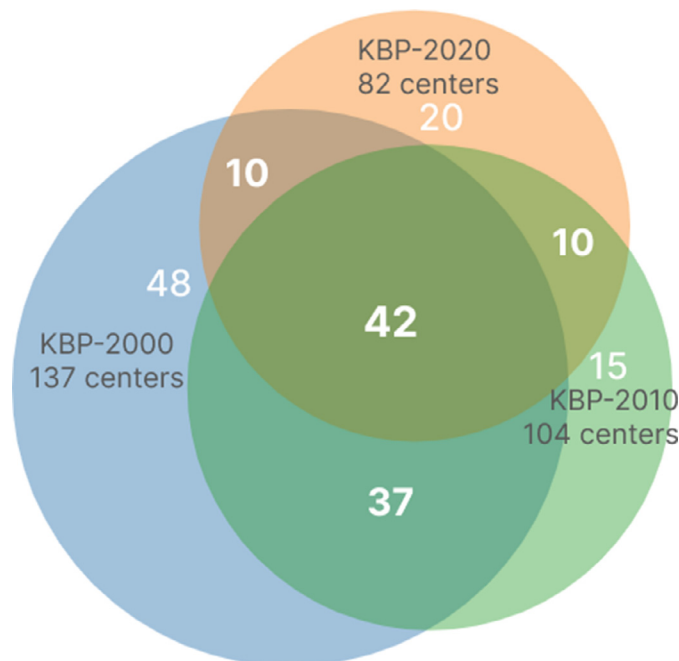


Figure 4. KBP-2000-2010-2020 centers - Venn diagram.

The favorable evolution of LC incidences of patients under 60 years is a positive perspective and could be assigned to smoking consumption diminution at least in men, in response to smoking cessation programs and tobacco advertising bans. Further analysis will be necessary to confirm this good trend.

In addition, the proportion of never-smokers in 2020 in the French general population was estimated at 35.5%.⁵ Indeed, LC in never-smokers is a particular entity.²⁴ This entity should be recognized by clinicians because of the very high prevalence of targetable oncogenic drivers,²⁵ as well as the high prevalence of exposure to occupational carcinogens and passive smoking.^{26,27}

The increase in LCs in never-smokers is of particular interest for the therapeutic approach and for implementing screening programs, as reported in other countries of the world. However, current evidence to support widespread implementation of screening among never-smokers is still lacking.²⁸ Other cancer risk factors should be considered and routinely investigated. Thereby, as radon exposure is an essential concern in France; we plan to further investigate the impact of environmental exposure by mapping risk levels related to housing.

Concerning the histological evolution over time, the most striking development has been the relevant trends towards a predominance of adenocarcinomas in both men and women, already noted in the 2010 cohort, whereas the other types were on decline. In 2000, 16.5% of LCs diagnosed were SCLCs, a proportion which had fallen to 13.5% in 2010 and 12.6% in 2020. This histology spectrum was similar to that observed in the Spanish study reported by Ruano-Ravina et al.¹⁷ Notably, this trend has been noticed since the early 1980's,¹⁶ according to the type of tobacco use.

According to our datasets, LC was shown to be diagnosed at fairly advanced stages, with 57.6% being classified Stage IV (58.3% in 2010 and 42.6% in 2000). However, these figures must be interpreted with great caution on account of new TNM classifications introduced in 2009 and 2017.²⁹ In the Spanish registry study, Ruano-Ravina et al. reported 50.8% of Stage IV cases at diagnosis in women and 43.6% in men.¹⁷ The proportion of early-stage cancer diagnoses can be used as a surrogate marker of the effectiveness of the screening strategy. Indeed, LCs evolve for a long time in a sub-clinical way and become symptomatic only at an advanced stage, which is more difficult to treat. The effectiveness of this strategy is illustrated by the comparison of the evolution of early stages between the United States (US) and France. Thus, the proportion of LCs discovered at a limited stage at diagnosis has risen sharply in the United States between 2000 and 2020 (from 17% during the mid-2000s, to 20% in 2013, and 28% in 2018),³⁰ while this proportion remained particularly stable in France during the same period of time (23% in 2000, 18% in 2010, and 22% in 2020) in our article.

This stage shift was shown to coincide with the recommendation and implementation of LC screening in US since 2013 by the US Preventive Services Task Force (USPSTF).³¹ Nevertheless, it must be stressed that systematic LC screening programs are still in their early step, without any official LC screening programs being applied in France.

LC remains a cancer with a poor prognosis with a high mortality rate, particular early. Early mortality data (1 and 3 months) in our cohorts have been shown to be very high and this for almost 20 years. This is probably due to a diagnosis that often remains late at a metastatic stage (57.6% in our cohorts). Despite everything, a slight improvement is noted in 2020 in all stage for NSCLC, especially for localized or locally advanced stage, but not for SCLC. This improvement is probably due to therapeutics progress in the last ten years (minimally invasive surgery for localized NSCLC, maintenance immunotherapy after chemo-radiotherapy for locally advanced NSCLC, targeted therapy and immunotherapy for metastatic NSCLC). We hope that this will be confirmed in the follow up of the KBP-2020 cohort at 2 and 5 years and will be translate in overall survival to be published in the future. Patients who died early constitute a population of frailty and comorbid patients at a very advanced stage. This strongly suggests that systematic organized LC screening could be recommended in certain high-risk patient groups. Indeed, a large high-quality study from the National Lung screening Trial revealed statistically significant 20% reductions in LC mortality over a 6.5-year follow-up, while using screening based on low-dose computed tomography compared with chest radiology.³² In the meta-analysis of nine randomized controlled trials including the UKLS trial, Field and al³³ reported a significant reduction in LC mortality (OR=0.84 [0.76 – 0.92]) when using LDCT screening program.

One of the strengths of our study was the methodology used, *i.e.*, an observational multicenter prospective cohort study, collecting real-life data. Meanwhile, the French registries are usually retrospective in nature contain no or very little clinical data.

In France, the NPHs form an excellent network throughout covering all regions. NPHs currently take care of nearly half of the LCs diagnosed in France. However, our cohort cannot be considered as a registry since it excluded patients from Academic hospital, Cancer centers, and Private clinics. Our cohort was not deemed representative of the general LC French population, it was considered rather representative of the large patient portion treated for LC in NPHs.

Conclusion

The KBP-CPHG-2020 study confirms the trends over a 20-year period, already previously observed, demonstrating a higher representation of women and never-

smokers with LC compared to the previous cohorts. A more positive highlight was the decrease in both percentages and absolute numbers of LC recorded in male patients under 60 years, in parallel to a decreasing trend in smoking habits, which was also observed in the elderly. With respect to the histological LC subtypes, the frequency of adenocarcinoma was found increasing, while that of the other subtypes was decreasing, especially SCLCs. A slight improvement in early mortality is observed in 2020 bringing hope for the future and overall survival of LC.

Contributors

DD, OM, LF, CL, DT, NM, HM, YD, BA, JT, SC, and AC are involved in study concepts, study design, statistical analysis, writing and manuscript preparation. DD, OM, LF, CL, DT, HM, YD, JT, JA, OB, RC, MF, and LM are involved in data acquisition. AL is involved in statistical analysis, writing and manuscript preparation. All authors read and approved the final manuscript.

Data sharing statement

Individual participant data that underlie the results reported in this Article (text, tables, figures, and appendices) will be shared after deidentification to researchers who provide a methodologically sound and ethically approved proposal.

Declaration of interests

The authors have no financial and personal relationship with other people or organization that could inappropriately bias this work. The scientific committee was fully independent from industrial sponsors.

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Supplementary materials

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References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
- Pujol JL, Thomas PA, Giraud P, et al. Lung cancer in France. *J Thorac Oncol*. 2021;16(1):21–29.
- International agency for research on cancer. Updated 2020. *Lung cancer fact sheet*. Accessed 16 August 2022. Available from: <https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf>.
- Defossez G, Uhry Z, Delafosse P, et al. Cancer incidence and mortality trends in France over 1990–2018 for solid tumors: the sex gap is narrowing. *BMC Cancer*. 2021;21(1):726.
- Pasquereau A, Andler R, Guignard R, et al. Consommation de tabac parmi les adultes en 2020: résultats du Baromètre de Santé publique France. *Bull Epidemiol Hebd*. 2021;(8):132–139.
- Health Data Hub. Updated 2020. Analyse de la prise en charge des patients atteints de cancer (poumon, VADS, d'un mélanome, rein) traités par chimiothérapie. Accessed 16 August 2022. Available from: <https://health-data-hub.fr/projets/analyse-de-la-prise-en-charge-des-patients-atteints-de-cancer-poumon-vads-dun-melanome-rein>.
- Blanchon F, Grivaux M, Collon T, et al. Epidemiologic of primary bronchial carcinoma management in the general French hospital centers. *Rev Mal Respir*. 2002;19(6):727–734.
- Grivaux M, Locher C, Bombaron P, et al. Étude KBP-2010-CPHG: recueil des nouveaux cas de cancer bronchopulmonaire primitif diagnostiqués dans les services de pneumologie des centres hospitaliers généraux du 1^{er} janvier au 31 décembre 2010. *Revue de Pneumologie Clinique*. 2010;66(6):375–382.
- Locher C, Debieuvre D, Coëtmeur D, et al. Major changes in lung cancer over the last ten years in France: the KBP-CPHG studies. *Lung Cancer*. 2013;81(1):32–38.
- 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(4):283–292.
- Lababede O, Meziane MA. The eighth edition of TNM staging of lung cancer: reference chart and diagrams. *Oncologist*. 2018;23(7):844–848.
- Lababede O, Meziane M, Rice T. Seventh edition of the cancer staging manual and stage grouping of lung cancer: quick reference chart and diagrams. *Chest*. 2011;139(1):183–189.
- Mountain CF. Revisions in the international system for staging lung cancer. *Chest*. 1997;111(6):1710–1717.
- Institut National du Cancer INCa. Les cancers en France 2018. Accessed 16 August 2022. Available from: https://www.e-cancer.fr/ressources/cancers_en_france/#page=31.
- Santé Publique France - Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018. Updated 2019. Accessed 16 August 2022. Available from: <https://www.santepubliquefrance.fr>.
- Schabath MB, Cote ML. Cancer progress and priorities: lung cancer. *Cancer Epidemiol Biomarkers Prev*. 2019;28(10):1563–1579.
- Ruano-Ravina A, Provencio M, Calvo de Juan V, et al. Are there differences by sex in lung cancer characteristics at diagnosis? A nationwide study. *Transl Lung Cancer Res*. 2021;10(10):3902–3911.
- Chowienzyk S, Price S, Hamilton W. Changes in the presenting symptoms of lung cancer from 2000–2017: a serial cross-sectional study of observational records in UK primary care. *Br J Gen Pract*. 2020;70(692):e193–e199.
- O'Keeffe LM, Taylor G, Huxley RR, Mitchell P, Woodward M, Peters SAE. Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis. *BMJ Open*. 2018;8(10):e021611.
- Sathish V, Martin YN, Prakash YS. Sex steroid signaling: implications for lung diseases. *Pharmacol Ther*. 2015;150:94–108.
- Siegfried JM, Stabile LP. Estrogenic steroid hormones in lung cancer. *Semin Oncol*. 2014;41(1):5–16.
- Ben Khedher S, Neri M, Papadopoulos A, et al. Menstrual and reproductive factors and lung cancer risk: apooled analysis from the international lung cancer consortium. *Int J Cancer*. 2017;141(2):309–323.
- World Health Organization. Age-standardized estimates of current tobacco use, tobacco smoking and cigarette smoking. updated: 2022-01-17. Accessed 16 August 2022. Available from: <https://apps.who.int/gho/data/node.main.TOBAGESTDCURR?lang=en>.
- Couraud S, Zalcman G, Milleron B, Morin F, Souquet PJ. Lung cancer in never smokers—a review. *Eur J Cancer*. 2012;48(9):1299–1311.
- Couraud S, Souquet PJ, Paris C, et al. BioCAST/IFCT-1002: epidemiological and molecular features of lung cancer in never-smokers. *Eur Respir J*. 2015;45(5):1403–1414.
- Couraud S, Debieuvre D, Moreau L, et al. No impact of passive smoke on the somatic profile of lung cancers in never-smokers. *Eur Respir J*. 2015;45(5):1415–1425.
- Paris C, Do P, Mastroianni B, et al. Association between lung cancer somatic mutations and occupational exposure in never-smokers. *Eur Respir J*. 2017;50(4).
- Kerpel-Fronius A, Tammemagi M, Cavic M, et al. Screening for lung cancer in individuals who never smoked: an international association for the study of lung cancer early detection and screening committee report. *J Thorac Oncol*. 2022;17(1):56–66.
- Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. *Chest*. 2017;151(1):193–203.
- Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7–33.
- Moyer VA, Force USPST. Screening for cognitive impairment in older adults: U.S. preventive services task force recommendation statement. *Ann Intern Med*. 2014;160(11):791–797.
- National Lung Screening Trial Research T, Aberle DR, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395–409.
- Field JK, Vulkan D, Davies MPA, et al. Lung cancer mortality reduction by LDCT screening: UKLS randomised trial results and international meta-analysis. *Lancet Reg Health Eur*. 2021;10:100179.