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► To cite this version:

David Boulate, Marine Fidelle, Caroline Caramella, Justin Issard, Olivier Planche, et al.. Epidemiological Study to Assess the Prevalence of Lung Cancer in patients with smoking-associated atherosclerotic cardiovascular diseases: PREVALUNG study protocol. *BMJ Open*, 2022, 12 (12), 10.1136/bmjopen-2022-067191 . hal-03926501

HAL Id: hal-03926501

<https://inria.hal.science/hal-03926501v1>

Submitted on 16 Nov 2023

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BMJ Open Epidemiological Study to Assess the Prevalence of Lung Cancer in patients with smoking-associated atherosclerotic cardiovascular diseases: PREVALUNG study protocol

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To cite: Boulate D, Fidelle M, Caramella C, *et al.* Epidemiological Study to Assess the Prevalence of Lung Cancer in patients with smoking-associated atherosclerotic cardiovascular diseases: PREVALUNG study protocol. *BMJ Open* 2022;**12**:e067191. doi:10.1136/bmjopen-2022-067191

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-067191>).

Received 05 August 2022
Accepted 04 December 2022



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ABSTRACT

Introduction Eligibility criteria definition for a lung cancer screening (LCS) is an unmet need. We hypothesised that patients with a history of atheromatous cardiovascular disease (ACVD) associated with tobacco consumption are at risk of lung cancer (LC). The main objective is to assess LC prevalence among patients with ACVD and history of tobacco consumption by using low-dose chest CT scan. Secondary objectives include the evaluation LCS in this population and the constitution of a biological biobank to stratify risk of LC.

Methods and analysis We are performing a monocentric 'single-centre' prospective study among patients followed up in adult cardiovascular programmes of vascular surgery, cardiology and cardiac surgery recruited from 18 November 2019 to 18 May 2021. The inclusion criteria are (1) age 45–75 years old, (2) history of ACVD and (3) history of daily tobacco consumption for 10 years prior to onset of ACVD. Exclusion criteria are symptoms of LC, existing follow-up for pulmonary nodule, fibrosis, pulmonary hypertension, resting dyspnoea and active pulmonary infectious disease. We targeted the inclusion of 500 patients. After inclusion (V0), patients are scheduled for a low-dose chest CT and blood and faeces harvesting within 7 months (V1). Each patient is scheduled for a follow-up by telephonic visits at month 3 (V2), month 6 (V3) and month 12 (V4) after V1. Each patient is followed up until 1 year after V1 (14 February 2023). We measure LC prevalence and quantify the National Lung Screening Trial and Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) trial eligibility criteria, radiation, positive screening, false positivity, rate of localised LC diagnosis, quality of life with the Short Form 12 (SF-12) and anxiety with the Spielberger State-Trait Anxiety Inventory A and B (STAI-YA and STAI-YB, respectively), smoking cessation and onset of cardiovascular and oncological events within 1 year of follow-up. A case-control study nested in the cohort is performed to identify clinical or biological candidate biomarkers of LC.

Ethics and dissemination The study was approved according the French Jardé law; the study is referenced

STRENGTHS AND LIMITATIONS OF THE STUDY

- ⇒ The study evaluates the prevalence of lung cancer (LC) among patients with a history of atheromatous cardiovascular diseases (ACVDs) and tobacco consumption.
- ⇒ The intervention was a lung cancer screening (LCS) programme among patients with a history of ACVDs and tobacco consumption.
- ⇒ The study includes a nested case-control analysis of the blood and faeces biobanking at the time of LCS to identify potential biomarkers related to LC or suspicious pulmonary nodules.
- ⇒ The study is limited to 1-year follow-up and represents a monocentric experience.

at the French 'Agence Nationale de Sécurité du Médicament et des Produits de Santé' (reference ID RCB: 2019-A00262-55) and registered on clinicaltrials.gov. The results of the study will be presented after the closure of the follow-up scheduled on 14 February 2023 and disseminated through peer-reviewed journals and national and international conferences.

Trial registration number NCT03976804.

INTRODUCTION

Background

Lung cancer (LC) is the leading cause of cancer-related death worldwide and in France.^{1 2} Lung cancer screening (LCS) with low-dose CT (LDCT) scan has proven efficient to reduce LC-related mortality in patients selected on criteria based on age and tobacco consumption.^{3 4} In these studies, LC prevalence at the first screening round was around 1%. LCS eligibility criteria recommended by US Preventive Services and European guidelines are also based on age and tobacco consumption.^{5 6} Risk prediction



models proved useful in patients selected based on individual characteristics⁷; however, these models present limited validations and require calibration to be used in selected populations.⁸ In a recent review, optimising the identification of high-risk individuals has been defined as an unmet medical need for the diagnosis of presymptomatic LC and the future development of interceptive measures.⁸

Identifying eligible populations at high risk of LC remains a key priority to improve LCS. Therefore, one may propose original strategies to identify easy-to-reach populations from healthcare facilities caring for patients with high-risk LC. Atheromatous cardiovascular disease (ACVD) share similar risk factors with LC, namely, age and tobacco.^{9–11} Furthermore, around 40% of patients with LC have a history of CVD, mainly atherosclerotic such as coronary artery diseases and peripheral arterial diseases.¹² These patients are regularly followed up by cardiologists, cardiac surgeons and vascular surgeons to manage cardiovascular events and prevent future events.

We hypothesised that patients with atherosclerotic CVD associated with history of tobacco consumption could be a targetable population for LCS because (1) atherosclerosis is considered as an objective marker of tobacco exposure and toxicity; (2) the eligibility criteria (ie, history of ACVD and history of tobacco consumption) are objective criteria; and (3) patients are recruited among cardiovascular programmes including recurrent visits for cardiovascular disease management and secondary prevention, thus reducing constraints related to LCS that can be implemented concomitantly with cardiovascular visits. Furthermore, we considered that onset of atheromatous cardiovascular event in those below 50 years old can unveil an intensive and prolonged exposure to active tobacco consumption but also to unquantifiable second-hand smoking and environmental exposure that may justify start of LCS at 45 years old in this population.

Objectives

The primary objective is to estimate the prevalence of LC among patients managed for atherosclerosis-related cardiovascular events associated with tobacco consumption within an LCS programme.

The secondary objectives are

- ▶ To quantify the rate of patients eligible to National Lung Screening Trial (NLST) and NELSON studies.
- ▶ To quantify radiation induced by LC LDCT scan within the screening programme.
- ▶ To describe and quantify adverse events related to LCS.
- ▶ To quantify the rate of localised LC (\leq stage IIB).
- ▶ To quantify smoking cessation.
- ▶ To evaluate health-related quality of life and anxiety.
- ▶ To quantify the rate of positive detection based on first CT evaluation.
- ▶ To quantify the rate of invasive procedures for benign tumours among invasive procedures.

- ▶ To perform a biobanking to seek biological hallmarks of inflamaging and perturbed immunity and intestinal microbiota dysbiosis with the aim of correlating biological markers to LC prevalence.
- ▶ To quantify the annual rate of cardiovascular events.

METHODS AND ANALYSIS

Study design

Patients were recruited at Marie Lannelongue Hospital from the outpatient visit or the hospitalisation departments of vascular surgery, adult cardiology and adult cardiac surgery from 18 November 2019 to 18 May 2021. Patients who met the inclusion criteria were systematically proposed to participate in the study by the consultant in charge of the patient's atheromatous disease through minimal oral information. If the patient agreed to receive more information about the study, they were referred to the inclusion visit office that was run in parallel of the other outpatient visits by a pneumologist or a thoracic surgeon in charge of the inclusions. Consequently, a full-time outpatient visit dedicated to the Epidemiological Study to Assess the Prevalence of Lung Cancer (PREVALUNG) inclusions was set up for the period of inclusions. Patients who were hospitalised in corresponding departments, that is, adult cardiac surgery, vascular surgery and cardiology, were recruited following the same method. The study design is summarized in the [table 1](#).

During the inclusion visit, the inclusion criteria and exclusion criteria were verified, and oral and written information about the protocol was provided. After inclusion, the questionnaires were filled and the LDCT was scheduled within the next 7 months ideally at a date when the patients were scheduled to come to the hospital so as to reduce the constraints. A bag containing tubes for faeces harvesting with a nutrition and activity questionnaire was given. Blood withdrawal was also scheduled on the day of the CT scan. As the main objective was LC prevalence, we used thoracic CT performed within the previous 3 months, if available, to avoid unnecessary exposure to radiations. We only considered these CTs in an intent to screen. Should the patient be scheduled for the management of a nodule that was found on a previous CT, this patient would be considered within the exclusion criteria 'patient followed up for pulmonary nodule'.

The LDCTs were consistent with the American College of Radiology guidelines to minimise the radiation dose to the patients. They were performed on the same device (CT Revolution Apex, General Electric Healthcare) in a single breath hold from the lung apices to the costophrenic angles without contrast injection. The technical parameters were adjusted according to the weight of the patient. Images were read by a senior radiologist (OP or CC) expert in thoracic imaging and were automatically sent to an artificial intelligence (AI) device used on-label (Veye, Aidence, the Netherlands) for automatic detection of nodules. Positive screening CTs were defined by nodules with a larger diameter of ≥ 5 mm and/or a volume of ≥ 60 mm³ detected by the radiologist and/or the AI

Table 1 Study design

Actions	V0 Precreening /inclusion	V1 Within 7 months after V0	V2 3 months after V1 (optional)	V3 6 months after V1	V4 12 months after V1
Information	√				
Informed consent form signature	√				
Verification of inclusion and exclusion criteria	√				
Enrolment	√				
Eligibility to NLST and NELSON trials	√				
LC risk factors	√				
Cardiovascular history and risk factors	√				
Personal medical history (COPD, cancer history and others)	√				
Alcohol consumption (CAGE-DETA)	√				
Cannabis consumption (CAST)	√				
Health-related quality of life: SF-12	√		√	√	√
Anxiety: STAI-YA and STAI-YB	√		√	√	√
Tobacco consumption history and current status	√	√	√	√	√
Fagerström test (simplified) if active smoking	√				
Current treatments	√				
LDCT*		√			
Radiation quantification with LDCT		√			
Blood sampling and biobanking		√			
Faeces sampling and biobanking		√			
Multidisciplinary evaluation for positive screening		√			
Patient information of the screening results and follow-up management		√			
Quantification of invasive procedure following a positive detection			√	√	√
Benign tumour diagnosis			√	√	√
LC diagnosis		√	√	√	√
Localised stage (≤IIB) LC diagnosis		√	√	√	√
Cardiovascular events since last visit		√	√	√	√
Adverse event related with LC screening		√	√	√	√

CAGE-DETA, Cut down drinking Annoyed by criticism Guilty feelings Eye-opener - Diminuer Entourage Trop Alcohol; CAST, Cannabis Abuse Screening Test; COPD, chronic obstructive pulmonary disease; LDCT, low-dose CT scan; NLST, National Lung Screening Trial.

device. All positive screenings were evaluated during the weekly multidisciplinary tumour board. The decisions were based on the available European expert statement based on the British Thoracic Society Guidelines.^{5 13} The nodules were either ruled out, controlled at 3–6 or 12 months with a CT scan or considered true positive with an indication for diagnostic procedure. The patients were selected for surgery according to the available European guidelines.¹⁴

The biobanking consisted of plasma harvesting and isolation of peripheral blood mononuclear cell from 40 mL of heparinised whole blood using density gradient centrifugation for long-term storage, 10 mL of blood in EDTA free tubes for serum storage and faecal collection. A high dimensional multiomics analysis are performed based on matching patients with LC or nodule-bearing patients with controls. Matching criteria are usually confounding factors, such as age, gender, status and tobacco consumption. This biological analysis is based on clonal haematopoiesis of indeterminate prognosis (screening mutations associated with myelodysplastic

syndromes), on spectral flow cytometry to analyse circulating myeloid and lymphoid subsets, on mass spectrometry-based metabolomics and on shotgun metagenomics of faeces and on serum proteomics (Luminex and O-Link technology).

The follow-up was performed at 3 months (optional, V2), 6 months (V3) and 12 months (V4) after the CT (V1) by call (telephonic visits) to determine onset of oncological or cardiovascular diseases, smoking status and answer questionnaires. The smoking status was defined at baseline (V0) as active or not. If it was not active, it was specified whether it was a recent cessation (<1 year) or not. Regarding the smoking status follow-up, at V2, V3 and V4, we evaluated whether the smoking was unchanged or not compared with V0. If a cessation occurred, it was specified whether it is a full or partial cessation and the date of the cessation was reported.

Participants

Inclusion criteria

Inclusion criteria include

- ▶ Age 45–75 years old.
- ▶ Patient who has signed an informed written consent.
- ▶ Daily smoking for at least 10 years.
- ▶ History of cardiovascular disease among coronary artery disease, peripheral arterial disease, supra-aortic trunk stenosis or ischaemic stroke not from cardiac origin, aortic aneurysm and visceral or upper limb stenosis.

Exclusion criteria

Exclusion criteria include

- ▶ Patient followed up for pulmonary nodule.
- ▶ History of active cancer <5 years (except in situ cervical carcinoma and basal cell carcinoma of the skin).
- ▶ LC symptoms (involuntary weight loss of >6.8 kg in 1 year, haemoptysis).
- ▶ Active pulmonary parenchymal infection.
- ▶ Severe cardiac or respiratory insufficiency (resting dyspnoea).

Variables

LC prevalence is the number of diagnosed LCs over the number of included patients in whom the LC CT was performed and analysed. LC diagnosis is based on pathological analysis or on multidisciplinary decision in case of pathological evaluation deemed unnecessary or futile prior to treatment.

The rate of eligible patients to NLST³ or to NELSON (Dutch-Belgian Randomized Lung Cancer Screening Trial)⁴ is calculated as the ratio between the number of patients eligible to NLST or to NELSON, respectively, divided by the number of included patients.

Radiation induced by LCS corresponded to the dose delivered during the LDCT and CT of re-evaluation at 3–6 months when indicated. The dose was expressed in millisievert.

We analyzed qualitatively and quantitatively the side effects linked to invasive diagnosis procedures induced by the process of LCS following nodule biopsy guided by CT, bronchoscopy, endobronchial ultrasound (EBUS), general anaesthesia for a diagnosis procedure and lung surgery.

The rate of LC diagnosed at a localised stage is defined as the ratio between the number of LC diagnosed at a localised stage (stage \leq IIB) to the number of diagnosed LC.

Longitudinal evaluation of smoking cessation in active smokers by the status of absence, incomplete or complete cessation at each visit as well as evaluation of the level of nicotine dependence by the use of simplified Fagerström questionnaire (questions 1–6).¹⁵

The longitudinal evaluations of quality of life and anxiety were performed by using SF-12¹⁶ and STAI-YA and STAI-YB¹⁷, respectively.

Rate of positive screening is defined by the rate of detection of at least one nodule of ≥ 5 mm and/or a volume of ≥ 60 mm³ detected either by the radiologist or the AI device.

The rate of positive detection is defined by the need to re-evaluate the nodule at 3–6 months or the need for diagnosis or radiation without pathological proof among positive screening.

The rate of false positive is the proportion of invasive procedures undertaken for the diagnosis of a benign nodule among the invasive procedures.

A descriptive and exploratory analysis of blood samples and faeces will consist in a case–control analysis of biological profiles of patients with LC and without LC (1:2 ratio). The case–control matching will be performed based on age (± 5 years), sex, NLST/NELSON eligibility profile, history of atheromatous disease and history of smoking (quantity and active status).

We measured the incidental rate of cardiovascular events within 1 year after LDCT.

We measured the incidental rate of oncological events within 1 year after LDCT.

Data sources

At V0, day of inclusion, the clinical data are acquired during the inclusion visit and immediately reported in the electronic case report form (eCRF) after information and consent of the patient.

At V1, the data of the LDCT (radiation dose) and its interpretation (positivity, nodule characteristics and additional findings) were reported in the eCRF by the radiologist. The data related to the AI (Veye) were reported by the radiologist in the eCRF.

Positive CTs were automatically signalled by email from the eCRF to the principal investigator. Positive screenings are presented at the weekly multidisciplinary staff meeting for decision. The decision regarding the nodule management is registered in the eCRF as follows: no need of further evaluation (negative screening), intermediate status requiring re-evaluation at 3–6 months by LDCT and positive screening requiring a diagnostic procedure. The nodule re-evaluations and diagnosis or therapeutic procedures were performed at Marie Lannelongue–Gustave Roussy LC programme including a minimally invasive surgery programme and were considered as current care. The data related to CT re-evaluation, diagnosis procedures, surgical procedures, hospitalisations and pathological results related with the nodule management are extracted from the patient electronic medical record and entered in the eCRF.

Patients with negative screening were informed by a phone call medical visit by the principal investigator. During this visit (V1), the negative finding was announced to the patient; the tobacco status was checked; and a proposition for smoking cessation was renewed in case of active smoking; a status of cardiovascular events, oncological events and any new health-related event was checked and reported in the eCRF. The quality of life and anxiety questionnaires were sent to the patients by email or mail.

At V2, V3 and V4, the visits are performed by a phone call to collect tobacco status and propose help for cessation in case of active smoking, cardiovascular events,

oncological events, new health-related events and questionnaires. Death, patient loss during the follow-up and patient withdrawn are prospectively reported in the eCRF.

Bias

In order to measure the prevalence of LC in an intent to screen setting in the population of interest, we recruited only patients from cardiovascular departments. We paid attention not to include patients with existing lung nodule follow-up or symptoms compatible with LC as foreseen by the exclusion criteria.

As we used available lung CT performed for vascular diseases work-up within the last 3 months, we paid attention not to include patients for whom an incidental lung nodule was already managed by a specialist. However, we included patients if an incidental nodule was found by the investigator while this nodule was not already managed. The objective was not to perform unnecessary CT; while maintaining an 'intent to screen' protocol. The quality of these 'existing CTs' was evaluated by the radiologist. If the CT quality was judged not adequate for LCS, an LDCT was scheduled.

So as to minimise biological artefacts due to invasive procedures, we managed to perform blood and faeces harvesting prior to vascular interventions or at least 2 weeks after.

As the smoking cessation was not biochemically verified, there may exist an overestimation of declared smoking cessation. However, telephonic follow-up precluded a systematic biochemical assessment.

Study size

There is a scarcity of data related to the prevalence of LC in the study population. We hypothesised that the prevalence was 4% based on the prevalence of LC observed in patients with abdominal aortic aneurysm reported by Harthun and Lau.¹⁸

With 500 patients, an alpha risk of 5%, the power to conclude that 4% is superior to 2% will be 86% with a unilateral test and 81% with a bilateral test, 2% being the superior limit of LC prevalence in LCS trials.¹⁹ Therefore, we intended to recruit 500 patients within 1 year. This number of patients was compatible with a workflow of two inclusions per working day.

Patient and public involvement

The development of the research question and outcome was not informed by patients' priorities, experience and preference. The patients were not involved in the design of the study. The patients were not involved in the recruitment to and conduct of the study. The results will be disseminated by social media and through associations of patients interested in LC and LCS.

Statistical methods

The planned study is a prospective cohort study. It will therefore be reported on the basis of the criteria of the Strengthening the Reporting of Observational Studies in Epidemiology statement (<https://www.strobe-statement.org>).

The variables will be compared between the groups using standard tests: Student's t-test or non-parametric Wilcoxon test for the quantitative parameters according to the distribution of the variables and the χ^2 test or the Fischer test for the proportions. Results will be presented as mean \pm 1 SD if the parameter follows a Gaussian distribution and median (IQR) if the distribution is non-Gaussian for quantitative parameters. For qualitative parameters, the results will be presented as numbers (proportions).

No technique for replacing missing data is envisaged.

The analysis will be performed after reviewing and then locking the database. It will be carried out with the R software (R Core Team (2021), R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; <https://www.R-project.org/>).

The significance level of the statistical tests (two-sided) will be set at a p value of <0.05.

ETHICS AND DISSEMINATION

The study was approved by the French Institut National du Cancer and by a dedicated ethical committee according the French Jardé law for 'interventional research with minimal risks and constraints'; the study is referenced at the French 'Agence Nationale de Sécurité du Médicament et des Produits de Santé' under the reference ID RCB: 2019-A00262-55. PREVALUNG is registered on clinicaltrials.gov.

Safety considerations: The adverse events are prospectively reported.

Dissemination plan: the PREVALUNG protocol was presented at the 2021 IASLC meeting.²⁰ Furthermore, a nested case-control study will compare biological profiles of patients with LC or positive screening versus patients with negative screening. The aim of the omics study is to identify candidate biological risk factors of LC development and to stratify the population at risk based on distinct biological classifiers. The final results of the study will be presented after the closure of the follow-up scheduled on 14 February 2023.

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Contributors DB, OM, BB, OP and LZ advanced the initial idea of the protocol. DB, MF, LZ, CC and GC drafted the manuscript with major contributions. DB, OM, CC, BB, LZ, MF, JI, OP, PP, DG, OH, LL, MZ, HB, GC and EF have contributed to build the design of the study protocol, reviewed the draft and accepted the final version.

Funding This work is supported by Institute National du Cancer (grant TABAC 18-012), CRC3F (grant number not available) and Astra Zeneca (grant number not available).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request at d.boulate@ghpsj.fr.

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