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Original article

Epidemiology of metastatic lung cancer in France between 2013 and 2021: Observational study using the French claims database

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Keywords
Epidemiology
Metastatic lung cancer
Trend analysis
Claims data

Summary

Introduction > Treatment landscape in metastatic lung cancer has progressed quickly over the last decade, mainly due to immunotherapies and targeted therapies. This study aimed to describe change in epidemiological data of patients with metastatic lung cancer.

Methods > A cohort of patients identified between 2013 and 2021 with lung cancer and a marker of metastases (ICD-10 code or reimbursement for Bevacizumab or Pemetrexed) was built from the French claims database. A trend analysis of the rate of newly-diagnosed metastatic patients and the proportion of deaths over the study period was performed using Joinpoint® software.

Results > Between 2013 and 2021, 147,760 metastatic lung cancer patients were identified (men: 66.5%, median age: 66 years). A statistically significant decrease in the crude rate of newly-diagnosed metastatic patients was observed in men (−1.18% per year in average), whereas a statistically significant increase was described in women (+2.36% per year in average). A downward trend in the proportion of deaths was found for both gender (−4.37% and −5.07% per year on average, respectively).

Discussion > This study provides unpublished epidemiological data on metastatic lung cancer in France and confirms sex-differentiated trends in the rate of newly-diagnosed metastatic patients, already observed for all stages combined. A statistically significant decrease in the proportion of deaths among metastatic lung cancer patients is observed in both genders. These results underline the importance of ongoing investments in prevention and screening initiatives to reverse the incidence trends observed in women. Moreover, it highlights the criticality of therapeutic innovation in sustaining the increase in survival.

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Mots clés
Épidémiologie
Cancer du poumon métastatique
Test de tendance
Données de remboursement

Résumé

Épidémiologie du cancer du poumon métastatique en France entre 2013 et 2021 : étude observationnelle à partir du Système national des données de santé

Introduction > *L'offre thérapeutique dans le cancer du poumon métastatique a progressé rapidement ces dix dernières années, principalement grace aux immunothérapies et thérapies ciblées. Cette étude visait à décrire l'évolution des données épidémiologiques des patients avec un cancer du poumon métastatique.*

Méthode > *Une cohorte de patients avec un cancer du poumon et un marqueur de métastases (code CIM-10 ou remboursement de bévacizumab ou pémétrexed) entre 2013 et 2021 a été constituée avec les données de remboursements françaises. Un test de tendance du taux de patients nouvellement diagnostiqués métastatique et de la proportion de décès a été réalisé avec le logiciel Joinpoint®.*

Résultats > *Parmi les patients, 147 760 atteints de cancer du poumon métastatique ont été identifiés (hommes : 66,5 %, âge médian : 66 ans). Une diminution statistiquement significative du taux de patients nouvellement diagnostiqués métastatique chez les hommes (−1,18 % par an en moyenne) et une augmentation statistiquement significative chez les femmes (+2,36 % par an en moyenne) ont été observées. Une baisse de la proportion de décès a été observée pour les deux sexes (−4,37 % et −5,07 % par an en moyenne, respectivement).*

Discussion > *Cette étude fournit des données épidémiologiques inédites sur le cancer du poumon métastatique en France et confirme des tendances différenciées selon le sexe pour le taux de patients nouvellement diagnostiqués métastatique, déjà observées tous stades confondus. Elle révèle cependant une diminution similaire de la proportion de décès. Ces résultats soulignent l'importance des investissements dans les actions de prévention et de dépistage pour inverser l'évolution de l'incidence chez les femmes, et rappellent la nécessité des innovations thérapeutiques pour améliorer la survie des patients.*

Introduction

Worldwide, with an estimated 2.2 million new cancer cases and 1.8 million deaths, lung cancer is the leading cause of cancer death (18.0% of the total cancer deaths) and the second most commonly diagnosed cancer (11.4% of total cases), right after female breast cancer (11.7% of total cases) [1]. Overall, the risk of developing lung cancer is higher in developed countries [1]. In France, lung cancer is the second most common cancer in men and the third one in women, with 52,777 new cases in 2023, and the leading cause of cancer-related deaths [2,3]. Over the 2010–2023 period, the number of newly-diagnosed patients fell slightly in men (−0.5% per year) and rose in women (+4.3% per year) [2]. According to the French KBP-2020-CPHG study, 60.4% of lung cancer patients were diagnosed at stage IV [4]. Moreover, among cancers diagnosed at a localized or locally advanced stage, about 40% will progress to an advanced or metastatic stage within a year [5]. Lung cancer is therefore associated with a poor prognosis and represents a major public health issue.

Significant advances in lung cancer management have been made to improve disease survival, particularly in the advanced/metastatic stage. Indeed, for many years, the management of advanced or metastatic lung cancer (mLC) was a primary systemic anti-cancer therapy based on platinum (since the 70s) with or without an association to a third-generation cytotoxic agent (gemcitabine, vinorelbine and taxanes) (since the 90s). In 2004, EGFR mutation was discovered, followed, a few years after, by the identification of other oncogenic alterations (e.g. ALK, MET, KRAS, ROS-1, RET, BRAF, NTRK). These recent breakthroughs in precision medicine have had an important impact on overall survival, safety and quality of life of patients with first the development of targeted therapy (since 2006 in non-mutated cancer and since 2010 in EGFR positive cancer) [6,7]. More recently, the arrival of PD-1/PD-L1 checkpoint inhibitors has brought new hope in the management of this disease (since July 2015 for nivolumab, then May 2017 for pembrolizumab, and February 2019 for atezolizumab), and became the new standard of care in advanced lung disease. Indeed, these new therapeutic approaches have proved particularly effective in targeting cancer cells while preserving healthy cells, offering more precise and less invasive results. Compared with conventional treatments, these innovative therapies offer better symptom management, limiting severe complications and reducing the need for frequent full hospitalization [8,9].

With patients' prognosis improving, the epidemiology of lung cancer is therefore evolving, as well documented in the

literature [1,10,11]. However, data specifically on the metastatic stage are scarce. The goal of this study was to provide as-yet unexplored and exhaustive data about trends in mortality and incidence of patients with mLC between 2013 and 2021, using the French nation-wide claims database.

Methods

Data sources

This study was based on the French National Health data System (Système National des Données de Santé, SNDS) which currently covers 98.8% of population leaving in France (about 67 million in 2021) [12]. It contains anonymous individual information on patients' sociodemographic characteristics, all non-hospital reimbursed healthcare expenditures (without corresponding medical diagnoses), and all hospital discharge summaries (ICD10-code-based). The SNDS does not provide direct information on behavioral or clinical baseline characteristics (tobacco smoking, body mass index, etc.), nor laboratory results, any information on drug dispensed during a hospital stay (except for specific costly medications), any data on cause of death [12].

Study population and study design

This study is an observational, retrospective dynamic cohort of patients identified with a mLC between January 1st, 2013 and December 31st, 2021 in France. Patients were included if they met the two following criteria during the inclusion period:

- a long-term disease status (LTD, i.e. status providing full coverage for all medical expenses related to a specific condition) or hospitalization for lung cancer (C34 or C399 ICD-10 codes);
- and a marker of metastasis: a LTD or hospitalization for secondary malignant neoplasm (C77-C79 ICD-10 codes) or at least one reimbursement for bevacizumab or pemetrexed (i.e. used as proxy for metastasis).

The first occurrence of one of these inclusion criteria was defined as the index date. Patients were followed until death, the last patient's health record (i.e. last care recorded in the database before a period of 6 months without any reimbursed care) or the end of the study period (i.e. December 31st, 2021), whichever occurred first. A pre-study period of seven years before index date was used to select only patients with primary lung cancer by excluding patients with probable pulmonary metastases (i.e. patients with a marker of metastases or of another cancer before the first lung cancer diagnosis). Patients were excluded if they were under 18 years old at index date or if they were not affiliated to the general health insurance scheme (data from all health insurance schemes not available for entire study period), during the pre-study and the follow-up period.

Variables

Three epidemiological indicators were considered:

- the number of patients living with a mLC each year, corresponding to all patients included in the cohort and with at least one day of follow-up the year *n*;
- a) the crude rate of patients newly diagnosed with mLC each year, corresponding to patients with an index date the year N and without marker of metastasis during the pre-study period, relative to the French population (estimated from statistics of French National Institute of Statistics and Economic Studies (INSEE)). This crude rate was estimated overall, by sex, by age group and crossing age and sex. This denominator has been replaced by the number of persons affiliated to the general health insurance scheme as part of a sensitivity analysis (see sensitivity analysis section hereafter); b) the age- and sex-standardized rate of newly-diagnosed patients and the age-standardized rate for men and women using direct standardization. The French population as of January 1st, 2019, retrieved from the population census data published by INSEE, was used as the standard population [13];
- the proportion of deaths among patients living with a mLC (1) each year. In 2020 and 2021, the likely COVID-19-related deaths were also described, i.e. patients who died at hospital, with a main diagnosis of COVID-19 (U07.10, U07.11, U07.14 and U07.15 ICD-10 codes) or an associated diagnosis of multisystemic inflammatory syndrome associated to COVID-19 (ICD-10 code U10.9) at hospital discharge.

Statistical analysis

Descriptive analysis

Sociodemographic and clinical characteristics (comorbidities and long term oxygenotherapy use) of the global cohort of patients with mLC were provided using descriptive statistics.

Trend analysis

The trend in the crude and standardized rate of patients newly diagnosed with mLC and in the proportion of deaths over the 2013–2021 period was studied using the National Cancer Institute's (NCI) Joinpoint Regression Program (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, MD, USA), version 5.0.2 [14]. The analysis started with the minimum number of joinpoints (i.e., 0 joinpoint representing a straight line) and it has been tested whether one joinpoint was statistically significant and must be added to the model (one jointpoint being the maximum number recommended with seven to eleven observation points). Trends were measured using the average annual percent change (AAPC) over the study period and the annual percentage change (APC).

Sensitivity analysis

To estimate the rate of newly-diagnosed patients with mLC, two denominators were considered:

- the overall French population (i.e. not restricted to patients affiliated to the general health insurance scheme) from INSEE data or;
- people affiliated to the general health insurance scheme in France, from data provided by the national inter-scheme

directory of health insurance beneficiaries *(Répertoire national interrégimes des bénéficiaires de l'Assurance maladie [RNIAM])*.

Since our study population was restricted to patients affiliated to the general health insurance scheme, this subpopulation was supposed to be the most suitable denominator for the main analysis. However, RNIAM data are overestimated [15], and this overestimation is not homogeneous over the study period. Indeed, a greater overestimation is observed in 2020 and 2021, due to a delay in updating the data. Considering this limitation, RNIAM data were therefore used in a sensitivity analysis.

Apart from the study of trend, all analyses were performed using SAS (SAS Institute, North Carolina, USA), Version 9.4.

Ethics

This study was approved by the French Institute for Health Data (approval No. 2262161 from 3 September 2020). It was conducted with anonymized data, as requested by the National Informatics and Liberty Commission [CNIL], approval no.920444), from 4 March 2021.

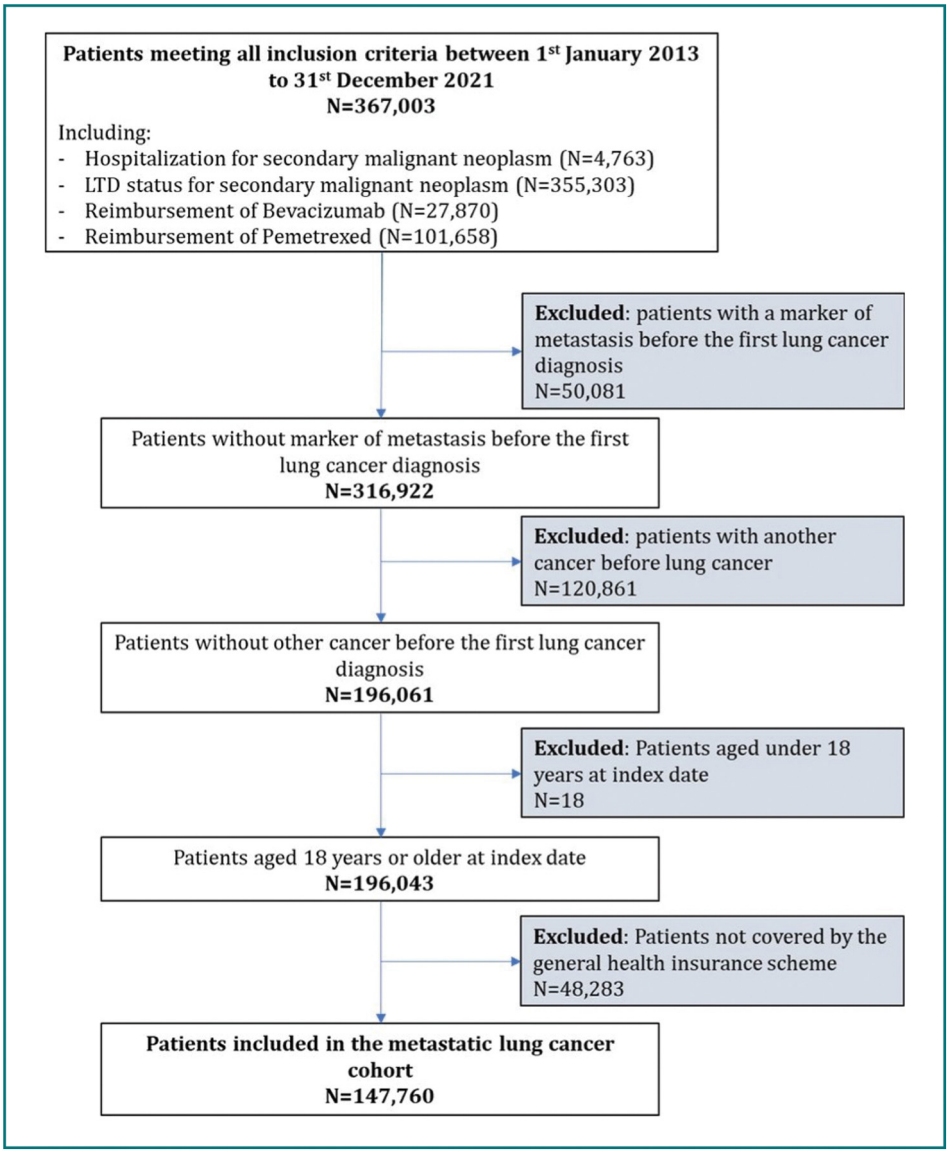

FIGURE 1
Flow chart

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Results

Selection and follow-up

Between 2013 and 2021, both lung cancer diagnosis and metastasis marker were recorded in 367,003 patients (*figure 1*). After excluding patients with a marker of metastases or of another cancer before the first lung cancer diagnosis (i.e. probable pulmonary metastases), patients under 18 and those not covered by the general health insurance scheme, 147,760 patients were included in the mLC cohort. The median follow-up was 6.8 months (Q1–Q3: 2.3–17.6).

Patients' characteristics

Among 147,760 patients included, two thirds were male (66.5%; *table I*). Median age was 66.0 years (Q1–Q3: 58.0–73.0). Patients had a high comorbidity burden (median Charlson score of 14.0 [Q1–Q3: 13.0–15.0]), including 54.9% with cardiovascular diseases, 27.9% with severe chronic respiratory insufficiency, 17.2% with cancer (other than lung cancer) and 16.7% with diabetes.

Table I
Characteristics of the study population

	Metastatic lung cancer cohort (*n* = 147,760)
Gender, *n*(%)	
Male	98,221 (66.5%)
Age (years)	
Median (Q1–Q3)	66.0 (58.0–73.0)
Age (years), *n* (%)	
< 55	21,637 (14.6%)
[55–70[	72,762 (49.2%)
[70–80[	34,932 (23.6%)
≥ 80	18,429 (12.5%)
Comorbidities	
Diabetes type 1 and 2	24,627 (16.7%)
Cardiovascular diseases	81,125 (54.9%)
Inflammatory diseases	3,071 (2.1%)
Severe chronic respiratory insufficiency	41,238 (27.9%)
Severe chronic nephropathy and nephrotic syndrome	6,403 (4.3%)
Cancers other than lung cancer	25,360 (17.2%)
Malnutrition	53,356 (36.1%)
Long term oxygenotherapy use, *n* (%)	11,399 (7.7%)
Charlson score	
Median (Q1–Q3)	14.0 (13.0–15.0)

Epidemiological indicators

Number of patients living with mLC

The number of patients living with a mLC increased over the study period, from 24,595 in 2013 to 40,321 in 2021, including 14,587 (59.3%) and 15,225 (37.8%) newly-diagnosed patients, respectively (*figure 2*).

Rate of newly-diagnosed patients with mLC

- The overall crude rate of newly-diagnosed patients with mLC was stable over the 2013–2021 period (AAPC of −0.02%; 95% CI: −0.42 to 0.38; *figure 3*). In men, a statistically significant decrease was observed overall (AAPC of −1.18%, 95%CI: −1.67 to −0.69), and for all age groups, with the greatest decrease observed in the youngest patients (AAPC of −4.04%, 95%CI: −5.06 to −3.00). In women, a statistically significant increase was found overall (AAPC of 2.36%, 95%CI: 1.81 to 2.91) and for the following age groups: [55–70[(AAPC of 2.21%, 95%CI: 1.41 to 3.01) and [70–80[(AAPC of 3.09%, 95%CI: 2.61 to 3.58).
- The trend analysis of the age− and sex-standardized rate of newly-diagnosed patients estimated a statistically significant decrease of 1.12% each year (95%CI: −1.52 to −0.72; *figure 4*). Different trends for men and women were confirmed with the age-standardized rate, with a decrease of 2.32% (95%CI: −2.79 to −1.84) each year for men and an increase of 1.47% (95%CI: 0.90 to 2.05) each year in women.

Proportion of deaths in patients living with a mLC

The proportion of deaths in patients living with a mLC has fallen from 47.9% (11,786/24,595 patients) in 2013 to 33.3% (13,424/40,321 patients) in 2021. The trend analysis showed a statistically significant decrease of 4.74% per year over the 2013–2021 period (95%CI: −5.12 to −4.37, *figure 5*). This decrease was observed for both men and women and for all age groups. A gradient in the percentage of decrease was observed, from the older to the younger age group (AAPC of −2.2%, −2.96%, −5.37% and −7.59%, for patients aged over 80, between 70 and 80, between 55 and 70 and under 55, respectively). For patients aged between 70 and 80, it was estimated that the rate decreased until 2019 (APC of −4.00%) and then stabilized (APC of 0.24%).

Among patients who died in 2020 and 2021, 2.6% and 2.8% were likely COVID-19-related, respectively. These patients (*n* = 720) were mostly males (69.7%) and had a median age of 69 years (Q1–Q3: 62.0–75.0). More than a third (35.3%) of these patients were aged between 70 and 80.

Sensitivity analysis

The trend analysis of the crude rate of newly-diagnosed patients with mLC among the population covered by the general health

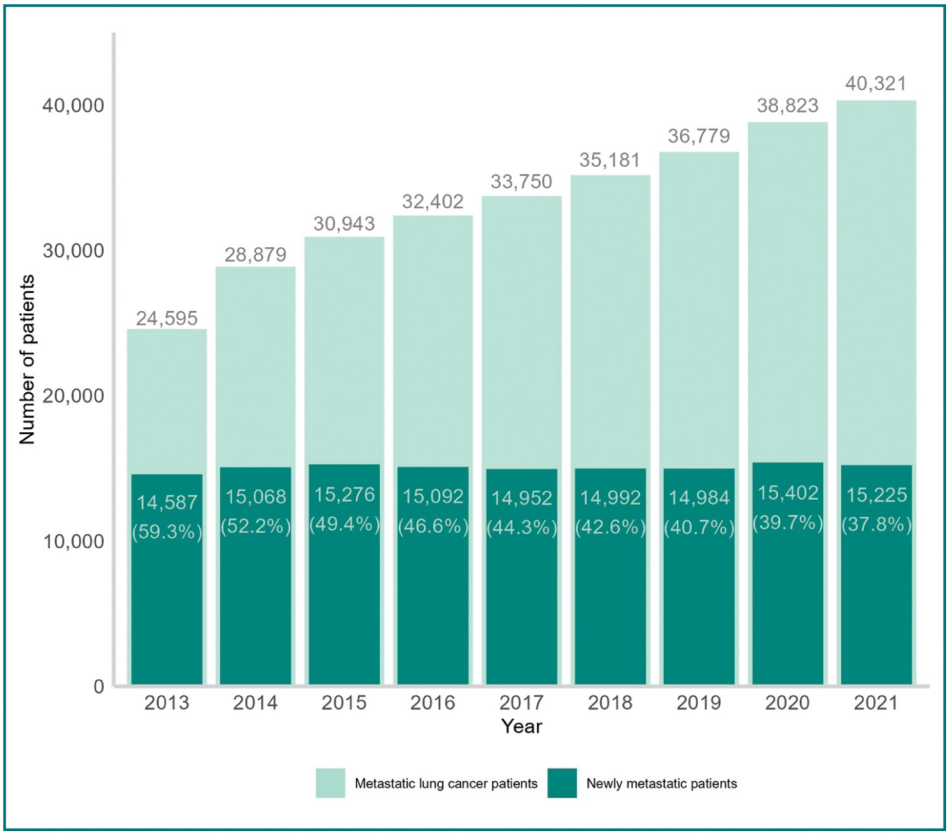

FIGURE 2

Number of patients living with a metastatic lung cancer, including patients newly diagnosed, between 2013 and 2021

insurance scheme also confirmed a differentiated trend between men (AAPC of −2.34%, 95%CI: −3.45 to −1.22) and women (AAPC of 1.12%, 95%CI: −0.16 to 2.42) (*figure S1*). In women, the increase was statistically significant only between 2013 and 2019 (APC of 2.19%, 95%CI: 1.02 to 3.38 versus AAPC of 2.36%, 95% CI: 1.81 to 2.91), when estimated among the French population over the entire study period.

Discussion

Summary of key findings

To our knowledge, this study is the first to provide epidemiological data on lung cancer at metastatic stage over time in France. These results confirmed differentiated trends in the rate of newly-diagnosed patients between men and women, already observed for all stages combined. Indeed, between 2013 and 2021, this rate has fallen significantly in men (−1.18%) and risen significantly in women (+2.36%). A statistically significant decrease in the proportion of deaths among metastatic lung cancer patients was observed overall (−4.74% per year), in both gender (Men: −4.37%, Women: −5.07%) and in each age group (−2.20%, −2.96%, −5.37% and −7.59%, for patients aged over 80, between 70 and 80, between 55 and 70 and under 55, respectively) over the study period.

Interpretation of results

The results of this study are of major interest given that lung cancer is the third most common cancer, the leading cause of cancer-related mortality, is mainly diagnosed at the metastatic stage, and has been the subject of numerous therapeutic innovations over the last 10 years. The trends observed in this study for the rate of newly-diagnosed patients with mLC are aligned to those observed for lung cancer all stages combined. Indeed, differentiated trends between men and women are described in the literature worldwide, as in this study. In France, for men, *Santé Publique France* observed a slight downward trend in the world-Standardized Incidence Rates (SIR) of lung cancer all stages combined since 2005, with an average annual variation of −0.3% over the recent 2010–2018 period [10]. The decrease of the French age-standardized rate observed in this study for the metastatic stage in the 2013–2021 period is more accentuated (−2.32%). In contrast, the world SIR for women is rising

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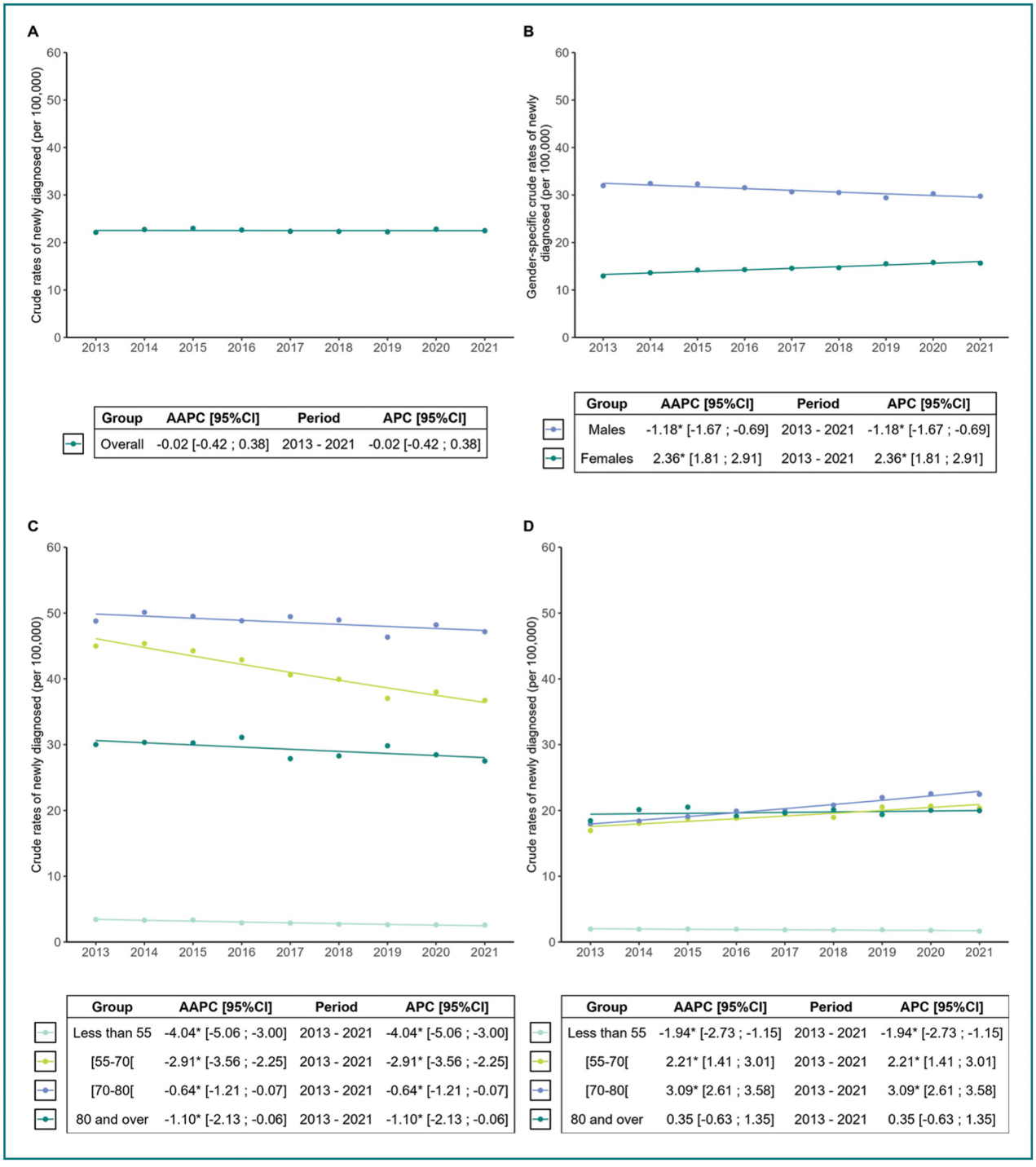


Group	AAPC [95%CI]	Period	APC [95%CI]
Overall	-0.02 [-0.42 ; 0.38]	2013 - 2021	-0.02 [-0.42 ; 0.38]

Group	AAPC [95%CI]	Period	APC [95%CI]
Males	-1.18* [-1.67 ; -0.69]	2013 - 2021	-1.18* [-1.67 ; -0.69]
Females	2.36* [1.81 ; 2.91]	2013 - 2021	2.36* [1.81 ; 2.91]

Group	AAPC [95%CI]	Period	APC [95%CI]
Less than 55	-4.04* [-5.06 ; -3.00]	2013 - 2021	-4.04* [-5.06 ; -3.00]
[55-70[	-2.91* [-3.56 ; -2.25]	2013 - 2021	-2.91* [-3.56 ; -2.25]
[70-80[	-0.64* [-1.21 ; -0.07]	2013 - 2021	-0.64* [-1.21 ; -0.07]
80 and over	-1.10* [-2.13 ; -0.06]	2013 - 2021	-1.10* [-2.13 ; -0.06]

Group	AAPC [95%CI]	Period	APC [95%CI]
Less than 55	-1.94* [-2.73 ; -1.15]	2013 - 2021	-1.94* [-2.73 ; -1.15]
[55-70[	2.21* [1.41 ; 3.01]	2013 - 2021	2.21* [1.41 ; 3.01]
[70-80[	3.09* [2.61 ; 3.58]	2013 - 2021	3.09* [2.61 ; 3.58]
80 and over	0.35 [-0.63 ; 1.35]	2013 - 2021	0.35 [-0.63 ; 1.35]

FIGURE 3

Trend analysis of the crude rate of patients newly diagnosed with metastatic lung cancer/100,000 inhabitants (French population from INSEE data). A. overall. B. By sex. C. By age group in men. D. By age group in women

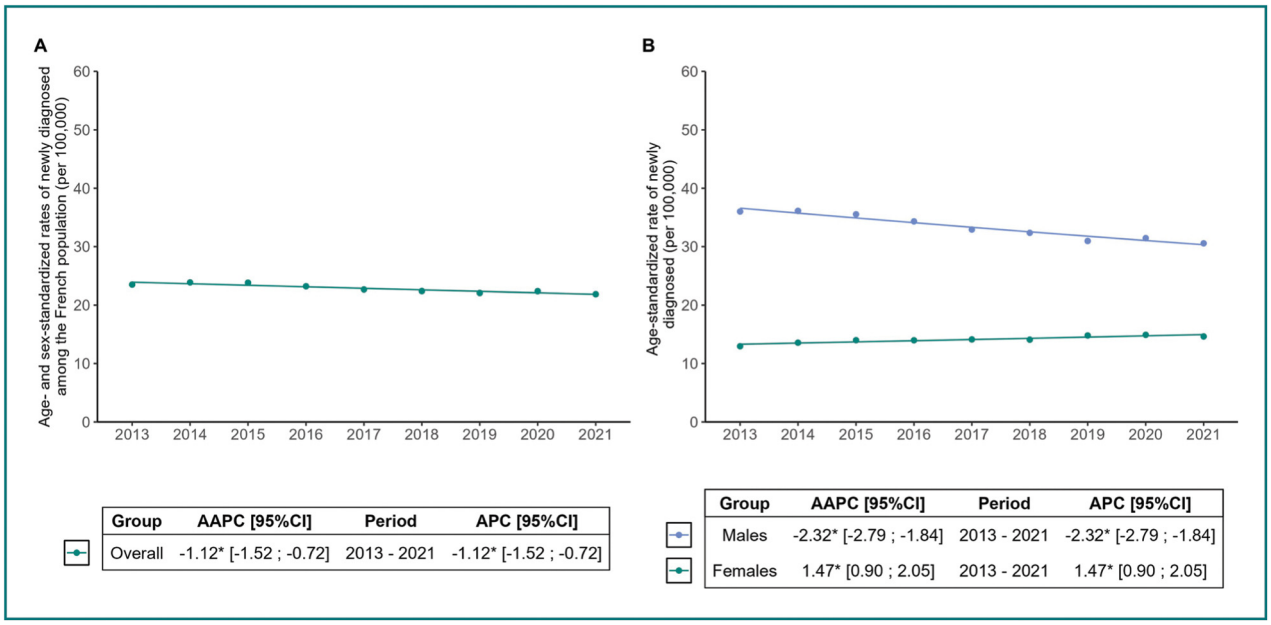


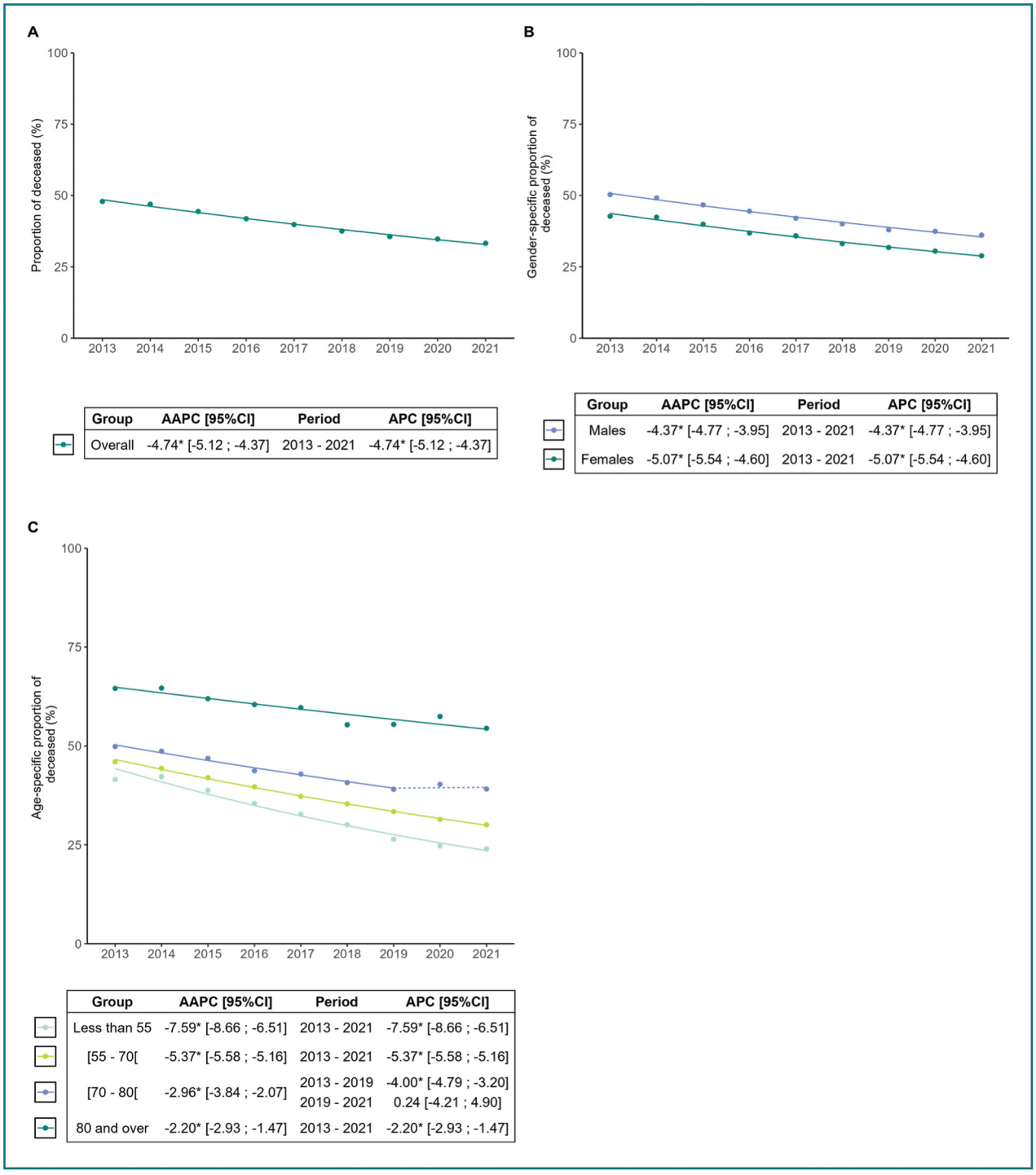
FIGURE 4

Age and sex-standardized rate of newly diagnosed patients with mLC per 100,000 inhabitants. A. Overall. B. By sex

sharply, at +5.3% per year since 1990 (+5.0% over the period 2010–2018), which is higher than the 2.36% observed in this study for the metastatic stage. However, it should be noted that, in addition to having been performed on two different populations (metastatic vs. all stages), our study and the Santé Publique France's one, used different standard populations (French population vs. world population), which may also partly explain these differences.

The evolution of this epidemiological indicator, differently for men and women, may be the consequence of changes in certain behaviors and exposures, such as smoking which is the main risk factor for lung cancer, responsible for 8 lung cancers on 10 [16]. These trends may therefore reflect changes in smoking practices observed over the last 50 years, partly thanks to anti-smoking measures implemented in France from 1976 (the Veil law) [17–21]. The impact of these measures is particularly noticeable among men, where there was a significant drop in the proportion of smokers and regular smokers in all age groups between 1953 and 2000 [22]. In contrast, they have not had the same impact on women, for whom smoking has increased since the Second World War, with the proportion of regular smokers rising from 10% in the 1960s to 21% in the 2000s [22]. This may be mainly explained by an evolution of the society and social norms (smoking was a symbol of freedom and emancipation for women). Hence, women have reached the age where the effects of smoking on lung cancer risk are visible. However, when we look by age group, a decrease is observed for the youngest women (under 55), which may suggest that a peak has been reached and that the overall incidence will soon fall, as it is already observed in the United States and some European countries [1,23]. Decrease in incidence at metastatic stage could be greater with early detection. Indeed, lung cancer is a silent disease, diagnosed in 60% of cases at a stage that is already metastatic. Newly available data showed that low-dose CT screening in high-risk persons led to lower detection of stage IV cancers and earlier detection of cancers, as well as a reduction in specific mortality [24–26]. To date, there is no organized lung cancer screening program in France. However, in the light of this new scientific data, the French National Authority for Health initiated in 2022 a pilot project in real-life and drafting additional studies, evaluating the effectiveness and benefit/risk balance, with a view to obtaining answers that are still missing but are essential for the implementation of a program [27]. The earlier detection of lung cancer through a national organized screening program can be even more beneficial with the introduction of innovative therapies at early stages. This combination holds great potential for improving patient prognosis and enhance survival rates.

While different trends in incidence are observed in men and women, this study shows similar trends in mortality. The results presented in this study are not directly comparable with the mortality figures found in most studies, as the latter represent the number of deaths in the general population and are therefore driven by the change in the incidence of mLC patients. This is what was observed in the *Santé Publique France* study, which showed an increase in the mortality rate among women [10]. To



Group	AAPC [95%CI]	Period	APC [95%CI]
Overall	-4.74* [-5.12 ; -4.37]	2013 - 2021	-4.74* [-5.12 ; -4.37]

Group	AAPC [95%CI]	Period	APC [95%CI]
Males	-4.37* [-4.77 ; -3.95]	2013 - 2021	-4.37* [-4.77 ; -3.95]
Females	-5.07* [-5.54 ; -4.60]	2013 - 2021	-5.07* [-5.54 ; -4.60]

Group	AAPC [95%CI]	Period	APC [95%CI]
Less than 55	-7.59* [-8.66 ; -6.51]	2013 - 2021	-7.59* [-8.66 ; -6.51]
[55 - 70[	-5.37* [-5.58 ; -5.16]	2013 - 2021	-5.37* [-5.58 ; -5.16]
[70 - 80[	-2.96* [-3.84 ; -2.07]	2013 - 2019 2019 - 2021	-4.00* [-4.79 ; -3.20] 0.24 [-4.21 ; 4.90]
80 and over	-2.20* [-2.93 ; -1.47]	2013 - 2021	-2.20* [-2.93 ; -1.47]

FIGURE 5

Trend analysis of the proportion of deaths between 2013 and 2021. A. Overall. B. By sex. C. By age group/INSEE: *Institut national de la statistique et des études économiques* (National Institute of Statistics and Economic Studies)

assess the mortality independently of changes in incidence, we studied changes in the proportion of deaths among patients with mLC. Hence, this study revealed a decrease in the proportion of deaths of 5.1% each year in women, and a similar result was observed for men (−4.4%). Some studies have chosen to study the change in the 1-, 3- and/or 5-year survival, whose trends are more comparable to those of our study. These studies showed an increase in survival of patients with lung cancer from the 2000s [28–31], both in men and women, which is in line with our results [31]. Preliminary results from the KBP-2020-CPHG study in France also showed that the two-year survival rate has more than doubled in 20 years, from 21% in 2000 to 48% in 2020 [32]. This was also observed for patients at a metastatic stage (+26% and +19% for non-epidermoid and epidermoid lung cancer, respectively). It may be hypothesized that therapeutic innovations over the past ten years have partly contributed to this decrease in the mortality of lung cancer at metastatic stage. Indeed, targeted therapies and immunotherapies, are both associated with an improved survival and less side effects than chemotherapies [8,9]. Moreover, in this study, the period studied includes the years 2020 and 2021, during which the COVID-19 pandemic occurred (2.6% and 2.8% of deaths were likely COVID-related, respectively). Hence, we cannot know if the decrease would have been greater if the pandemic did not occur. In addition, the proportion of patients aged 70 to 80 years was higher in patients who probably died from COVID-19 than in the overall study population, which may explain why the proportion of deaths stopped decreasing in 2020 and 2021 in this age group. Lastly, these results complement those of a previous study assessing trends in the costs of a patient with mLC over the same study period, showing that despite that the global cost of metastatic lung cancer management increase, no uptrend in the mean monthly cost per patient was observed in parallel with this reduction in mortality.

Strengths and limitations

Some limitations should be pointed out. The advanced or metastatic stage of the cancer was approached by the presence of ICD-10 codes of secondary malignant neoplasm in main, related or associated diagnoses of hospitalizations and of LTD status. However, the use of these codes is not mandatory and can be delayed or not provided. Hence, bevacizumab and pemetrexed administrations, two treatments specifically used at metastatic stage in non-squamous non-small cell lung cancer (NSCLC) over the study period, were also used as proxy to reduce this bias. As there is no specific treatment for squamous NSCLC and for small cell lung cancer (SCLC), they were only identified based on ICD-codes and patients with miscoding may have been missed. Moreover, by using only ICD-codes and hospital treatments as selection criteria, it is likely that part of patients receiving only outpatient treatments, or who were untreated, without any hospitalization, have been missed. Hence, we were not able to consider these estimates as a reflection of the incidence and prevalence of mLC in France. However, the number of patients missed is estimated to be low and our study provides the most comprehensive view among the available data sources. Moreover, these biases could be considered constant over time and therefore have no impact on the trend analyses performed.
We focused on general scheme patients, as these were the only ones with sufficient data history (7 years prior to the index date), enabling us to apply an algorithm to be specific of mLC by excluding patients with probable pulmonary metastases, often coded as lung cancer. However, being specific, some patients may have been wrongly excluded, leading to an underestimation of the number of patients with mLC. This may also have led to selection bias if the incidence and mortality rates are different in patients not covered by the general health scheme. Moreover, as mentioned below, in view of the overestimation of the number of patients affiliated to the general scheme with RNIAM data, we have chosen to not use this population as denominator for the estimation of the rate of newly-diagnosed patients with mLC in the main analysis, and to use the overall French population instead, which allowed to consider the population growth and to perform trend analyses. However, this rate is therefore underestimated and cannot be compared to the literature. Sensitivity analyses showed similar trends and support the robustness of our analyses.

Conclusion

This study confirms a gender-differentiated trends in the rate of newly-diagnosed metastatic patients already observed for all stages combined, with a statistically significant increase among women. These results underline the need to continue the investments in prevention to reverse the incidence trend in women. As a decline has been observed in the youngest women, it would be interesting to follow trends in incidence rates over the next few years to see whether overall incidence will fall in women, as has already been observed in the USA and some European countries. An organized screening program combined with introduction of innovative therapies at earlier stages could be a key tool for reducing the incidence of metastases in patients with lung cancer, improving patient prognosis and enhance survival rates. It would be of great interest to follow the impact of the pilot project of the French Health Authority. A statistically significant decrease in the proportion of deaths among metastatic lung cancer patients is observed in both gender over the study period, which could result in part from therapeutic innovations over the past ten years. These results remind the crucial importance of therapeutic innovations to continue the increase in survival. Further investigations are necessary to validate the first trends observed with more perspective.

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