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Par Mohamad EL ZOGHBI

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Relations entre Phénotypes des cancers broncho-pulmonaires, expositions professionnelles aux particules inhalées et consommation tabagique

Sous la direction de : Pr. Patrick BROCHARD
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Soutenue lundi 19 Décembre 2016 à Bordeaux - France

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Dedication

This thesis is dedicated to my family. A special feeling of gratitude to my loving wife, Asmaa El Hajj, for her continuous support and encouragement and for being always there for me during the doctorate years; to my girl Lea and my son Adam for being patient and understanding when I did not have enough time for them because of my studies, and whose smiles gave me positivity and assurance; to my father and mother whose prayers have enlightened my way all along; to my brother, my sister, Khaled, and Nour.

I also dedicate this thesis to my father-in-law and my mother-in-law who have supported me throughout the process; to Mustafa, Lama, Khaled, Hadi and Mona. I will always appreciate all they have done, especially their encouragement and belief in me.

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Last but not the least; I would like to thank my family: my great wife and lovely daughter and son for supporting me by all possible means since the very beginning of this journey.

Titre : Relations entre phénotypes des cancers broncho-pulmonaires, expositions professionnelles aux particules inhalées et consommation tabagique.

Résumé

Introduction :

Le cancer broncho-pulmonaire est une des causes principales de décès parmi les hommes et les femmes. Le cancer broncho-pulmonaire est le cancer le plus fréquent avec 1,8 million (12,8%) de nouveaux cas de cancer et la principale cause de décès liés au cancer avec 1,6 million (19,5%) de décès par cancer en 2012 dans le monde.

En général, le tabagisme est la cause majeure du cancer broncho-pulmonaire. Cependant, le cancer broncho-pulmonaire a été aussi identifié chez les non-fumeurs qui ont été exposés aux carcinogènes professionnels, y compris l'amiante et la silice cristalline. En plus, les phénotypes du cancer broncho-pulmonaire sont associés avec plusieurs facteurs de risque comme le tabagisme. Pour les types histologiques, les carcinomes épidermoïdes et les carcinomes à petites cellules sont plus fréquents chez les fumeurs que les adénocarcinomes. Il existe moins de données qui supportent une association pareille entre la localisation de la tumeur et l'âge au diagnostic.

Outre l'association avec le tabagisme, il existe une évidence limitée concernant l'association entre l'amiante et/ou la silice cristalline et des phénotypes spécifiques du cancer broncho-pulmonaire (type histologique, la localisation de la tumeur et l'âge au diagnostic). La présence d'interaction entre le tabagisme et autres expositions aux carcinogènes professionnels reste encore à établir.

L'objectif de cette thèse est d'analyser la prévalence des expositions professionnelles dans plusieurs séries (séries cliniques et population générale) agrégées de cancer broncho-pulmonaire représentant près de 10 000 cas, par application de matrices emplois-expositions (MEE) ciblées sur les polluants particulaires dont la cancérogénicité est reconnue (amiante, silice cristalline), et comparer cette prévalence en fonction du phénotype des cancers (type histologique, âge de diagnostic). Un autre objectif est d'évaluer la modification de l'effet de l'association entre le tabagisme et le type histologique, la localisation de la tumeur, et l'âge au diagnostic par l'exposition professionnelle à l'amiante ou à la silice cristalline.

Matériels et Méthodes :

Une revue systématique a été réalisée au début de cette thèse pour évaluer l'interaction statistique entre le tabac et l'exposition professionnelle à l'amiante, silice cristalline et les émissions des moteurs diesel. Quinze études originales ont été incluses pour l'interaction amiante-tabac, sept pour l'interaction silice-tabac et deux pour l'interaction diesel-tabac.

Par la suite, les données de l'étude CaProMat ont été analysées. L'étude CaProMat est une étude « case-only » rétrospective qui inclut des cas incidents de cancer broncho-pulmonaires colligés par les centres de consultation de pathologie professionnelle (RNV3P, Réseau National de Vigilance et de Prévention des Pathologies Professionnelles), des cas de l'étude cas-témoins française ICARE, et des cas d'une étude cas-témoins menée à Canada. Les études françaises ont été menées dans différentes régions de France entre 1999 et 2011, et l'étude canadienne a été menée à Montréal entre 1996 et 2001. La population de l'étude CaProMat est formée de 9,623 cas de cancer broncho-pulmonaire (7,256 hommes et 2,367 femmes).

Tous les cas de cancer broncho-pulmonaire ont été identifiés d'une façon histologique, et tous les types histologiques ont été inclus. La type histologique (carcinome épidermoïde, carcinome à petites cellules, adénocarcinome, carcinome à grandes cellules, et autres types

histologiques), la localisation de la tumeur (lobe supérieur *versus* lobe inférieur) et l'âge au diagnostic ont été collectés des fichiers médicaux.

Pour les cas hospitaliers, les données ont été recueillies par le médecin du travail en utilisant un questionnaire standardisé sur la santé au milieu du travail, tandis que pour les cas de la population, les données ont été recueillies par des intervieweurs formés utilisant un questionnaire standardisé. Les données comprenaient le sexe, date de naissance, niveau d'éducation, réponse par un proche, l'histoire détaillée du tabagisme, et les détails du calendrier professionnel pour tout emploi occupé pendant plus de six mois.

Deux Matrices Emplois-Expositions (MEEs) ont été utilisées pour évaluer rétrospectivement l'exposition professionnelle à l'amiante et à la silice cristalline. Une probabilité d'exposition à l'amiante ou à la silice cristalline a été attribuée automatiquement par les deux MEEs pour chaque emploi signalé par les sujets. Cette probabilité d'exposition a été exprimée sur une échelle de 5 catégories pour l'amiante et sur une échelle continue de 10% pour la silice cristalline.

La prévalence de l'exposition professionnelle à l'amiante et à la silice cristalline suivant les types histologiques et l'âge au diagnostic a été calculée exclusivement chez les hommes français avec cancer broncho-pulmonaire (n=6,521). Pour prendre en compte la plus grande probabilité d'exposition pour chaque sujet, une prévalence pondérée de l'exposition professionnelle à l'amiante et à la silice cristalline a été dérivée. La prévalence pondérée d'exposition professionnelle est égale à la somme de la plus grande probabilité d'exposition professionnelle à l'agent (amiante ou silice cristalline) pour chaque sujet divisé par le nombre total de sujets. La prévalence pondérée de l'exposition a été obtenue et comparée en fonction des types histologiques et de l'âge au moment du diagnostic.

L'analyse statistique pour évaluer l'interaction a inclus 7,256 hommes Français et Canadiens avec cancer broncho-pulmonaire. Pour les interactions statistiques, les sujets ont été définis comme exposés à l'amiante ou à la silice cristalline si la plus grande probabilité d'exposition est supérieure à 30%. D'après les données sur le tabagisme rapportées dans le questionnaire, le « Comprehensive Smoking Index » (CSI) a été calculé. Le CSI regroupe divers détails sur les habitudes de consommation de tabac, y compris l'intensité du tabagisme, la durée du tabagisme et le temps écoulé depuis la cessation. Nous avons également catégorisé les sujets comme non-fumeur/faible (sujets avec des valeurs CSI inférieures au 25ème percentile) et les fumeurs moyen-élevé (sujets ayant des valeurs CSI au-dessus du 25ème percentile). Les interactions statistiques entre le tabagisme et l'exposition professionnelle à l'amiante et à la silice cristalline ont été estimées en ajoutant un terme de produit croisé (terme d'interaction) aux modèles de régression logistique non conditionnelle pour les types histologiques et la localisation de la tumeur et aux modèles de régression linéaire pour l'âge au diagnostic.

Toutes les analyses ont été effectuées à l'aide du logiciel statistique SPSS (Statistical Package for Social Sciences), version 21.0 (Chicago, IL, USA).

Résultats :

Les résultats de la revue systématique suggèrent l'absence d'interaction multiplicative entre les trois carcinogènes pulmonaires professionnels et le tabagisme. Il n'y a pas assez de preuves de la littérature pour conclure pour l'interaction additive.

Pour l'étude CaProMat, la première analyse statistique comprenait 6 521 cas de cancer broncho-pulmonaire chez les hommes français correspondant à 28 385 emplois occupés pour plus de six mois. Les deux types histologiques les plus fréquents étaient l'adénocarcinome (37,5%) et le carcinome épidermoïde (32,6%). L'âge moyen au moment du diagnostic était de 62,2 (± 10,1)

ans. Selon le tabagisme, 2,8% des cas étaient des non-fumeurs, tandis que 57,4% et 39,8% étaient des fumeurs actuels et des ex-fumeurs, respectivement.

La prévalence pondérée de l'exposition à l'amiante était de 33,9% [IC 95% : 32,8 - 35,1], tandis que la prévalence pondérée de l'exposition à la silice cristalline était de 25,7% [IC 95%: 24,7 - 26,8]. Pour l'exposition professionnelle à l'amiante, il n'y a pas eu de différence statistiquement significative en termes de prévalence pondérée de l'exposition entre les types histologiques de cancer du poumon (p = 0,13). D'autre part, pour la silice cristalline, une différence statistiquement significative a été observée entre les types histologiques en termes de prévalence pondérée de l'exposition (p = 0,049).

Quel que soit le statut tabagique, il n'y avait pas de différences significatives en termes de prévalence pondérée de l'exposition professionnelle à l'amiante entre les types histologiques de cancer du poumon. Quel que soit le statut tabagique, il n'existait pas de différences significatives en termes de prévalence pondérée de l'exposition professionnelle à la silice cristalline, à l'exception des ex-fumeurs, où une différence statistiquement significative était observée (p = 0,045).

Il existait une différence statistiquement significative en termes de prévalence pondérée de l'exposition entre les catégories d'âge au diagnostic pour l'exposition professionnelle à l'amiante (p = 0,014) et l'exposition professionnelle à la silice cristalline (p = 0,018). Indépendamment du statut tabagique, il n'y a pas eu de différences significatives en termes de prévalence pondérée de l'exposition professionnelle à l'amiante, sauf pour les fumeurs actuels, où une différence statistiquement significative a été observée (p = 0,003). Indépendamment du statut tabagique, il n'y avait pas de différence significative en termes de prévalence pondérée de l'exposition professionnelle à la silice cristalline entre les différentes catégories d'âge au diagnostic.

Globalement, nous n'avons pas identifié de différence de prévalence pondérée de l'exposition professionnelle à l'amiante avec et sans stratification par le tabagisme. Pour la silice cristalline, un excès limite de la prévalence pondérée de l'exposition a été observé pour le carcinome épidermoïde, confirmé chez les ex-fumeurs. La prévalence pondérée de l'exposition professionnelle a été maximisée chez les cas de cancer du poumon diagnostiqués entre 50 et 59 ans pour l'amiante et moins de 50 ans pour la silice cristalline.

La deuxième analyse statistique comprenait 7 256 cas de cancer broncho-pulmonaire chez les hommes français correspondant à 31 332 emplois occupés pour plus de six mois.

Les carcinomes épidermoïdes et les adénocarcinomes représentaient 69,9% des types histologiques avec respectivement 32,9% et 37,0%. La localisation des tumeurs bronchiques était disponible pour 4 689 cas représentant 64,6% de la population étudiée. Il y avait une prédominance des tumeurs du lobe supérieur avec 68,2%. L'âge moyen au diagnostic était de 62,4 (± 10,0). Les non-fumeurs représentaient 2,7% de l'étude de population, tandis que 58,5% et 38,8% étaient des fumeurs actuels et des ex-fumeurs, respectivement.

Les résultats ont montré que chez les sujets non exposés à l'amiante, le tabagisme était positivement associé aux carcinomes épidermoïdes comparés à d'autres types histologiques (OR = 1,52 [IC 95% : 1,20-1,92]) ou aux adénocarcinomes seulement (OR = 1,89 [IC 95% : 1,47-2,44]). Il n'y a pas eu d'interaction statistique multiplicative entre le tabagisme et l'exposition professionnelle à l'amiante (p = 0,90 et p = 0,46 respectivement). Des observations similaires ont été observées pour les carcinomes à petites cellules.

Les résultats ont montré que chez les sujets non exposés à la silice cristalline, le tabagisme était positivement associé aux carcinomes épidermoïdes comparés à d'autres types histologiques

(OR = 1,62 [IC 95% : 1,36-1,93]) ou aux adénocarcinomes seulement (OR = 1,92 [IC 95%: 1,58-2,33]). En effet, il n'y a pas eu d'interaction statistique multiplicative entre le tabagisme et l'exposition professionnelle à la silice cristalline (p = 0,17 et p = 0,12, respectivement). En ce qui concerne les carcinomes à petites cellules versus d'autres types histologiques ou adénocarcinomes seulement, des résultats similaires ont été observés (p = 0,90 et p = 0,59, respectivement).

Pour la localisation de la tumeur, il n'y avait ni association ni interaction entre le tabagisme et l'exposition à l'amiante (β = 0,08 ; p = 0,66), ou l'exposition à la silice cristalline (β = -0,02 ; p = 0,91).

L'interaction statistique additive entre le tabagisme et l'exposition professionnelle à l'amiante et à la silice cristalline en fonction de l'âge au diagnostic a été évalué. En général, il n'y a pas d'interaction statistique additive pour tous les types histologiques.

Conclusions :

Le tabagisme était le principal facteur lié aux types histologiques ; il était associé au carcinome épidermoïde et aux carcinomes à petites cellules. Aussi, le tabagisme était le principal facteur lié à un âge plus précoce au diagnostic. L'exposition professionnelle à l'amiante et à la silice cristalline n'ont pas été associée aux types histologiques et à l'âge au diagnostic. Ni le tabagisme ni l'exposition professionnelle à l'amiante ou à la silice cristalline n'ont influencé la localisation de la tumeur.

Une exposition supplémentaire à l'amiante ou à la silice cristalline n'a pas modifié l'effet du tabagisme pour les types histologiques, la localisation de la tumeur et l'âge au diagnostic.

Par conséquent, le type histologique, la localisation de la tumeur, et l'âge au diagnostic ne peuvent pas être utilisés comme indicateurs de l'exposition professionnelle à l'amiante ou à la silice cristalline.

Mots clés : Cancer Broncho-pulmonaire, Prévalence, Tabagisme, Expositions professionnelles, Amiante, Silice Cristalline, Types histologiques, Localisation de la tumeur, Age au diagnostic.

Title: Relationships between the phenotypes of lung cancer, occupational exposure to inhaled particles, and tobacco smoking.

Abstract

Introduction:

Lung cancer remains the leading cause of cancer deaths among males and females. As a matter of fact, tobacco smoking is the main cause of lung cancer, but it is not the sole causal factor. Indeed, lung cancer cases have been identified in non-smokers groups but exposed to different types of occupational exposures, including asbestos and crystalline silica. Additionally, the phenotypes of lung cancer are associated with certain risk factors such as tobacco smoking. For histological types, squamous cell carcinomas and small cell carcinomas are more frequent among smokers than adenocarcinomas.

There is less data supporting such association for tumor location and age at diagnosis. Besides smoking, there was limited evidence concerning the association between asbestos or crystalline silica and specific phenotypes of lung cancer (histological type, tumor location and age at diagnosis). Also, subjects exposed to occupational lung carcinogens including asbestos and crystalline silica are mostly blue-collar workers. Moreover, blue-collar workers were also those who are mostly smokers.

Therefore, the general objective of this thesis was to study the association between tobacco smoking and occupational exposure to asbestos and crystalline silica with the phenotypes of lung cancer, with emphasis on the statistical interactions between tobacco smoking and occupational exposures.

Methods:

The CaProMat study is a pooled retrospective case-only study of seven original studies conducted between 1999 and 2011 in different areas in France, and one original study conducted between 1996 and 2001 in Montreal, Canada. The CaProMat study population consisted of 9,623 lung cancer cases (7,256 males and 2,367 females).

All lung cancer cases were histologically confirmed, and all histological types of lung cancer were included. Histological type (squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma and other histological types), tumor location (upper lobe *versus* lower lobe), and age at diagnosis were collected from medical records.

For hospital-based cases, data were collected through standardized occupational health questionnaire administered by the occupational physician, whereas for the population-based cases, data were collected by trained interviewers using standardized questionnaires. Data included gender, date of birth, educational level, respondent status, smoking history details, and occupational history details for any job held for more than six months. Two job-exposure matrices (JEMs) were used to assess occupational exposure to asbestos and crystalline silica.

The prevalence of occupational exposure to asbestos and crystalline silica according to histological types and age at diagnosis was conducted exclusively among male lung cancer cases (n=6,521). To take into account the highest probability of exposure of each of the subjects, a weighted prevalence of occupational exposure to asbestos and crystalline silica was derived. This *weighted prevalence (Pw)* of occupational exposure was equal to the sum of the highest probability of occupational exposure to the agent (asbestos or crystalline silica) for each subject divided by the total number of subjects.

For the statistical interactions, subject was defined as exposed to asbestos or crystalline silica if he had held highest probability of exposure superior to 30%. The statistical analysis to evaluate interactions included 7,256 male lung cancer cases from France and Canada. Statistical interactions between tobacco smoking and occupational exposure to asbestos or crystalline silica were assessed by adding a cross-product term to the unconditional logistic regression models for histological types and tumor location and to the linear regression models for age at diagnosis.

Results:

Globally, we did not identify a difference of weighted prevalence of occupational exposure to asbestos with and without stratification by smoking status. For crystalline silica, a borderline excess of weighted prevalence of exposure was observed for squamous cell carcinoma, confirmed among ex-smokers. The weighted prevalence of occupational exposure was maximized among lung cancer cases diagnosed between 50 and 59 years for asbestos and less than 50 years for crystalline silica.

Otherwise, tobacco smoking was associated with squamous cell carcinoma and small cell carcinomas as well as an earlier age at diagnosis. Additional exposure to either asbestos or crystalline silica did not modify the effect of tobacco smoking for both histological types and age at diagnosis. Neither tobacco smoking nor occupational exposure to asbestos or crystalline silica influenced tumor location.

Conclusions:

Tobacco smoking was the main factor related to histological types and age at diagnosis. Those associations were not modified by occupational exposure to asbestos or crystalline silica. There was absence of association between tobacco smoking and occupational exposures with tumor location. The histological type, tumor location, and age at diagnosis cannot be used as an indicator for the occupational exposure to asbestos or crystalline silica.

Keywords: Lung cancer, Prevalence, Interaction, Tobacco smoking, Occupational Exposures, Asbestos, Crystalline Silica, Histological Types, Tumor Location, Age at Diagnosis.

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Publications

Accepted – in Press:

Article 1: Absence of Multiplicative Interactions between Occupational Lung Carcinogens and Tobacco Smoking: A Systematic Review Involving Asbestos, Crystalline Silica and Diesel Engine Exhaust Emissions.

Authors: Mohamad El Zoghbi, Pascale Salameh, Isabelle Stücker, Patrick Brochard, Fleur Delva, and Aude Lacourt.

Journal: « BMC Public Health ».

Minor revision:

Article 2: Prevalence of occupational exposure to asbestos and crystalline silica according to phenotypes of lung cancer from the CaProMat study: a case-only study.

Authors: Mohamad El Zoghbi, Pascale Salameh, Isabelle Stücker, Christophe Paris, Jean Claude Pairon, Antoine Gislard, Jack Siemiatycki, Vincent Bonneterre, Bénédicte Clin, Patrick Brochard, Fleur Delva, and Aude Lacourt.

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Submitted:

Article 3: Phenotypes of Lung Cancer and Statistical Interactions between Tobacco Smoking and Occupational Exposure to Asbestos and Crystalline Silica from a Large Case-only Study: The CaProMat Study:

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Other Publications:

Mohamad El Zoghbi, Christa Boulos, Nadine Saleh, Sanaa Awada, Samar Rachidi, Wafaa Bawab, and Pascale Salameh. Association between cognitive function and nutritional status in elderly: a cross-sectional study in three institutions of Beirut—Lebanon. Geriatric Mental Health Care. 2013 Dec 31;1(4):73-81.

Mohamad El Zoghbi, Christa Boulos, Sanaa Awada, Samar Rachidi, Amal Al-Hajje, Wafaa Bawab, Nadine Saleh, and Pascale Salameh. Prevalence of malnutrition and its correlates in older adults living in long stay institutions situated in Beirut, Lebanon. J Res Health Sci. 2014 winter; 14(1):11-7.

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1 General Introduction

Cancer is the uncontrolled growth of abnormal cells in any part of the body. Worldwide, the estimated number of new cancer cases reported in 2012 was 14.1 million, with 7.4 million (52.5%) among men, and 6.7 million (47.5%) among women. On the other hand, 4.7 million (57.3%) men and 3.5 million (42.7%) women died by cancer in 2012.(1-3)

Among the different types of cancer, lung cancer is the most frequent cancer worldwide and the leading cause of cancer-related deaths. In 2012, 12.8% of global new cancer cases were lung cancer cases, and 19.5% of cancer deaths were caused by lung cancer. Lung cancer, the most frequent cancer in the world, is also of poor prognosis. The age-standardized 5-year net survival was low (10%-20%) in most developed and developing countries, except for very few countries. (4, 5) Thus, lung cancer presents a major public health problem affecting both men and women, and an important topic to be studied in clinical and epidemiologic research.

Evidence from literature shows that tobacco smoking is the most potent lung carcinogen (6), classified by the International Agency for Research on Cancer (IARC) as a lung carcinogen (group 1) back in 1986. (7) In addition to tobacco smoking, others risk factors have been classified as lung carcinogens with sufficient evidence by IARC including occupational exposures. (8-11) In many countries, smoking cessation interventions and smoking prevention programs (e.g. anti-smoking campaigns) were introduced to reduce the proportion of smokers in the population. In addition, many countries issued laws and regulations to ban or to control the use and the exposure to different lung carcinogenic agents in workplaces.

In fact, many studies were conducted globally to determine the risk factors of lung cancer and to evaluate the carcinogenicity of different suspected agents. In contrary, there is a very limited evidence on the effect modification of the association between tobacco smoking and lung cancer by occupational exposures. This brings into light the importance of studying the statistical interactions between different risk factors, especially tobacco smoking, the most potent lung carcinogen, and occupational exposures.

Within the EPICENE team (Epidemiology of Cancer and Environmental Exposures team) in the INSERM- U1219 research center (Institut National de la Santé et de la Recherche Médical), we had the opportunity to collect a large number of lung cancer cases (11,228 primary lung cancer cases) with comparable investigations concerning diagnosis, occupational exposure and smoking habits in the context of CaProMat Project. In addition, two pre-developed Job-Exposures Matrices (JEMs) were available to be used for the assessment of occupational exposures to asbestos and to crystalline silica (12, 13).

Thus, we proposed in the present thesis to conduct a systematic literature review on the interaction between tobacco smoking and the most frequent occupational exposures, namely asbestos, crystalline silica, and diesel engine exhaust emissions. Secondly, we proposed to conduct a study, as part of the CaProMat study, to estimate the prevalence of occupational exposure to asbestos and crystalline silica according to the phenotypes of lung cancer (histological type and age at diagnosis), and to assess the statistical interactions between tobacco smoking and the two occupational exposures (asbestos and crystalline silica) on the phenotypes of lung cancer.

2 State-of-the-Art

2.1 Lung Cancer

Among the wide range of respiratory diseases, the lung cancer (bronchial carcinoma) is considered the most serious of which, and unfortunately the most common due to lifestyle, occupational and environmental factors. Lung cancer is the uncontrolled growth of abnormal cells that begins in the tissues of the bronchi, the trachea, the bronchioles or the alveoli. There are two major kinds of lung cancer; primary and secondary; the primary kind starts in the lungs, while the secondary one originates somewhere else in the body and reaches the lungs by metastasis.(14, 15)

We present the epidemiology, the clinical aspects and the risk factors of lung cancer in the following section.

2.1.1 Epidemiology

Worldwide, lung cancer is the most common cancer with 1.8 million (12.8%) new cancer cases, and the leading cause of cancer-related deaths with 1.6 million (19.5%) cancer deaths in 2012. Lung cancer was the leading cause of cancer deaths among men with an estimation of 1.1 million deaths corresponding to 23.4% of all cancer deaths, and the second leading cause of cancer deaths among women with an estimation of 0.5 million deaths corresponding to 14.3% of all cancer deaths. Otherwise, 39.4% (6.3 million) of lung cancer deaths were occurred in more developed regions, while 60.6% (9.7 million) were occurred in less developed regions.(1-3)

Smoking is the main cause of lung cancer accounting for 80% to 90% of the cases (7, 16); as a matter of fact, lung cancer incidence and mortality rate trends are the reflection of smoking habits changes of a population, which explains the variation of lung cancer patterns between countries and world regions. In addition, the difference in the smoking habits between men and women lead to a variation of lung cancer patterns in the same country or region. (16) In developed countries, lung cancer is the leading cause of cancer deaths in men and women, while in developing countries it is the leading cause of cancer deaths among men and the second leading cause of cancer deaths among women after breast cancer. The highest lung cancer incidence rates were reported in Europe and Northern America for both men and women.(1, 2).

In Canada, lung cancer is the leading cause of cancer deaths among men and women. In 2012, it was estimated that 14% (25,000) of new cancer cases and 27% (20,100) of cancer deaths are caused by lung cancer. Lung cancer was the leading cause of cancer deaths among men with an estimation of 10,700 deaths corresponding to 28% of all cancer deaths, and the leading cause of cancer deaths among women with an estimation of 9,400 deaths corresponding to 27% of all cancer deaths. In men, the lung cancer mortality rate increased after 1950 and reached 55 deaths per 100,000 in 1990, after that it started to decrease and reached 33 deaths per 100,000 in 2012. In women, the lung cancer mortality rate was almost 4 deaths per 100,000 in 1950, and it started to increase after 1960 and reached 25 deaths per 100,000 in 2005 and it started to slightly decrease after that. (1-3)

In France, lung cancer was the leading cause of cancer with an estimation of 12% (40,000) of new cancer cases, with 71% occurred among men. In addition, lung cancer was responsible of 20% (31,600) of cancer deaths, with 71% occurred among men. Lung cancer is the leading cause of cancer deaths among men with an estimation of 23,000 deaths corresponding to 25% of all cancer deaths, and the second leading cause of cancer deaths among women (after breast

cancer) with an estimation of 8,600 deaths corresponding to 13% of all cancer deaths in France. Looking at the history of lung cancer among men in France, an increase of lung cancer incidence was observed from 1980 until 2005, afterward an annual decrease of 0.3% was marked. The lung cancer mortality rate increased after 1950 and reached 45 deaths per 100,000 in 1990, after that it started to slightly decrease and reached 37 deaths per 100,000 in 2012. In women, lung cancer incidence increased by 5.3% per year between 1980 and 2012. As a consequence, the lung cancer mortality rate was stable from 1950 to 1980 with almost 4 deaths per 100,000, after that it started to increase and reached 13 deaths per 100,000 in 2012. (1-3) The decrease of smoking prevalence among men and its increase among women was the main cause of discrepancy in incidence trends between men and women.(17)

2.1.2 Clinical Aspects

In addition to the trends of cancer rates across the world, the world health organization (WHO) was interested on developing histological definitions of cancer types through a uniform nomenclature. WHO started from 1967 to publish volumes on the *International Histological Classification of Tumours*. In the same year, the first edition of *Histological Typing of Lung Tumours* was published, (18) and revised in 1981. (19, 20) With the accumulation of information on lung cancer, three other classifications of lung tumours were published to reflect the updated knowledge. The three versions were published in 1999 (21), 2004 (22) and 2015 (23). The differences between the different classifications of lung tumors could have a potential impact on epidemiological descriptions. The variations in the results of epidemiological studies evaluating the association with histological type of lung cancer could be partially related to the variations in tumor classification for each study.

In general, the non-small cell lung cancer and small cell lung cancer are the two main categories of primary lung cancer. The non-small cell lung cancer is the most common category accounting for 85% of the cases and mainly includes adenocarcinoma, squamous cell (epidermoid) carcinoma and large cell (undifferentiated) carcinoma. The small cell lung cancer accounts for 15% of the cases.(23) The prognosis of lung cancer is associated with phenotypes of lung cancer, especially the histological type. Thus, it is very critical to distinguish the histological type of lung cancer, as the growth and the spreading rates are determined by the histological type, and thus the treatments given as well.(14, 24, 25)

In industrial countries, like France and Canada, the fraction of squamous cell carcinoma decreased with time while adenocarcinoma increased. In France, for the period between 1978 and 2002 (based on registries), the percentage was 30.4% *vs* 46.0% for adenocarcinoma, 42.2% *vs* 20.8% for squamous cell carcinoma, 14.1% *vs* 15.9% for small cell carcinoma, and 9.4% *vs* 10.5% for large cell carcinoma, for males and females respectively. In Canada, for the same period, the percentage was 39.5% *vs* 47.8% for adenocarcinomas, 31.7% *vs* 21.2% for squamous cell carcinoma, 17.0% *vs* 18.6% for small cell carcinoma, and 10.1% *vs* 9.9% for large cell carcinoma, for males and females respectively. In France, squamous cell carcinoma was more prevalent among males, while adenocarcinoma was more prevalent in Canada. For females, the distribution of histological types was similar in France and Canada, where the adenocarcinomas were the most prevalent. (26)

The bronchial tumor location occurred more frequently in the upper lobe than in the lower lobe irrespective to tobacco smoking (27, 28). More than 80% of lung cancer cases among men occurred after 60 years old. (29) In France, the median age at diagnosis was 63 years (30), while it was 70 years in the United States of America (USA) (31).

In general, prognosis of lung cancer is poor and varies between countries (4), including European countries (5). In general, the age standardized s-year net survival is between 10% and 20% for most the world regions. (5) Lung cancer prognosis is highly associated with the histological type, stage at diagnosis and age at diagnosis. In Canada, the 5-year survival rate was 56% for adenocarcinomas versus 28% for squamous cell carcinomas staged I and II for the period between 1994 and 2000. (32) In the context of The French network of cancer registries (FRANCIM), and based on the 33,850 lung cancer cases for the period between 2005 and 2010, the 5-year net survival rate was 17% (16% among men *versus* 20% among women). Additionally, the 5-year net survival rate decreases with age at diagnosis, from 25% among cases diagnosed at age between 15 and 45 years to reach 10% among cases diagnosed at 75 years and more. Among men, the 5-year net survival rate was 20% among cases diagnosed at age between 15 and 45 *versus* 10% among cases aged 75 years and more. Among women, the 5-year net survival rate was 32% among cases diagnosed at age between 15 and 45 *versus* 11% among cases aged 75 years and more. For the period between 2008 and 2013, and for lung cancer cases staged I and II at the time of diagnosis (TNM classification of lung cancer), the 5-year survival rate was 62% for adenocarcinomas *versus* 47% for squamous cell carcinomas among men.(33)

2.2 Risk Factors

Different studies were conducted globally to evaluate the carcinogenicity of different suspected agents. Since 1971, interdisciplinary working groups members of which were international expert scientists from the IARC assessed the degree of carcinogenicity of more than 900 agents including chemicals, physical agents, biological agents, complex mixtures, personal habits and occupational exposures based on the experimental, toxicological and epidemiological studies. Several monographs have been published, where more than 400 factors were classified in five categories:

1. Group 1: the agent is *carcinogenic to humans.*
2. Group 2A: the agent is *probably carcinogenic to humans*.
3. Group 2B: the agent is *possibly carcinogenic to humans*.
4. Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.
5. Group 4: The agent is *probably not carcinogenic to humans.*

From the 900 agents evaluated by IARC, 28 agents were classified as lung carcinogenic agents with sufficient evidence in humans (group 1).(34)Tobacco smoking and occupational exposures to asbestos, crystalline silica and diesel engine exhaust emissions were reassessed and classified as lung carcinogen (group 1) in 2012.

In the present thesis, we proposed to conduct a review to evaluate the evidence from the literature on the association between tobacco smoking and three occupational exposures (asbestos, crystalline silica, and diesel engine exhaust emissions) on the risk of lung cancer after the monographs of 2012. Those lung carcinogens were selected as they are among the most common lung carcinogen found in workplaces. In addition, asbestos-related diseases are a major public health problem, and it is estimated that 5 to 7% of global lung cancer cases are attributed to occupational asbestos exposure.(35) For crystalline silica, and in a population-based study conducted in Italy, it is estimated that 5.7% of lung cancer deaths are attributed to occupational exposure to crystalline silica.(36) In a pooled analysis of two case-control studies

conducted in Montreal (Canada), it is estimated that 3% of lung cancer deaths were attributed to occupational exposure to crystalline silica.(37) For diesel engine exhaust emissions, and in a large US study, it is estimated that 6% of deaths by lung cancer are attributed to diesel engine exhaust emissions.(38) Otherwise, it is estimated that 2.7% of lung cancer cases are attributed to diesel engine exhaust emissions in a population-based case-referent study conducted in Sweden.(39)

2.2.1 Literature Review on the Main Lung Carcinogens

A literature review was conducted on the association between tobacco smoking, asbestos, crystalline silica, and diesel engine exhaust emissions on the risk of lung cancer was conducted. Articles were identified using two bibliographic databases: PubMed and Scopus. The selected studies were limited to meta-analyses and reviews, published in English or French, after January 1, 2012. The most recent research was conducted in September 30, 2016. For tobacco smoking, asbestos, crystalline silica and diesel engine exhaust emissions, all records of the two bibliographic databases were searched using the following key words respectively: ["smoking" and "lung cancer"], ["asbestos" and "lung cancer"], ["silica" and "lung cancer"], and ["diesel" and "lung cancer"].

Studies were included in this review if they met the following criteria: meta-analyses, reviews, human studies, studies published in peer-reviewed journals, studies evaluating the association between one of the four selected lung carcinogens and lung cancer. In general, studies not meeting the inclusion criteria were excluded: clinical trials, in vitro studies, animal studies, cross-sectional studies, cohort studies, case-control studies, case reports and case series.

Records identified through the two bibliographic databases were checked for duplications. Duplicated records were removed, and the remaining records were screened to distinguish those met the inclusion criteria. The screening phase was done in two steps: 1) selection of articles that studied the association between one of the four occupational exposures and lung cancer based on titles and abstracts, 2) the full-text was screened to select relevant studies.

Using this methodology, 1,270 articles were identified for tobacco smoking: 568 from PubMed and 702 from Scopus. Overall, 248 articles were duplicated and excluded. From the remaining 1,022 articles, 1,020 papers were excluded, and only two meta-analyses were included (Figure 1).

For asbestos, 155 articles were identified: 64 from PubMed and 91 from Scopus. 36 articles were duplicated and excluded. From the remaining 119 articles, 116 papers were excluded, and one meta-analysis, one systematic review, one literature review were included (Figure 2).

For crystalline silica, 35 articles were identified: 14 from PubMed and 21 from Scopus. Five articles were duplicated and excluded. From the remaining 30 articles, 28 papers were excluded, and one meta-analysis and one literature review were included (Figure 3).

For diesel engine exhaust emissions, 28 articles were identified: 14 from PubMed and 14 from Scopus. Seven articles were duplicated and excluded. From the remaining 21 articles, 18 papers were excluded, and one meta-analysis and two systematic reviews were included (Figure 4).

PRISMA 2009 Flow Diagram

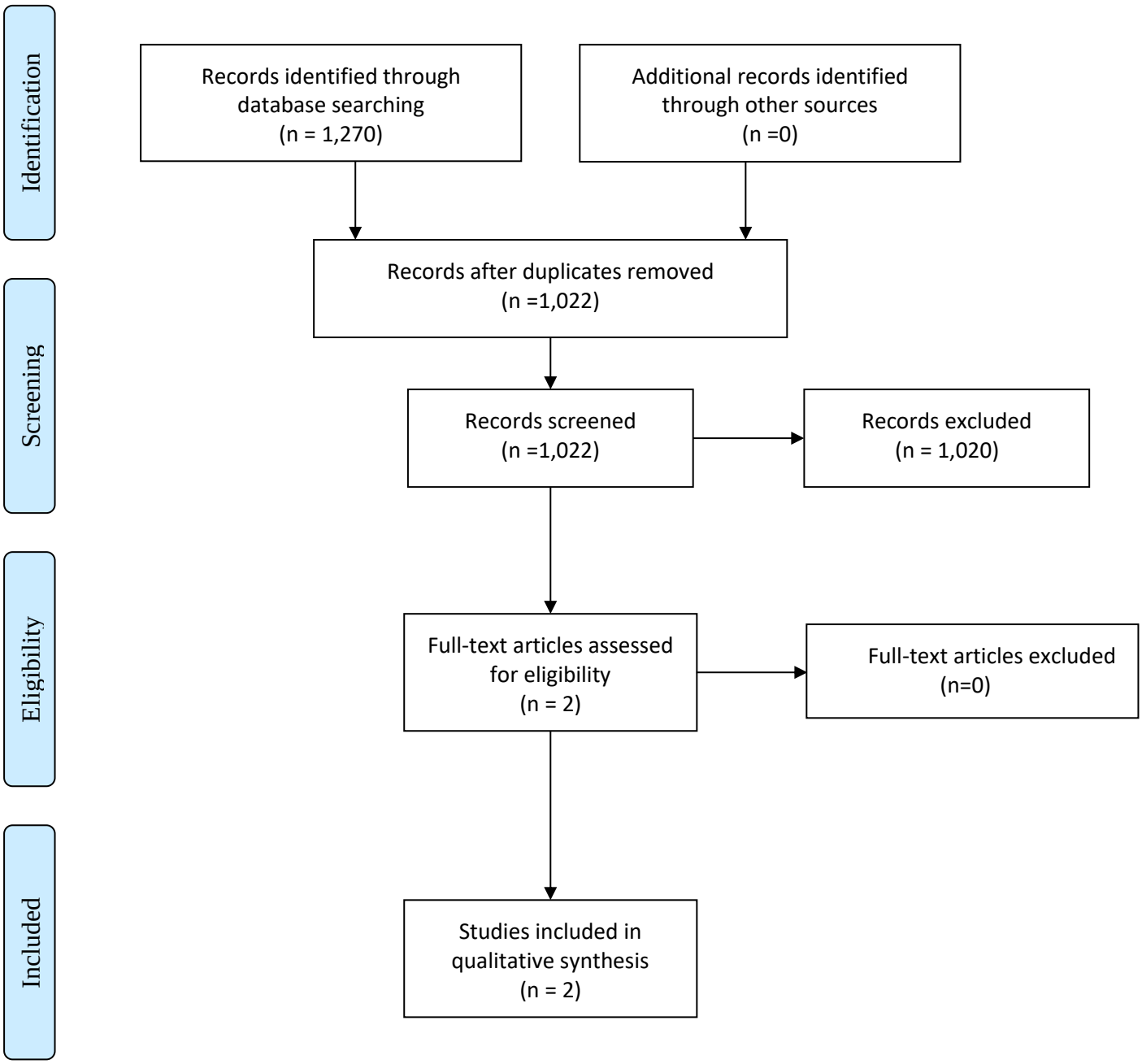

Figure 1 Study selection process for the association between tobacco smoking and lung cancer.

PRISMA 2009 Flow Diagram

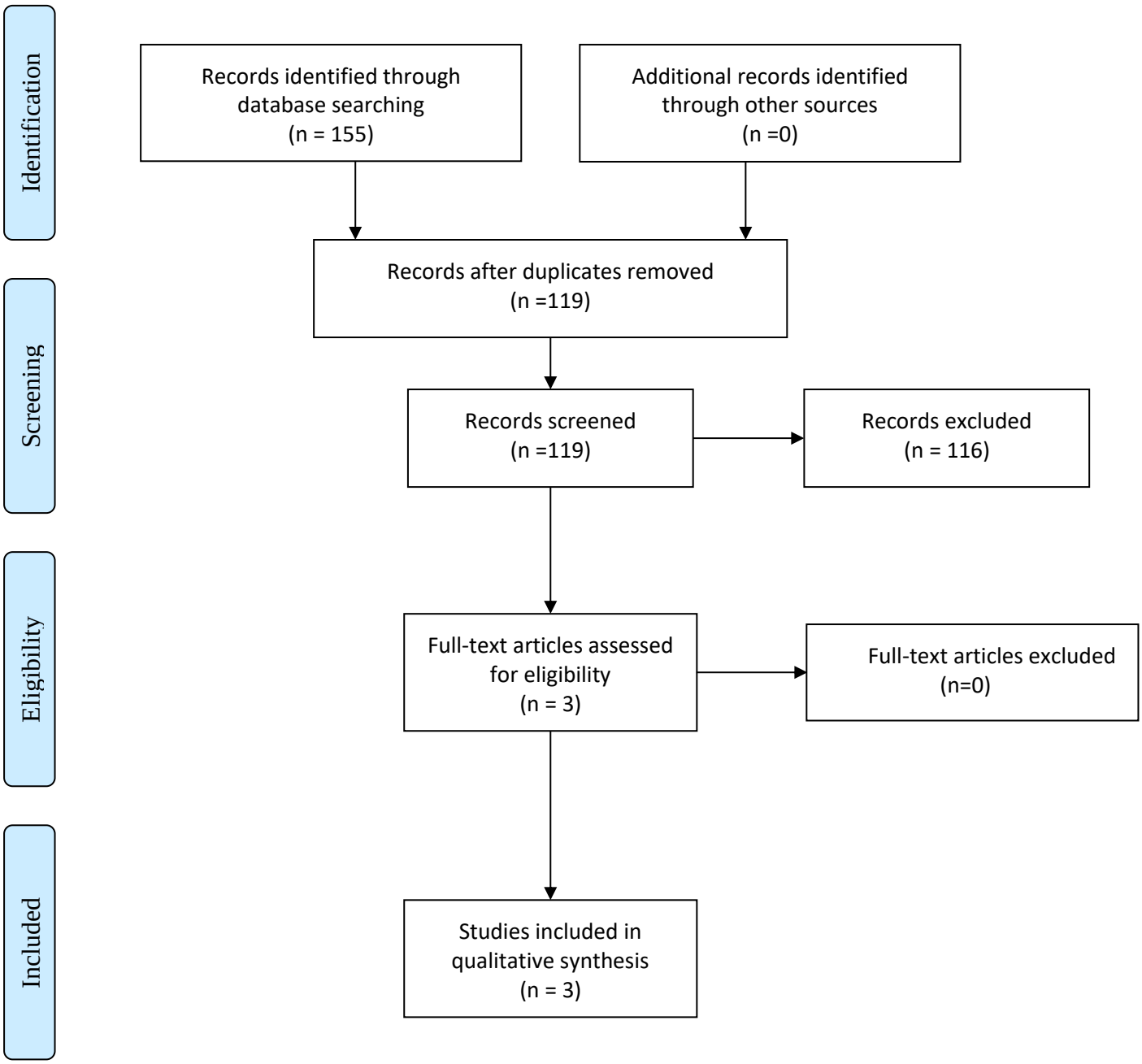

Figure 2 Study selection process for the association between asbestos exposure and lung cancer.

PRISMA 2009 Flow Diagram

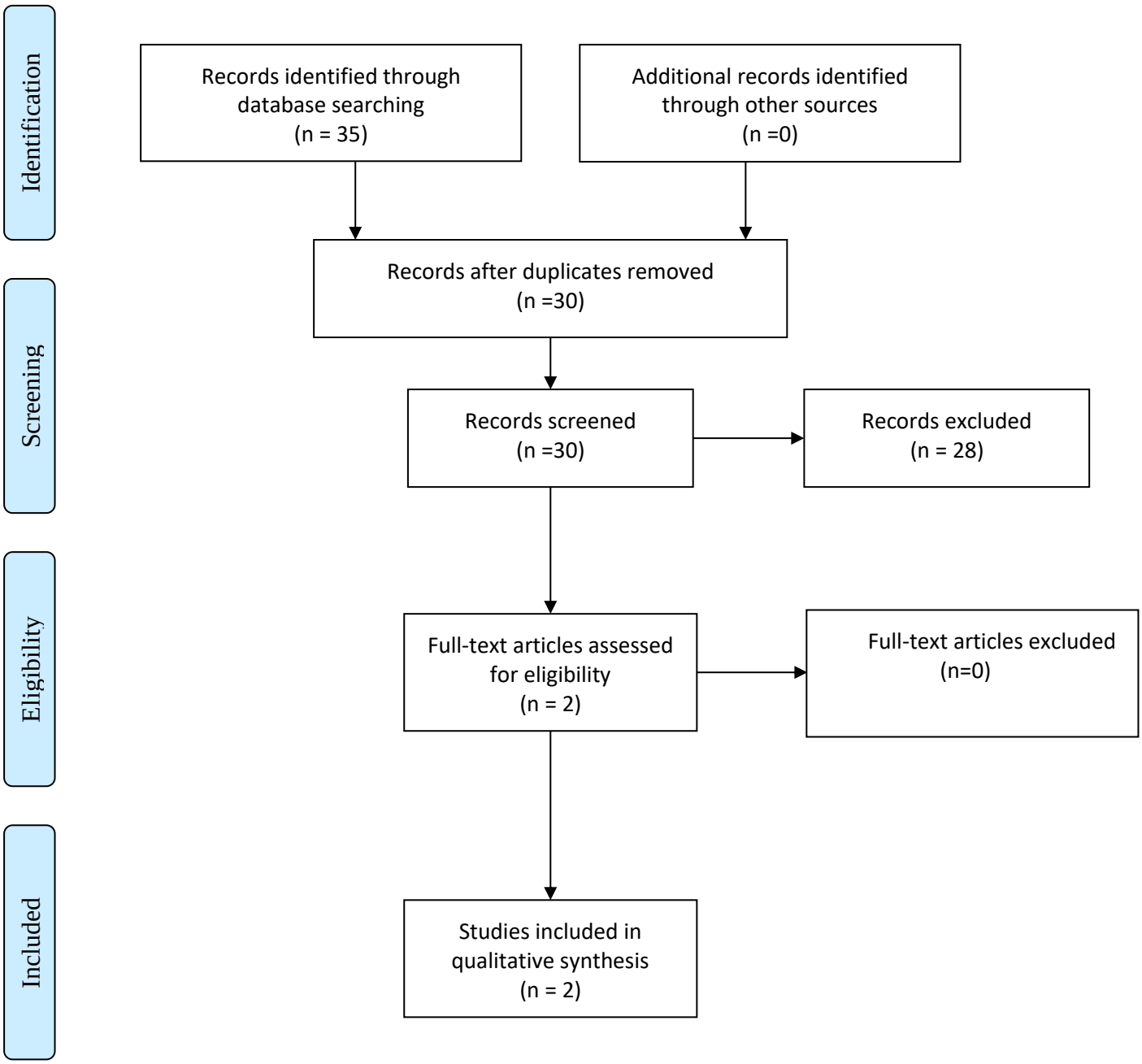

Figure 3 Study selection process for the association between crystalline silica exposure and lung cancer.

PRISMA 2009 Flow Diagram

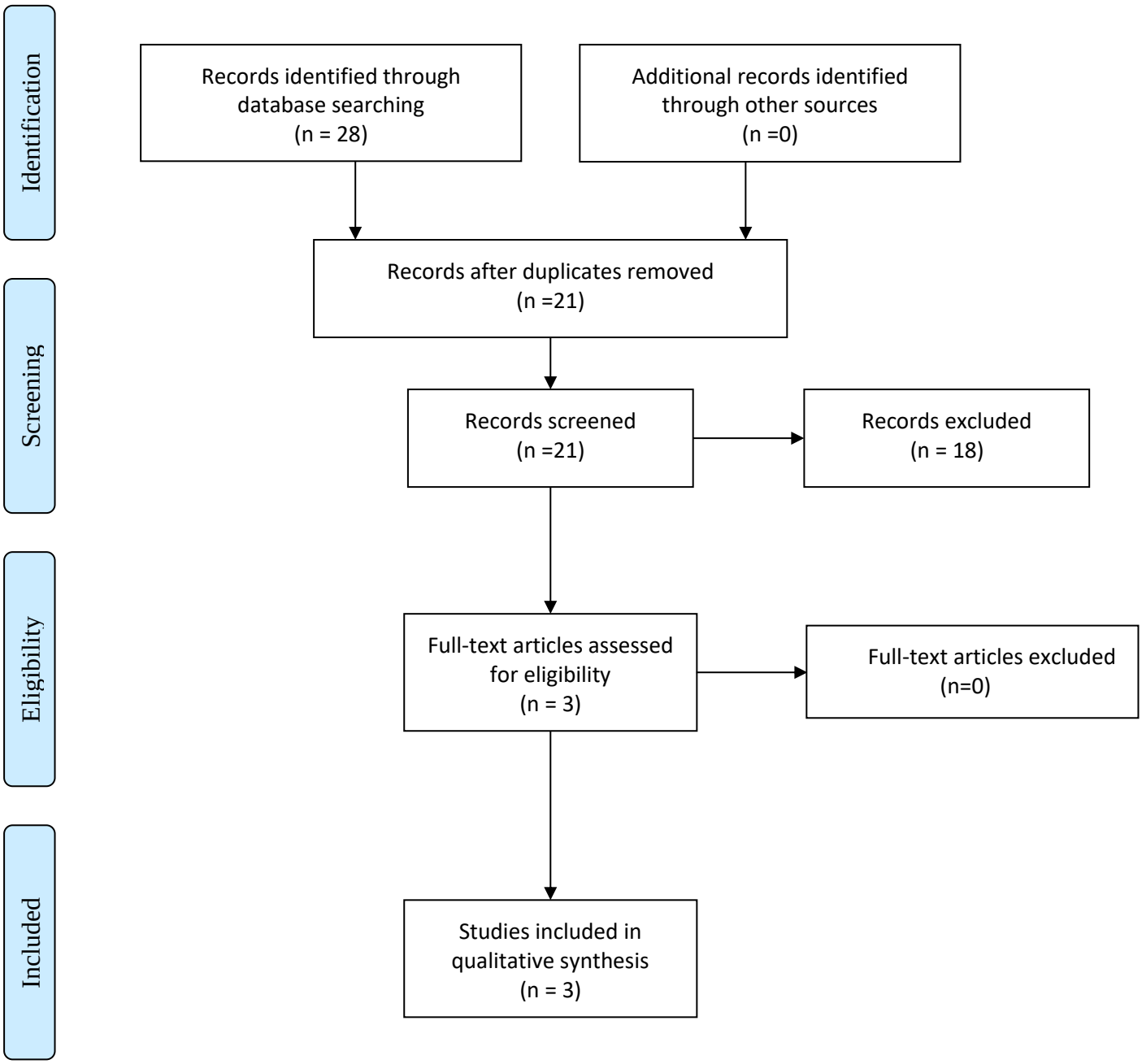

Figure 4 Study selection process for the association between diesel engine exhaust emissions and lung cancer.

In the following section, we will present the studies included in this review for each lung carcinogen.

2.2.1.1 Tobacco Smoking

Tobacco smoking was classified by the IARC as lung carcinogenic to humans (group 1) since 1986.(7) Thereafter, IARC reclassified tobacco smoking as lung carcinogenic in two monographs published in 2004 (40) and 2012 (41). Tobacco smoking remains the main cause of lung cancer; as a matter of fact, it was published that it was responsible for 60% to reach 80% of the lung cancer deaths across countries' population in France, Canada and USA. (16, 40, 42-45) In general, people start smoking at a young age, especially during teenage years, and they become addicted to nicotine and cannot stop the habit of smoking. Nicotine leads the person to become addicted to tobacco smoking. Tobacco smoking consists of a mixture of tobacco constituents existing naturally in tobacco and tobacco ingredients (flavors and additives) added to tobacco during manufacturing process.(46) There are more than 5,000 compounds in tobacco smoke, of which 70 are considered carcinogenic in laboratory animals or humans (16 of the 70 agents are classified as *lung carcinogenic to humans*).(40, 47)

A pooled analysis of case-control studies was published in 2012 including 13,169 cases of lung cancer (10,653 males, 2,516 females) and 16,010 controls from hospitals and general population (12,758 males, 3,252 females). Cases and controls were recruited between 1985 and 2005 from 15 study centers in 11 European countries and Canada (eight European and one Canadian case-control studies). Subjects were categorized as current smokers if they smoked more than one pack-year (PY) and were still smokers for the last two years. The squamous cell carcinoma and small cell carcinoma were the predominant histological types among male smokers, while adenocarcinoma was predominant among non-smokers and women. The odds ratios (ORs) of the association between current smokers and lung cancer was 23.6 [95% CI: 20.4-27.2] for males and 7.8 [95 % CI: 6.8-9.0] for females. The risk of lung cancer increased with the increment of PYs. For males, the odds ratios of the association between current smokers and lung cancer was minimum for smokers between one and 20 PY [8.9; 95 % CI: 7.4-10.6], and maximum for smokers of 60 PY and more [47.7; 95 % CI: 38.5-59.0]. For females, the odds ratios of the association between current smokers and lung cancer was minimum for smokers between one and 20 PY [3.5; 95 % CI: 2.9-4.3], and maximum for smokers of 60 PY and more [25.7; 95 % CI: 14.5-45.5]. For ex-smokers, the ORs of lung cancer started to drop soon after quitting smoking; The OR among ex-smokers who quit between 2 and 5 years was 18.3 [95 % CI: 15.3-21.8] among males, and 6.7 [95 % CI: 5.1-8.9] among females. For males, the OR of ex-smokers never reached the OR of non-smokers even after 35 years of quitting smoking [2.2; 95 %: 1.8–2.8], while among females the OR reached the OR of non-smokers after 26 years of quitting smoking [1.0; 95 %: 0.6–1.6]. For histological types of lung cancer, the ORs for current smokers were higher for small cell lung cancer [45.7; 95% CI: 29.9-70.0] and squamous-cell carcinoma [45.6; 95% CI: 34.3-60.6] than adenocarcinoma [10.8; 95% CI: 8.7-13.3] among males. For females, the same findings were observed among current smokers; the ORs were higher for small cell lung cancer [21.7; 95% CI: 15.5-30.1] and squamous-cell carcinoma [13.6; 95% CI: 10.5-17.7] than adenocarcinoma [4.2; 95% CI: 3.5-5.0]. For age at initiation of tobacco smoking, the ORs of lung cancer increased with the earlier starting age among males and females.(16)

A meta-analysis was published in 2012 to study the epidemiological evidence on the association between smoking and lung cancer. This meta-analysis included 267 studies which was published before 2000 and involved more than 100 cases of lung cancer. The association between ever smoking and lung cancer was very clear with a relative risk (RR) of 5.5 [95 % CI: 5.1-6.0]. This association was stronger for current smokers [8.4; 95 % CI: 7.7-9.3] than for ex-smokers [4.3; 95 % CI: 3.9-4.7]. Among current smokers, the association was stronger for squamous cell carcinoma [16.9; 95 % CI: 13.1-21.8] than for adenocarcinoma [4.2; 95 % CI:

3.3-5.3]. Among ex-smokers, the association was stronger for squamous cell carcinoma [8.7; 95 % CI: 6.9-11.0] than for adenocarcinoma [2.8; 95 % CI: 2.2-3.7]. The risk of lung cancer increased with intensity, duration, and age at initiation of tobacco smoking, and decreased with time of quitting smoking.(6)

In conclusion, tobacco smoking is associated with all histological types of lung cancer in men and women. Tobacco smoking is more associated with squamous cell carcinoma and small cell carcinoma than adenocarcinoma. Adenocarcinoma is predominant among women and non-smokers. The risk of lung cancer increases with intensity, duration, and the age of starting smoking, while it decreases with time of quitting smoking. The risk of lung cancer drops soon after quitting smoking but never reaches the same level of risk as non-smokers, especially in men.(6, 16) In addition, it has been hypothesized that the changes in the trends of lung cancer incidence and mortality and the incidence of histological types are more likely due to changing of smoking habits and to changing of cigarette composition.(48-50)

2.2.1.2 Asbestos

IARC evaluated asbestos carcinogenicity in four monographs published in 1973, 1977, 1987 and 2012. In the latest monograph published in 2012, all forms of asbestos were classified as lung carcinogenic to humans (group 1).(51) Asbestos designates a group of natural mineral fibers (hydrated silicates) that have been widely used in construction and industry before it was banned in some countries especially European countries. Asbestos is classified into two main groups: serpentine and amphibole. Serpentine includes only chrysotile (white asbestos), whereas amphiboles include five types: amosite (brown asbestos), crocidolite (blue asbestos), anthophyllite, actinolite and tremolite. Asbestos are magnesium or calcium silicates with refractory properties. Asbestos fibers have specific physicochemical properties (chemical stability, acoustic insulation, thermal resistance, and tensile strength) and a low production cost. For these reasons, asbestos have been used in many industries [insulation, thermal and water insulation, textile industry, automobile industry (friction products: clutch and brakes), shipbuilding and construction industry (asbestos cement)]. In general, asbestos cement represents most asbestos use. (35, 51, 52)

A meta-analysis published in 2013 estimated the risk of lung cancer for low cumulative exposures to asbestos by using non-linear models. It included 17 cohort studies, one nested case-control study in a cohort, and one case-control study. The estimated RR of lung cancer for an exposure of 4 f/ml.year was 1.03 [95% CI: 1.02-1.03), while it was 1.30 [95% CI: 1.22-1.39] for an exposure of 40 f/ml.year.(53)

A systematic literature review published in 2014 examined the association between asbestos and lung cancer. It included 24 cohorts and 4 case-control studies. The authors concluded that dose-effect relationship is linear, but stabilizes at high exposure (> 150 f/ml.year). On the other hand, 5 studies showed that the RR increased between 0.01 and 0.04 per f/ml.year, corresponding to a doubling of risk at 25 to 100 f/ml.year. Otherwise, a case-control study of high quality showed a doubling of RR at 4 f/ml.year. Based on the cohort studies, lung cancer risk continues to decrease for decades after the exposure was stopped. Finally, there was no minimum latency established for lung cancer risk associated with asbestos.(54)

Another literature review was published in 2014 and reported that for high exposures to asbestos, there is an increased risk of lung cancer with a latency period that is approximately 15 to 20 years. The risk of developing lung cancer increases linearly as the cumulative exposure to asbestos.(55)

We can confirm the presence of positive association between occupational exposure to asbestos and lung cancer, with a positive dose-response relationship.

2.2.1.3 Crystalline Silica

There are several monographs published by IARC (1987, 1997, and 2012) and evaluated the lung carcinogenicity of crystalline silica. In the last update of 2012, IARC has classified crystalline silica as lung *carcinogenic to humans* (group 1).(51) Crystalline silica is naturally found in soil, sand, granite and other minerals. The most common form of crystalline silica is quartz; the term "quartz" is also often used instead of the general term of crystalline silica. The other main varieties of crystalline silica are cristobalite and tridymite. Quartz is naturally found in the majority of the sand and rocks and it can be synthesized industrially. This is the form of crystalline silica most encountered in the workplace. Cristobalite is rare in nature, it is present in volcanic rocks, but it can also be synthesized industrially. It is the second form of professionally encountered crystalline silica; in contrary, tridymite is rarely found in nature and in the workplace. Crystalline silica is used in a large number of products such as cements, mortars and concretes. In addition, it can be used as a raw material in industrial processes. It is also found in the form of dust in the air in many activities (work in mines and quarries, manufacturing dentures, stone carving, casting, glassware, crystal, jewelry, ceramics industries and porcelain industries, etc.).(51)

In 2014, Steenland & Ward published a literature review on crystalline silica and lung cancer. They presented the results of a cohort study of 34,000 miners published in 2013 in which a significant dose-response relationship was reported. The RR for each quartile of cumulative exposure (0, 0.01 - 1.12, 1.12 - 2, 91, 2.91 - 6.22 and more than 6.22 mg / m^3.years) compared to subjects non-exposed to crystalline silica were estimated to be 1.26, 1.54, 1.68, and 1.70, respectively. (56, 57)

In 2016, a meta-analysis was conducted to examine the dose-response relationship between crystalline silica and lung cancer by including 85 studies (cohorts, case-controls and mortality proportion studies). There was a positive association between crystalline silica and lung cancer among silicotic and non-silicotic subjects. The pooled standardized mortality ratio (SMR) [2.32; 95 % CI: 1.91–2.81 and 1.78; 95 % CI: 1.07–2.96, respectively] was positively significant among silicotic and non silicotic subjects. In contrary, the pooled standardized incidence ratio (SIR) [2.49; 95 % CI: 1.87–3.33 and 1.18; 95 % CI: 0.86–1.62, respectively] was positively significant among silicotic subjects only. In addition, a positive dose-response association was observed between cumulative exposure to crystalline silica and lung cancer risk. (58)

Overall, there is a positive association between occupational exposure to crystalline silica and lung cancer, also a positive dose-response relationship exists.

2.2.1.4 Diesel Engine Exhaust Emissions

IARC classified the exposure to diesel engine exhaust emissions as lung carcinogenic to humans (group 1) in the latest update of the monograph 105 in 2013, after it was previously classified as probably carcinogenic to humans (group 2 A) in a monograph of 1989. (59, 60)

Diesel is used for road vehicles (e.g. cars, buses, heavy vehicles), non-road vehicles (e.g. train and boat), heavy equipment in many industrial sectors (e.g. mines and construction), and in electrical generators especially in developed countries. The emissions from these devices are complex and can vary in composition. The quantitative and qualitative composition of the diesel

engine exhaust emissions depends on the fuel type, the age of the equipment, the state of its engine and its maintenance, the use of an emission control system and its condition. The technology of vehicles using diesel has evolved over time to limit emissions. (59, 60)

A systematic literature review and meta-analysis examined the association between professional driver activity (potentially exposed to diesel engine exhaust emissions) and the risk of lung cancer from twenty studies published between 1996 and 2011. Twenty articles were included in the literature review, while only nineteen studies were included in the meta-analysis because one study does not provide the OR confidence interval. From the meta-analysis, the RR of lung cancer associated with exposure to diesel engine exhaust emissions was estimated to be 1.21 [95% CI: 1.10-1.32] among professional drivers. The RR is estimated to be 1.19 [95% CI: 1.06-1.34) from studies where job duration was equal or more than 10 years and adjusted for smoking status. (61)

In 2014, a systematic literature review was conducted where authors applied a JEM developed from the MEGA database (industrial hygiene database) exposure level jobs given in selected publications. The authors identified 42 cohort studies and 32 case-control studies. However, the cumulative dose of exposure to diesel engine exhaust emissions were only available for six cohort studies. Overall there was no dose-response relationship. From the case-control studies, quantitative or semi-quantitative exposure data were available for six studies. In general, there was a higher RR of cancer for jobs with supposed highest level of exposure. Using JEMs, there was absence of dose-effect relationship. (62)

A meta-analysis was published in 2014 evaluating the dose-response relationship between exposure to diesel engine exhaust emissions and lung cancer mortality from three cohorts in the workplace. The inclusion criteria were the following: measurement of the cumulative exposure to elemental carbon, unexposed reference group or low exposure and no major methodological bias. Only three studies were included. The results of the meta-analysis showed that for every increase of 1 $\mu g/m^3 \times$years of cumulative exposure to elemental carbon, the RR of lung cancer mortality increase by 0.09% [95% CI: 0.055 - 0.014].(38)

In general, there is a positive association between occupational exposure to diesel engine exhaust emissions and lung cancer, but the presence of dose-response is not confirmed.

2.2.2 Other Occupational Lung Carcinogens

In addition to tobacco smoking, asbestos, crystalline silica, and diesel engine exhaust emissions, many other agents were classified as lung carcinogens (Table 1). In this section, we present the latest evidence from the literature for occupational lung carcinogens.

Table 1 List of lung carcinogenic agents for humans as per the latest update of IARC

1. Acheson process, occupational exposures associated with Aluminum production
2. Arsenic and inorganic arsenic compounds
3. Asbestos (all forms)
4. Beryllium and beryllium compounds
5. Bis(chloromethyl)ether; chloromethyl methyl ether (technical grade)
6. Cadmium and cadmium compounds
7. Chromium(VI) compounds
8. Coal, indoor emissions from household combustion
9. Coal gasification
10. Coal-tar pitch
11. Coke production
12. Engine exhaust, diesel
13. Hematite mining (underground)
14. Iron and steel founding
15. MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)
16. Nickel compounds
17. Outdoor air pollution
18. Painting
19. Particulate matter in outdoor air pollution
20. Plutonium
21. Radon-222 and its decay products
22. Rubber production industry
23. Silica dust, crystalline
24. Soot
25. Sulfur mustard
26. Tobacco smoke, secondhand
27. Tobacco smoking
28. X-radiation, gamma-radiation

Source: IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. List of classifications by cancer site. June 2016. Available at: https://monographs.iarc.fr/ENG/Classification/Table4.pdf

2.2.2.1 Aluminum Production

The occupational exposures associated with aluminum production was classified as lung carcinogenic to humans (group 1) in the latest update of 2012 (monograph 34, Sup 7, 100F) (63).

One study evaluated mortality among workers in an aluminum production plant in France. The cohort consists of 2,133 men worked at least one year in the factory between 1950 and 1994. The authors study a dose-response relationship depending on the duration of exposure. The SMR for risk of lung cancer was 0.37 [95% CI: 0.08 - 1.08] for 0 to 9 years of exposure, 1.07 [95% CI: 0.39-2.34] for 10 to 19 years, 0.49 [95% CI, 0.13-1.24] for 20 to 29 years, and 0.73 [95% CI: 0.27 - 1.60] for 30 years or more. (64)

A cohort study of 1,790 men employed over 5 years in an aluminum production plant in Norway studied the risk of lung and bladder cancer. Exposure is measured by the particulate concentration of Polycyclic Aromatic Hydrocarbons (PAHs) in µg/m^3. There was absence of dose-response relationship with the cumulative exposure to PAHs. (65)

Björ et *al.* reported in 2008 the results of a historical cohort of 2,264 men working in aluminum smelter in Sweden between 1942 and 1987. Regarding lung cancer, taking as a reference subjects who worked two years or less, the Hazard Ratio (HR) for subjects worked between 2 and 10 years was 0.95 [95% CI: 0.39 - 2.28], while the HR was 1.31 [95% CI: 0.60-2.88] for subjects worked fr more than 10 years. Using the population of northern Sweden as a reference, the risk of lung cancer increased after 10 years of work in foundries SIR = 1.99.(66)

2.2.2.2 Arsenic and Inorganic Arsenic Compounds

Arsenic and inorganic arsenic compounds was classified as lung carcinogen according to the latest IARC monograph (monograph 23, Sup 7, 100C) (11).

In 2011, a case-control study was conducted from 1998 to 2001 in 17 centers in 7 countries of Central Europe, Eastern Europe and the United Kingdom. Incident cases of cancer were included. Controls were collected from hospitals or from the population. The exposure was assessed by experts. There was absence of dose-response relationship between exposure to arsenic and lung cancer risk. (67)

In 2012, Park et *al.* published a study where the association between arsenic and lung cancer was examined. This study included 606 smelter cohort workers for at least 6 months in a production area between 1940 and 1969. The RR was 13.2 ($p<0.01$) for a cumulative exposure to arsenic of 10.0 mg/m^3-years. There was a significant dose-response relationship.(68)

2.2.2.3 Beryllium and Beryllium Compounds

In the latest IARC 2012 monograph (23, Sup 7, 100C), beryllium and its compounds were classified as lung carcinogens. (11)

In 2011, a cohort study of 5,436 workers at three beryllium processing plants was published. Subjects exposed to asbestos were excluded, and the reference group consisted of subjects exposed to less than 0.6 µg/m^3 of beryllium per day. The RR of subjects exposed between 0.6 and 2 µg/m^3 was 1.30 [95% CI: 0.59 - 3.11], 2.41 [95% CI: 1.06 - 5.82] for those exposed between 2.0 and 8.0 µg/m^3, 7.22 [95% CI: 2.62-21.4] for those exposed between 8.0 and 12.0 µg/m^3, 6.68 [95% CI: 2.81 - 18.0] for those exposed between 12.0 and 50.0 µg/m^3, and 4.80 [95% CI: 1.74 - 14.2] for those exposed to 50 µg/m^3 or more. (69)

In the same year, the same authors report the results of a cohort mortality study of 9,199 workers at seven beryllium processing plants followed for mortality from 1940 to 2005. The SMR for lung cancer was 1.17 [95% CI: 1.08 - 1.28]. For exposure duration, the reference group was consisted of subjects exposed to less than 15 years. The standardized rate ratio (SRR) was 2.24 [95% CI: 0.78-6.45] for those exposed between 15 and 25 years, 2.83 [95% CI: 1.03-7.78) for those exposed between 25 and 35 years, and 3.68 [95% CI: 1.36-9.95] for those exposed to 35 years or more. For cumulative exposure to beryllium (in µg/m^3.years), the reference group was consisted of subjects exposed to less than 550 µg/m^3.years. The SRR was 0.96 [95% CI: 0.69-1.34] for those exposed between 550 and 2,500 µg/m^3.years, 0.91 (95% CI: 0.66 - 1.27) for those exposed between 2,500 and 10,300 µg/m^3.years, and 1.12 (95% CI: 0.79-1.60) for those exposed for more than 10,300 µg/m^3.years. (70)

In 2012, Boffeta et *al.* published a literature review. Based on the evidence from the literature, they conclude that there is no dose-response relationship between duration of use or cumulative exposure to beryllium and the risk of lung cancer. (71)

2.2.2.4 Bis(chloromethyl)ether (BCME); Chloromethyl methyl ether (CMME)

BCME and CMME were classified as lung carcinogenic to humans in the latest IARC monograph of 2012 (4, Sup 7, 100E). (63)

In 1993, Gowers et *al.* published a cohort study conducted among French workers in a manufacture of anion exchange resins since 1958, with documented exposure to BCME/CMME. Potential exposure to BCME/CMME was rated on a scale of 0 (very low exposures) to 6 (highest exposures). Cumulative exposure was calculated by multiplying the exposure score by the number of years of exposure. The RR of lung cancer was 5.0 [95% CI: 2.0 - 12.3] when comparing exposed versus non-exposed subjects. The dose-response relationship was studied by calculating the SMR in different exposure groups. SMR was 2.8 [95% CI: 0.1-15.5] among subjects with a median cumulative exposure of 2.5 score-years, 4.9 [95% CI: 0.6 - 17.6] among subjects with a median cumulative exposure of 6.3 score-years, 16.7 [95% CI: 2.0 - 60.2] among subjects with a median cumulative exposure of 12.5 score-years, 40.0 [95% CI: 4.8 - 144.5] among subjects with a median cumulative exposure of 24.0 score-years, and 18.2 [95% CI: 5.0 - 46.6] among subjects with a median cumulative exposure of 40.0 score-years. There was a positive dose-response relationship. (72)

In 1997, Weiss et *al.* published a cohort of 125 chemical workers of which 93 were exposed to CMME. Workers were followed from 1963 to 1992. An exposure index was calculated for each subject by multiplying the average exposure estimated by the exposure duration (in years). In this cohort, 25 of 67 subjects died of lung cancer. The SMR was 2.0 [95% CI: 0.41 - 5.84] for exposed subjects with an exposure index between 0 and 10, 7.49 [95% CI: 3.23 - 14.75] for exposure index between 10 and 20, and 15.21 [95% CI: 7.87-26.6] for exposure index of 20 and above. (73)

2.2.2.5 Cadmium and Cadmium Compounds

Cadmium and its compounds were classified as lung carcinogenic to humans in the latest IARC 2012 monograph (58, 100 C). (11)

In 2011, t'Mannetje et *al.* published a case-control study in 17 centers at 7 countries of Central Europe, Eastern Europe and the United Kingdom. For cadmium, the RR for lung cancer was 1.18 [95% CI: 0.83 - 1.67], adjusted for other occupational exposures including metals like arsenic. There was no dose-response relationship between exposure to cadmium and the risk of lung cancer for the duration of exposure. Using cumulative exposure, and non-exposed as reference group, the OR was 1.15 [95% CI: 0.56 - 2.35] for subjects exposed to cadmium between 0.001 and 28 mg/m^3.hours, 0.52 [95% CI: 0.24 – 1.14] for subjects exposed between 28 and 65 mg/m^3.hours, and 2.04 [95% CI: 1.07-3.90] for subjects exposed to more than 65 mg/m^3.hours. (67)

In 2012, Park et *al.* published a cohort study to examine the association between cadmium and lung cancer, taking into account exposure to arsenic. This study included 601 subjects, and there was an effect of cadmium on the risk of lung cancer Independent of that linked to arsenic. Thus, taking into account arsenic, for a cumulative exposure to cadmium of 10.0 mg/m^3.years, the RR was 3.2 (p = 0.012). (68)

2.2.2.6 Chromium (VI) Compounds

The latest IARC classified chromium (VI)compounds as lung carcinogenic to humans (monograph Sup 7, 100C) (11).

In 2013, a meta-analysis and systematic review was published by Seidler et *al.* to determine the dose-response relationship between chromium (VI) and the risk of lung cancer. This study included five studies from two cohorts of workers in chromium production in Baltimore, Maryland and Painesville, Ohio. Authors concluded that an excess of 4 deaths per 1000 subjects is associated with cumulative chromium (VI) exposure of 1µg/m^3. (74)

2.2.2.7 Coal Gasification

Coal gasification was classified by IARC as lung carcinogenic to humans (group 1) in the last update of 2012 (Monograph 92, 100F). (63)

Martin et *al.* examined the dose-response relationship of occupational exposure to coal gasification in a French nested case-control study in a cohort. The cohort includes all workers of the EDF-GDF (Electricité de France-Gaz de France) company between 1978 and 1989 and worked for more than one year. A JEM was used to assess exposures. There was no dose-response relationship when taking into account the duration of the employment or the quartiles of cumulative exposure during gas production. (75)

2.2.2.8 Coal-tar Pitch

Coal-tar pitch was classified as lung carcinogenic to humans in the latest update of 2012 (monograph 35, Sup 7, 100F, 2012) (63).

In 2002, Mori published a cohort study examining the risk of cancer among 332 man-made graphite electrode manufacturing workers exposed to coal-tar pitch. The concentration of tar and benzo (a) pyrene in the air was measured in 1973 and 1974. The SMR was 3.33 [95% CI: 0.03 - 1.86] for subjects exposed between 5 to 15 years, with a period between 5 and 15 years from the first exposure. For subjects with a period from the first exposure exceeds 15 years, SMR was 3.96 [95% CI: 1.29 - 9.24] for subjects exposed between 5 and 15 years, and 1.57 [95% CI: 0.32 - 4.59] for those exposed for more than 15 years. (76)

A Finnish study evaluated the dose-response relationship in a cohort of 9,643 subjects from six workers in Finnish road paving companies. The measurement of exposure to coal tar-pitch is semi-quantitative (very low / low / medium or high). A dose-response relationship was found between cumulative exposure to coal tar pitch and lung cancer mortality with a 15-year latency (p = 0.05). In the very low exposure group, the RR was 1.49 (no CI provided), in the mean exposure group the RR was 10.7 [95% CI: 2.36 - 48.9] based on only 3 cases. (77)

In 2010, Olsson et *al.* published the results of a nested case-control study in a cohort of European asphalt workers. In this study, 433 cases and 1,253 controls were included. The exposure assessment to the different agents was carried out in a semi-quantitative manner. Three exposure classes were defined for each use: no exposure, low exposure, significant exposure. For exposure to coal-tar pitch, taking as a reference the subjects never exposed, there is no dose-response relationship according to duration of exposure (p = 0.11), or according to cumulative exposure to coal tar pitch (p = 0.07). (78)

2.2.2.9 Coke Production

Coke production was classified as lung carcinogenic to humans in the latest update of 2012 (monograph 92, 100F) (63).

In 2012, Schnatter et *al.* examined the association between petroleum coke dust and lung cancer. This study Included 17,230 employees working in a Canadian petroleum company for at least one year between 1964 and 1994. The SIR was 0.58 [95% CI: 0.40 - 0.82] for subjects not exposed to petroleum coke dust, 1.49 [95% CI: 0.31 - 4.34] for those exposed 0 - 0.005 mg/m^3, 0.59 [95% CI, 0.07 - 2.13] for those exposed 0.006 - 0.070 mg/m^3, 1.49 [95% CI: 0.31 - 4.34] for those with an exposure greater than 0.070 mg/m^3. There was no dose-response relationship (p = 0.10) reported in this study. (79)

2.2.2.10 Hematite Mining (Underground)

In the latest IARC update of 2012, exposure to iron-ore mines was classified as lung carcinogenic to humans (IARC 78, 100D) (80).

In 2013, one study was published on the dose-response relationship between the work in iron-ore miners (northern Sweden) and the risk of lung cancer. The reference group was the subjects working on the surface. The RR was 1.39 [95% CI: 0.94 – 2.05] for subjects worked up to 4 years in the mines, 1.51 [95% CI: 1.05 - 2.20] for those worked between 5 and 14 years, and 2.08 [95% CI: 1.46-2.99] for those who worked more than 15 years. The dose-response relationship was significant. (81)

2.2.2.11 Iron and Steel Founding

In the latest IARC update of 2012, iron and steel founding was classified as lung carcinogenic to humans (IARC 78, 100D). (63).

Andersson et *al.* examined the association between exposure to quartz and lung cancer among Swedish iron foundries. They carried out a nested case-control study in a cohort of 10 foundries. All lung cancer cases identified by the Swedish Cancer Registry (n = 52) and 260 controls were included. Exposure to quartz was measured from samples taken from foundries. The reference group was consisted of subjects exposed to less than 0.5 mg/m^3.years. The OR was 1.02 [95% CI: 0.46 - 2.29] for the group of subjects exposed to 0.5-1 mg/ m^3.years, 1.17 [95% CI, 0.53 - 2.55] for the group exposed to 1-1.9 mg/m^3.years, and 0.79 [95% CI: 0.20 - 3.02] for the group exposed to 2 mg/m^3.years or more. Only 3 cases and 20 controls were included in the group of the highest cumulative exposure. (82)

Another study published in 2013 examined the dose-response relationship between quartz exposure in Swedish iron foundries and lung cancer, using the same data of Andersson study. In this study, Cox model was used, and the reference group was consisted of subjects exposed to less than 1 mg/m^3.years. The HR was 1.01 [95% CI: 0.55 - 1.84] for subjects exposed to 1-1.9 mg/m^3.years, and 0.78 [95% CI: 0.24 - 2.57] for subjects exposed to 2 or more mg/m^3.years (83).

2.2.2.12 Nickel Compounds

The Nickel compounds was classified as lung carcinogenic to humans by the IARC in 2012 (49, 100C monograph) (11).

In 2011, t'Mannetje et *al.* published a case-control study in 17 centers at 7 countries of Central Europe, Eastern Europe and the United Kingdom. The association between cumulative exposure to nickel and lung cancer was not significant. (67)

In 2012, De Matteis et *al.* Published a study (based on the EAGLE case-control study) to examine the association between nickel-chromium and lung cancer. This study included 2,100 lung cancer cases and 2,100 controls. The occupational exposure was assessed by "DOM-JEM". The reference group consisted of non-exposed subjects. The OR was 1.18 [95% CI: 0.90 - 1.53] for subjects with a low cumulative exposure, and 1.31 [95% CI: 0.86 - 1.97] for those with a significant cumulative exposure. (36)

2.2.2.13 Painting Jobs

The latest IARC monograph 47, 98, 100E (2012) classified the painting jobs as a lung carcinogen. (63)

In 2011, Guha et *al.* (2011) conducted a meta-anlysis included 47 cohort and case-control studies. The combined analysis involved more than 11,000 incident cases or deaths from lung cancer in painters. The meta-RR was 1.35 [95% CI: 1.29 - 1.41]. The reference group consisted of non-exposed subjects. Based on the duration of exposure, the meta-RR was 1.95 [95% CI: 1.26-3.02] for those exposed to 10 years or more, and 2.00 [95% CI: 1.01 - 3.92] for those exposed to 20 years or more. There was a positive dose-response relationship.(84)

2.2.2.14 Plutonium

In the latest IARC update of 2012, exposure to plutonium was classified as lung carcinogenic to humans (IARC 78, 100D). (80)

In 2013, Gilbert et *al.* published a study on the association between exposure to plutonium and the risk of death from lung cancer. This cohort included 25,757 active workers during the period 1948-1982. The follow-up is carried out until 2008. The analyses were based on 14,621 workers followed for at least five years and for which the dose of plutonium could be estimated. The dose-response relationship is well described by a linear function. (85)

2.2.2.15 Radon-222 and its Decay Products

In the latest IARC update of 2012, exposure to radon and its decay products was classified as lung carcinogenic to humans (IARC 78, 100D). (80)

In 2012, Tirmarche et *al.* published a report on the association between radon and the risk of death from lung cancer for the International Commission on Radiological Protection (ICRP). The authors presented the Excess Relative Risk (ERR) of 100 Working Level Month (WLM) ERRs reported in five studies published since 1993 based on combined analyzes of studies among miners. A dose-response relationship was observed between radon exposure and the risk of lung cancer (86).

2.2.2.16 Rubber Production Industry

The latest IARC monograph 28, Sup 7, 100E (2012) classified rubber production as lung carcinogenic to humans. (63)

In 2013, a study was conducted among German rubber industry workers with a follow-up for mortality from 1981 to 2000. In general, there was significant elevated SMRs for lung cancer.

The SMR was 1.68 [95% CI: 1.05 - 2.54] for subjects worked between 1 and 9 years, 1.36 [95% CI: 1.09 - 1.68] for those worked between 10 and 19 years, 1.24 [95% CI: 1.06 - 1.44] for those worked between 20 and 29 years, 1.01 [95% CI: 0.82 - 1.22] for those worked between 30 and 39 years, and 1.64 [95% CI: 1.24 - 2.13] for those worked for 40 years or more. (87)

The Mortality by lung cancer was also studied among an Italian cohort of employees working in the rubber industry between 1954 and 2008. This cohort included 6,246 men. The SMR was 78 [95% CI: 59 – 102] for subjects employed for less than 10 years, 85 [95% CI: 58 – 120] for those employed between 10 and 19 year, and 72 [95% CI: 52-97] for those employed for 20 years or more. There was no significant dose-response relationship observed. (88)

2.2.2.17 Soot Exposure

The IARC classified soot exposure as lung carcinogenic to humans in the last update of 2012 (IARC monograph 35, Sup 7, 100E). (63)

In 2013, Hogstedt et *al.* published a study in a cohort of Swedish chimney sweepers including 6,320 subjects followed between 1958 and 2006 are included in this cohort. The overall SIR for lung cancer was 2.14 [95% CI: 1.77 - 2.56]. SIR was 2.69 [95% CI: 1.93 - 3.65] for subjects exposed between 0 and 9 years, 1.71 [95% CI: 1.03-2.66] for those exposed between 10 and 19 years, 1.90 [95% CI: 1.12 - 3.00] for those exposed between 20 and 29 years, and 2.07 [95% CI, 1.49 - 2.81] for those exposed for 30 years and more. There was absence of dose-response relationship ($p = 0.32$). (89)

2.2.2.18 X-radiation, Gamma-radiation

The exposure to X-rays and gamma radiation was classified as lung carcinogenic to humans (group 1) in the most recent IARC of 2012 (IARC 78, 100D). (80)

A nested case-control study investigated the relationship between exposure to ionizing radiation exposure and risk of lung cancer death adjusted for potential confounding factors. The 1,097 cases of lung cancer and the 3,291 controls were from the same cohort of workers at the Portsmouth naval shipyard. Measurement of exposure is carried out for each worker based on measures and job title. RR was 1.17 [95% CI: 0.86 - 1.60] for 1 - 10 mSv, 1.45 [95% CI: 1.01-2.09] for 10 - 50 mSv, and 1.13 [95% CI: 0.72-1.75] for 50 mSv or higher: (90)

In 2008, a study of the association between workers of shipyards involved in nuclear powered ship overhauls revisions exposed to low levels of radiation are reported (93). The population study included 28,000 workers exposed to 5.0 mSv and above, 10,462 workers exposed to less than 5.0 mSv and 33,353 unexposed workers. The exposure was measured individually from thermal luminescent dosimeters (between 1973 and 1974). The reference group consisted of subjects exposed between 5 and 10 mSv and without latency period. RR was 1.08 [95% CI: 0.8 – 1.6] for subjects exposed between 10 and 50 mSv, and 1.26 [95% CI: 0.9 - 1.9] for subjects exposed to more than 50 mSv.(91)

Worldwide, the percentage of smokers is higher among blue-collar workers than white-collar worker.(92) In a study conducted in Netherlands, 1,843 (87.5%) subjects out of 2,107 men blue-collar workers were smokers (ex-smokers and current smokers). (93) In a study conducted in 7 different countries in Europe, the percentage of smokers (ex-smokers and current smokers) was 86.2%. (94)

In conclusion, occupational exposures to asbestos, crystalline silica and diesel engine exhaust emissions are among the most frequent and potent occupational lung carcinogens. In addition, a high proportion of blue-collar workers are smokers concomitantly exposed to occupational lung carcinogens. Thus, we examined in the following section a systematic review on the statistical interaction between tobacco smoking, and the three main occupational lung carcinogens; asbestos, crystalline silica, and diesel engine exhaust emissions on the occurrence of lung cancer.

2.3 Systematic Review on Interaction

2.3.1 Introduction

Tobacco smoking and the three occupational exposures described previously (asbestos, crystalline silica and diesel engine exhaust emissions) were classified by the IARC as lung carcinogens to humans. The occupational exposures to all forms of asbestos, crystalline silica and diesel engine exhaust emissions were among the top most frequent occupational exposures. Asbestos has been widely used for over 100 years. It is estimated that 125 million people are exposed to asbestos at their workplace each year. For crystalline silica, occupational exposure exists in wide varieties of industries and occupations due to the natural presence of crystalline silica in the earth's crust and the extensive use of products that include crystalline silica. It was reported that 1.7 million USA workers and 3.2 million European workers are potentially exposed to crystalline silica. As for diesel engine exhaust emissions, occupations that are associated with high exposure levels include mining, railways, construction and transportation. It is estimated that 1.4 million workers in the USA and 3 million workers in Europe are exposed to diesel engine exhaust emissions in their workplace.(8-10, 51)

As a matter of fact, the rate of smoking was higher among blue-collar workers than white-collar worker. (92-97) Thus, a significant proportion of workers are concomitantly exposed to tobacco smoking and to at least one occupational lung carcinogen including asbestos, crystalline silica, and diesel engine exhaust emissions. This brings into light the importance of studying the statistical interactions between tobacco smoking and the occupational exposure to asbestos, crystalline silica and diesel engine exhaust emissions.

Statistical interactions between tobacco smoking and these carcinogens were evaluated using various methodologies. The differences between the methodologies are related to study design, data collection methodology, data processing and statistical analysis. Therefore, it is not easy to compare the studies' results and to conclude the statistical interaction nature. In addition, different studies conclude the nature of the statistical interaction on additive and multiplicative scales, while interaction was only evaluated on one scale. Many studies as well conclude the nature of the interaction without assessing if the scale used to evaluate the statistical interaction is significant. Thus, the studies' conclusions are not always accurate and may suggest the presence or absence of an additive or multiplicative interaction based on weak or wrong evidence.

In the following section, we present a systematic review on the interaction between the three most important occupational lung carcinogens, namely asbestos, crystalline silica and diesel engine exhaust emissions and tobacco smoking to define if the interaction nature is similar irrespective of the lung carcinogen, or if the interaction nature is specific for each carcinogen.

2.3.2 Methods

This systematic review was reported based on the PRISMA statement (published in 2009) and the PRISMA-P for developing review protocols (2015).

The PRISMA statement consists of a checklist and a flow diagram. The checklist consists of 27 items to be reported in the systematic review, related to the title, abstract, methods, results, discussion and funding (Appendix A). The flow diagram presents the inclusion and the exclusion of records through the different phases of the systematic review. It indicates the number of identified articles, excluded articles and the reasons of exclusions, and the number of articles included in the systematic review.(98, 99)

2.3.2.1 Search Strategy

Articles reviewed were identified using three bibliographic databases: PubMed, Scopus and Web of Science. The selected studies were limited to those published in English or French, without limitation to time. The most recent research was conducted in June 30, 2016.

For asbestos-tobacco, silica-tobacco and diesel-tobacco statistical interactions, all records of the three bibliographic databases were searched using the following key words respectively: ["asbestos" and "lung cancer" and "smoking"], ["silica" and "lung cancer" and "smoking"], and ["diesel" and "lung cancer" and "smoking"].

2.3.2.2 Inclusion Criteria

Studies were included in this review if they met the following criteria: human studies, studies published in peer-reviewed journals, cohort or case-control studies, studies evaluating the statistical interaction between tobacco smoking and one of the three studied occupational exposures on lung cancer, studies reporting the occupational exposure assessment, studies reporting the smoking behavior assessment, studies reporting the statistical analysis performed to assess the statistical interaction, and studies reporting the results of the statistical interaction and their statistical significance (*p*-value or 95% CI). For studies analyzing the same population, the most recently published article evaluating the statistical interaction that met all the previous criteria was included.

2.3.2.3 Exclusion Criteria

In general, studies not meeting the inclusion criteria were excluded: clinical trials, in vitro studies, animal studies, cross-sectional studies, systematic reviews, meta-analyses, case reports and case series. Articles studying the statistical interactions between environmental exposures to asbestos, crystalline silica and diesel engine exhaust emissions and tobacco smoking on lung cancer were also excluded. Finally, articles that investigated the statistical interactions between asbestosis, silicosis, and smoking without taking into consideration asbestos and crystalline silica exposures were also excluded.

2.3.2.4 Articles Selection Process

Records identified through the three bibliographic databases were checked for duplications. Duplicated records were removed, and the remaining records were screened to distinguish those met the inclusion criteria. The screening phase was done in three steps: 1) selection of articles that studied the association between one of the three occupational exposures and lung cancer, 2) selection of the articles that studied the interaction based on the title or the abstract, and 3)

for the remaining articles, the full-text was screened to select studies that evaluated the interaction between one of the three occupational exposures and smoking. The reference list of the selected articles was reviewed to identify other relevant articles. The full-text articles remained was assessed for eligibility to determine the final list of articles included in the qualitative synthesis.

2.3.2.5 Data Extraction

Data extraction was performed by one author (MZ), and reviewed by two other authors (FD and AL). The following data were extracted from each study included in the present review : first author, publication year, geographic area, study type (prospective cohort study, retrospective cohort study, nested case-control study, population-based case-control study, hospital-based case-control study), exposure type, industry type, total number of subjects (population and cases/cases and controls), the method to collect the occupational exposure and smoking status details, the definition of occupational exposure, the definition of smoking status, the outcome (lung cancer) classification, the methodology of the statistical interaction evaluation, and the results of the statistical interaction evaluation.

2.3.2.6 Statistical Interaction Concepts

Rothman et *al.* stated that "the concept of interaction is that the effect of an exposure, compared with a reference unexposed group, may depend on the presence of one or more other factors". In addition, they specified that the statistical interaction is potentially scale-dependent.(100)

The statistical interaction is equivalent to the concept of effect-measure modification or heterogeneity of effect; this could occur on both additive and multiplicative scales. There is an effect-measure modification, or statistical interaction, on the difference scale (additive scale), when the risk differences are heterogeneous across categories of the other factor. On the other hand, there is an effect-measure modification, or statistical interaction, on the risk ratio scale for the effect (multiplicative scale), when the risk ratios for one factor are heterogeneous across categories of the other factor. Rothman et *al.* demonstrated that if both factors have effects, and there is no modification (heterogeneity) of the risk differences for one factor by the other one, there has to be modification of the risk ratios, and vice versa.(100) In different studies, authors used Rothman demonstration to conclude, for example, there is a multiplicative interaction, when the additive interaction is not evident. In this thesis, we have determined the nature of the statistical interaction based exclusively on the scale(s) used in the study.

In cohort studies, risks and risk ratios can be easily generated and used to evaluate the additive and the multiplicative interactions, respectively. The additive interaction is generally evaluated by using the variation in risk differences known as Interaction Contrast (IC), while risk ratios are used to evaluate the multiplicative interactions. Unfortunately, in case-control and cross-sectional studies, the risks cannot be estimated and the risk ratios cannot be calculated, but odds ratios are calculated and used as approximately equal to risk ratios when the outcome (e.g. lung cancer) is rare. Therefore, the multiplicative interaction is only evaluated (101, 102).

However, Rothman et *al*. proposed three alternative measures based on risk ratios to evaluate the additive interaction: 1) the Rothman's synergy index (*S*; equation 1), 2) the Relative Excess Risk due to Interaction (RERI; equation 2), also known as the Interaction Contrast Ratio (103-105) ICR) and 3) Attributable Proportion due to interaction (AP; equation 3). (106) In the following equations, RR00 is the relative risk of persons not exposed to either factor (reference group), RR10 is the relative risk due to smoking, RR01 is the relative risk due to occupational exposure, and RR11 is the relative risk due to both factors.

S equation is:

$$S = \frac{\mathrm{R11-R00}}{(\mathrm{R10-R00})+(\mathrm{R01-R00})} = \frac{\mathrm{RR11-1}}{(\mathrm{RR10-1})+(\mathrm{RR01-1})} \qquad \text{Equation 1}$$

S is the excess risk from both factors when there is interaction relative to the excess risks of each factor in the absence of the other without interaction. A value of *S* significantly above (or below) one indicates the presence of an additive interaction (103, 104, 107).

RERI equation is:

$$\mathrm{RERI} = \mathrm{ICR} = \frac{\mathrm{IC}}{\mathrm{R00}} = \frac{\mathrm{R11-R10-R01+R00}}{\mathrm{R00}} = \mathrm{RR11} - \mathrm{RR10} - \mathrm{RR01} + 1 \qquad \text{Equation 2}$$

RERI is the excess risk due to interaction relative to the risk without exposure. A value of RERI significantly above or below zero indicates an additive interaction (103-105).

AP equation is:

$$\mathrm{AP} = \frac{\mathrm{R11-R10-R01+R00}}{\mathrm{R11}} = \frac{\mathrm{RR11-RR10-RR01+1}}{\mathrm{RR11}} = \frac{\mathrm{RERI}}{\mathrm{RR11}} \qquad \text{Equation 3}$$

AP is the attributable proportion of disease due to interaction among persons with both exposures. A value of AP that is significantly above zero indicates an additive interaction (103). After the development of these alternative measures, risk ratios were widely used to evaluate additive and multiplicative interactions.

In case-control studies, the odds ratios are approximately equal to risk ratios when the outcome is rare, so authors use them directly to evaluate the additive interaction by substituting risk ratios (RRs) by odds ratios (ORs) in equations. Thus, the three measures of additive interaction based on RRs are properly estimated, only when ORs are good estimates of RRs. In addition, the selection of the measure to evaluate the interaction on a scale is important; AP is the best measure to be used when there is a positive additive interaction, while RERI (ICR) and *S* are the best measures when there is a negative additive interaction (102).

To evaluate the multiplicative interaction, the multiplicativity index (*V*) was developed and used in cohort, case-control and cross-sectional studies. (108) The equation of the multiplicativity index (*V*) is:

$$V = \frac{\mathrm{RR11*RR00}}{\mathrm{RR10*RR01}} \qquad \text{Equation 4}$$

A value of *V* which is statistically greater (or less) than one, indicates a multiplicative interaction (108, 109).

In addition to the multiplicativity index, the Relative Asbestos Effect (RAE) was used to evaluate the multiplicative interaction between smoking and asbestos. The RAE is the effect of smoking on the asbestos effect expressed as the ratio of the risk ratio due to asbestos exposure in non-smokers (RR01) to that in smokers (RR11). This measure is used to examine the heterogeneity of asbestos effect across categories of smoking status, to determine if there is effect-measure modification. If the asbestos effect is the same for non-smokers as for smokers, then the RAE is equal to one, whereas a value greater than one indicates that the effect of asbestos is greater in non-smokers than in smokers (negative multiplicative interaction), and vice versa (110). The equation of RAE is:

$$RAE = \frac{RR01}{RR11} \qquad \text{Equation 5}$$

In 2004, Berry and Liddell proposed a modified measure of Relative Asbestos Effect (RAE_m), defined as the ratio of the excess risk ratio due to asbestos exposure in non-smokers (RR01 – 1) to that in smokers (RR11 – 1). This modified measure was proposed because the original measure (RAE) cannot be generalized as a measure of the interactive effect for the low levels of asbestos exposure. The value of RAE_m would be higher than that of RAE. A value of RAE or RAE_m that is statistically greater (or less) than one, indicates a multiplicative interaction (111).

The equation of RAE_m is:

$$RAE_m = \frac{RR01-1}{RR11-1} \qquad \text{Equation 6}$$

In addition to these measures, logistic and Cox regressions were used to evaluate the multiplicative interaction, by adding an interaction term of occupational exposure and smoking to the model. A significant OR (95% CI) or a significant likelihood ratio test indicates a multiplicative interaction (36, 112, 113).

In epidemiologic studies, researchers examine the additive interaction or multiplicative interaction only for empirical reasons; and usually use the one that shows a better fit to the observations. In fact, statistical interactions are mostly evaluated on multiplicative scale, due to the statistical models used in the analyses (e.g. logistic regression), and that the models generate the multiplicative interaction result directly. If authors are interested in the evaluation of the statistical interaction, they should report results on additive and multiplicative scales. (114)

2.3.2.7 Quality Assessment and Risk of Bias

The Newcastle-Ottawa quality assessment scale (NOS) was used to assess the quality of the design and the conduction of the included studies at the outcome level.(115, 116)

2.3.3 Results

2.3.3.1 Study selection

Using the methodology previously delineated, 2,302 articles were identified for the asbestos-smoking interaction: 1,061 from Scopus, 628 from PubMed, and 613 from Web of Science. In addition, two articles were added from the reference list of the selected articles. 1,028 articles were duplicated and excluded. From the remaining 1,276 articles, 1,250 papers were irrelevant; studies not meeting the inclusion criteria, or meeting the exclusion criteria. After screening phase, 26 full-text articles were assessed for eligibility; 11 articles were excluded because of duplicates population and 15 articles were retained including 6 cohorts, 1 case-cohort study, and 8 case-control studies (Figure 5).

The same methodology was used for silica-smoking and diesel-smoking interactions. In the end, seven articles were included for silica-smoking interaction involving one cohort, one nested case-control study, and five case-control studies (Figure 6). For diesel-smoking interaction, only two articles were included involving one nested case-control study and one pooled case-control study (Figure 7).

The different phases of the study selection for the interactions between the three different occupational exposures and smoking are presented using the PRISMA 2009 flow diagrams.

PRISMA 2009 Flow Diagram

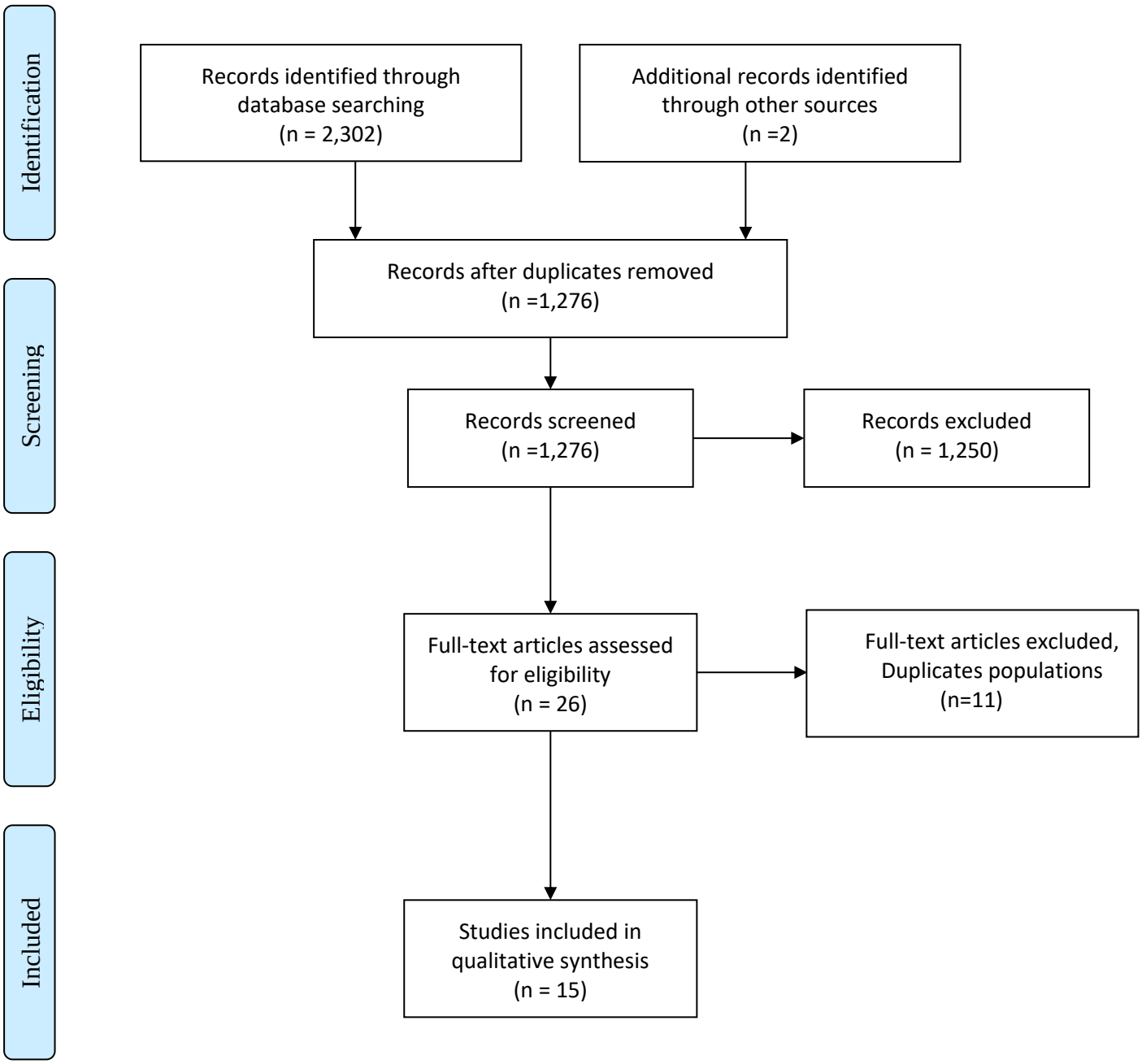

Figure 5 Study selection process for asbestos-smoking interaction.

PRISMA 2009 Flow Diagram

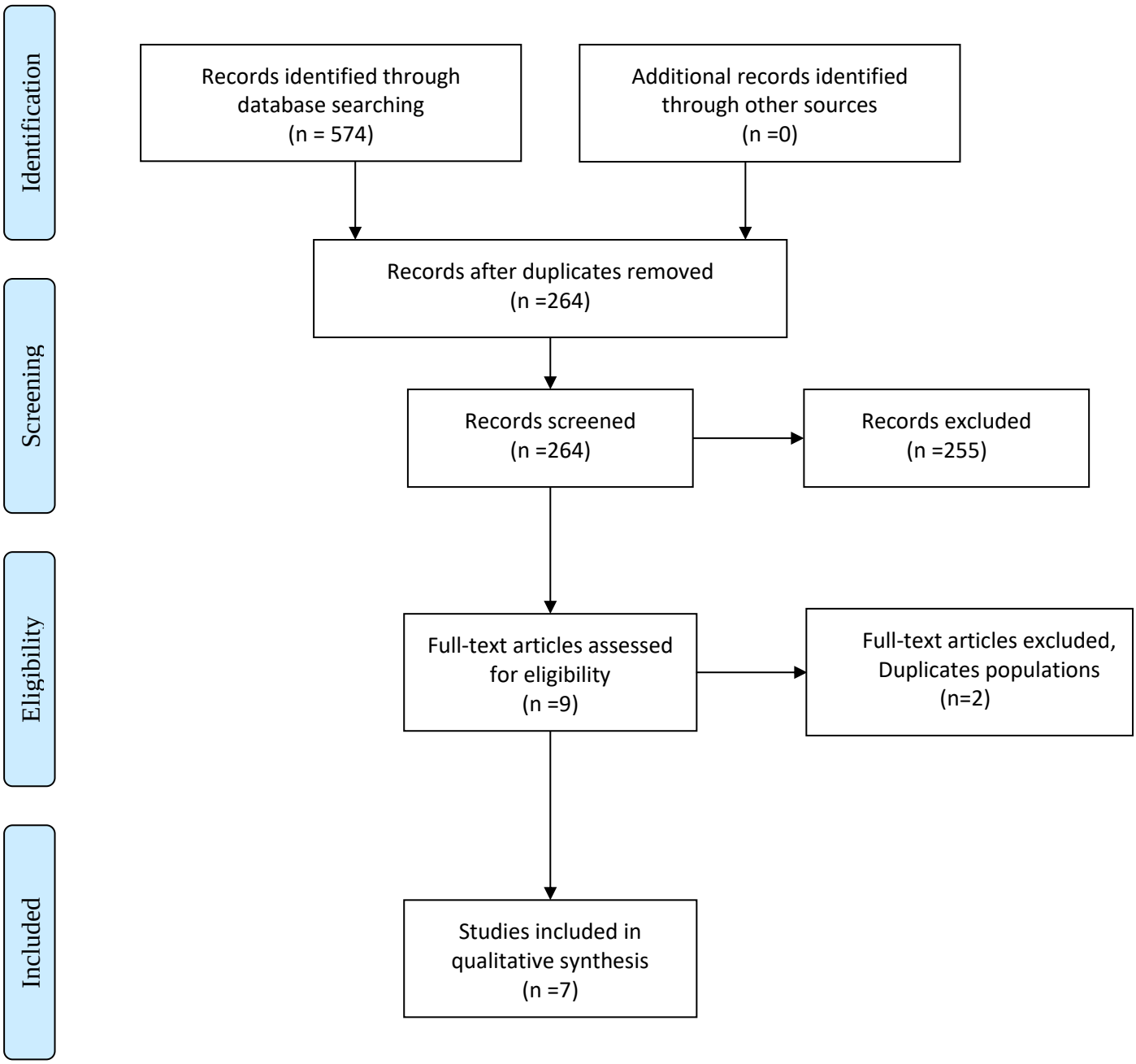

Figure 6 Study selection process for silica-smoking interaction.

PRISMA 2009 Flow Diagram

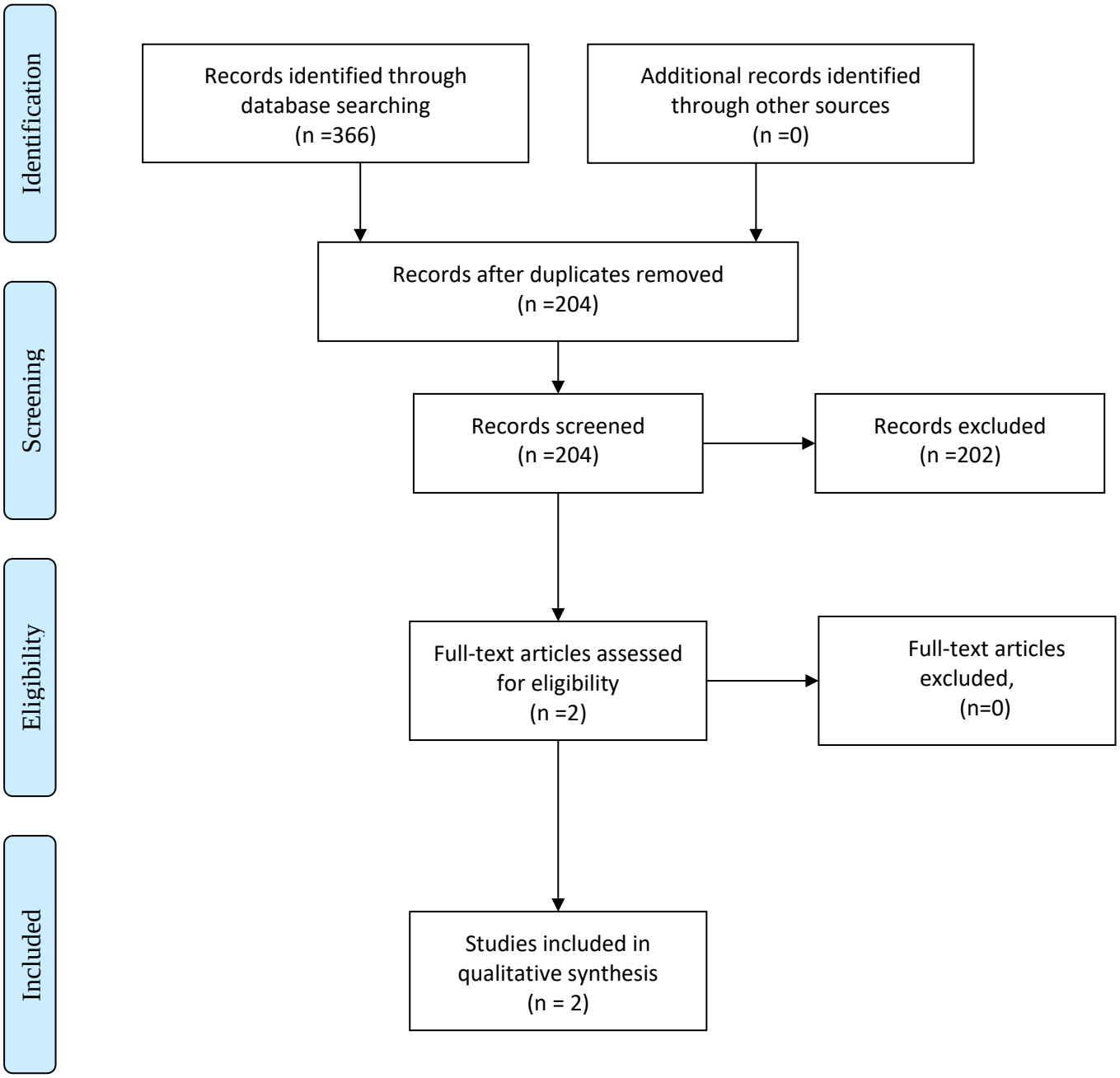

Figure 7 Study selection process for diesel-smoking interaction.

2.3.3.2 Smoking-Asbestos Interaction

2.3.3.2.1 Cohort Studies

The characteristics and the results of the six cohort studies and the case-cohort study evaluating asbestos-smoking statistical interaction are presented in Table 2 and Table 3.

Out of the seven studies, three studies assessed exclusively the multiplicative interaction. The study of Wang et *al.* (2012) evaluated the multiplicative interaction for the chrysotile workers of Qinghai mine in China by calculating the RAE; the RAE value was not significantly less than one [0.52; 95% CI: 0.07-1.11], indicating the absence of multiplicative interaction.(117)

In 2006, the multiplicative interaction was assessed among the crocidolite workers of Wittenoom (Australia). Authors calculated the RAE [1.23; 95% CI: 0.35-4.32] and the RAE_m [1.59; 95% CI: 0.12-20.50], and the results indicated also the absence of multiplicative interaction.(118)

In 1985, Berry et *al.* published a study to evaluate the multiplicative interaction among the asbestos factory workers of East London, where they calculated the RAE and 95% CI. The RAE value [3.0; 95% CI: 0.8-7.5] indicated the absence of multiplicative interaction.(110)

In a study of asbestos workers' cohort in Great Britain, the additive and multiplicative interactions were examined by calculating *S* (95% CI) and *V* (95% CI). The value of *S* [1.4; 95% CI: 1.2-1.6] indicated a positive additive interaction, and the value of *V* [0.9; 95% CI: 0.3-2.4] indicated that absence of multiplicative interaction.(109)

Additive and multiplicative interactions were also examined for the birth cohort of Quebec chrysotile miners and millers by calculating *S* [1.1; CI 95%:0.73-1.41] and RAE [1.69; CI 95%:0.87-3.28], showing the absence of additive and multiplicative interactions.(119)

The case-cohort study conducted by Offermans et *al.* (2014) evaluated the additive and the multiplicative interactions by using the RERI and by introducing a cross-product term in the regression, respectively. The RERI was equal to 0.47 [95% CI: -0.65-1.55] for former smokers, and to 1.94 (95% CI: -0.13-4.89) for smokers, indicating the absence of additive interaction. The researchers had a non-significant *p* value for the cross-product term (p=0.50), indicating the absence of multiplicative interaction.(93)

In addition to this, the additive interaction was assessed for a cohort of Chinese male asbestos plant workers by calculating *S*. The value of *S* [1.41; 95% CI: 0.73-3.99] was not significantly greater than one indicating the absence of additive interaction (120).

Table 2 Description of cohort studies included in the systematic review for the asbestos-smoking interaction

Ref.	Author (Year)	Study Design	Geographic Area	Industry Type	Fiber type	Outcome identification	Asbestos				Smoking			NOS
							Data collection	Exposure Identification	Non Exposed	Exposed	Data collection	Non-Smoker	Smoker	
(110)	Berry (1985)	Prospective	East London (UK)	Asbestos factory	Undetermined	Register	Employment record	Expert	Light and moderate	Severe	Questionnaire	Never	Ever	6
(119)	Liddell (2002)	Prospective	Quebec (Canada)	Mining and Milling	Chrysotile	Death certificate	Employment record	Measures	<30 mpcf.y	≥30 mpcf.y	Questionnaire	Never	Ever	7
(118)	Reid (2006)	Prospective	Wittenoom (Australia)	Mining and Milling	Crocidolite	Register	-Questionnaire -Employment record	Measures	Low	High	Questionnaire	Never and former >20 Y	Current and former <20 Y	8
(109)	Frost (2011)	Prospective	Great Britain	Different types	Undetermined	Register	Questionnaire	Expert	<10 Y	≥30 Y	Questionnaire	Never	Current	8
(117)	Wang (2012)	Prospective	Qinghai (China)	Mining and Milling	Chrysotile	Death certificate	Employment record	Measures	Non-miners and millers	Miners and millers	Interview	Never	Ever	6
(120)	Wang (2012)	Prospective	China	Asbestos factory	Chrysotile	Death certificate	-Employment record -Questionnaire	Measures	Electronics factory	Asbestos cohort	Questionnaire	Never	Ever	7
(93)	Offermans (2014)	Case-cohort	Netherlands	Undetermined	Undetermined	Register	Questionnaire	Matrix	Never	Ever	Questionnaire	Never	Current	7

NOS: the Newcastle-Ottawa quality assessment Scale; **S**: current smokers; **mpcf.y:** million particles per cubic foot x years; **Y**: years.

Table 3 Results of cohort studies included in the systematic review for the asbestos-smoking interaction

Ref.	Author (Year)	Subjects	Cases (sub-cohort)	Follow-up	NS/Exposed	S/Exposed	Interaction Estimation		Interpretation	
							Additive	Multiplicative	Additive	Multiplicative
(110)	Berry (1985)	M: 1250 F: 420	M: 64 F: 15	1971-1980	RR=7.3	RR=2.4	NA	RAE= 3.0 (0.8-7.5)	NA	No
(119)	Liddell (2002)	M: 7279	M: 533	1904-1992	SMR=0.62	SMR=1.71	S=1.1 (0.73-1.41)	RAE=1.69 (0.87-3.28)	No	No
(118)	Reid (2006)	M: 2550 F: 183	M: 132 F: 6	1979-2002	OR=2.02 (0.61–6.72)	OR=1.64 (1.124–2.37)	NA	RAE_m=1.59 (0.12-20.50)	NA	No
(109)	Frost (2011)	M: 93966	M: 1768	1971-2005	RR=1.6 (0.6–4.2)	RR= 26.2 (13.0–53.1)	S=1.4 (1.2-1.6)	V=0.9 (0.3-2.4)	Positive	No
(117)	Wang (2012 a)	M: 1539	M: 50	1981-2006	SMR=1.79 (0.49-6.51)	SMR=5.45 (4.11-7.22)	NA	RAE=0.52 (0.07-1.11)	NA	No
(120)	Wang (2012 b)	M: 577	M: 53	1972-2008	HR=7.52 (0.90-62.79)	HR=17.35 (2.38-126.57)	S= 1.41 (0.73-3.99)	NA	No	NA
(93)	Offermans (2014)	M: 2324	M: 2107	1986-2003	HR=1.79 (1.04–3.08)	HR=10.21 (7.26–14.35)	RERI=1.94 (0.13-4.89)	IT P=0.50	No	No

M: Males, **F**: Females, **S**: smokers, **NS**: non-smokers.
S: Synergy Index, **RERI:** Relative Excess Risk due to Interaction, ***V:*** Multiplicativity Index, **RAE:** Relative Asbestos Effect, **RAE_m**: the Modified Relative Asbestos Effect, **NA:** Not Available.

2.3.3.2.2 Case-control Studies

The characteristics and the results of the eight case-control studies evaluating asbestos-smoking statistical interaction are presented in Table 4 and Table 5.

In the study of Martischnig et *al.* (1977), there was no significant heterogeneity of asbestos RRs across smoking categories, indicating the absence of multiplicative interaction.(121)

In 1978, Blot et *al.* conducted a case-control study to examine the statistical interaction between smoking and asbestos among shipbuilding industry workers. The ORs of asbestos weren't heterogeneous across smoking categories (p>0.1), indicating the absence of multiplicative interaction.(122)

In the study of Jöckel et *al.*, the multiplicative interaction was evaluated by introducing a cross-product term to the logistic regression model. A p value of 0.73 indicates the absence of multiplicative interaction.(123)

In 2002, one case-control study, conducted in Sweden, evaluated the additive and multiplicative interactions. *S* [1.15; 95% IC: 0.77-1.72] showed the absence of an additive interaction, while the OR of product term [0.31; 95% CI: 0.11-0.86] showed the presence of a negative multiplicative interaction.(124)

In 2007, Carel et *al.* published an article including a high number of lung cancer cases (2,205 new males' lung cancer cases), from Central and Eastern Europe (CEE), and from the United Kingdom (UK). There was no heterogeneity among asbestos effects between smokers and non-smokers, in either CEE (p=0.37) or in the UK (p=0.62), indicating the absence of multiplicative interaction.(125)

A population-based case-control of 1,537 incident cases of lung cancer and 1,617 controls examined the multiplicative interaction between smoking and asbestos exposure. The p value of the likelihood ratio test (LRT) of the asbestos–smoking interaction (p=0.19) was used and showed the absence of multiplicative interaction.(36)

In 2012, a study of 1,681 incident cases of lung cancer and 2,053 controls recruited from eight Canadian provinces was published. The additive interaction was examined by *S* and the multiplicative interaction by *V*. The calculated values of the *S* and *V* indices were 2.10 and 0.99, respectively. The 95% CI were not calculated for both indices, so we could not conclude for interactions. Otherwise, the cross-product term between tobacco smoking and asbestos was not statistically significant (p=0.77), indicating the absence of multiplicative interaction.(96)

In 2015, Lacourt *et al.* published a pooled case-control study of two previous studies conducted in Montreal (Canada). 414 lung cancer cases and 321 controls were included to evaluate the association between construction workers and lung cancer. In this study, they evaluated the multiplicative interaction between the exposure of construction workers to asbestos and smoking by introducing a cross-product term in the unconditional logistic regression. The p value of the cross-product term (p=0.68) indicates the absence of a multiplicative interaction.(126)

In conclusion, the cohort and the case-control studies did not reveal any multiplicative interaction when they were assessed, and only one case-control study showed a negative multiplicative interaction. Otherwise, there was absence of enough evidence to conclude for additive interaction.

Table 4 Description of case-control studies included in the systematic review for the asbestos-smoking interaction

				Subjects identification		Asbestos					Smoking		
Ref	Author (Year)	Study Design	Geographic Area	Case	Control	Data collection	Exposure Identification	Non Exposed	Exposed	Data collection	Non Smoker	Smoker	NOS
(121)	Martischnig (1977)	Hospital-based	United Kingdom	Hospital	Hospital	Questionnaire	Expert	No occupational history	Occupational history	Questionnaire	0-14 C/D	> 14 C/D	7
(122)	Blot (1978)	Hospital-based	Coastal Georgia (USA)	-Hospital -Death certificate	Hospital	Interview	Auto-declaration	Not shipbuilder	Shipbuilder	Interview	< 10 C/D	≥ 10 C/D	6
(123)	Jöckel (1998)	Hospital-based	Germany	Hospital	Register	-Questionnaire -Interview	Matrix	Never	Exposed >5280 hours	-Questionnaire -Interview	Never and < 27.1 P.Y	≥ 27.1 P.Y	7
(124)	Gustavsson (2002)	Population-based	Sweden	Register	Register	Self-reported questionnaire	Industrial hygienist	Never	≥1.0 f-years	Self-reported questionnaire	Never	Current	7
(125)	Carel (2007)	Hospital-based	Europe	Hospital	-Hospital -Register	Questionnaire	Expert	Never	Exposed > 1 Y	Questionnaire	Never	Ever	8
(36)	De Matteis (2012)	Population-based	Italy	Hospital	Population databases	Questionnaire	Matrix	Never	Ever	Questionnaire	Never	-Former -Current	6
(96)	Villeneuve (2012)	Population-based	Canada	Register	General population	Self-reported questionnaire	Industrial hygienist	Never	Medium or high	Self-reported questionnaire	<10 P.Y	≥10 P.Y	7
(126)	Lacourt (2015)	Pooled	Montreal (Canada)	Hospital	Population (electoral lists)	Questionnaire	-Chemist -Industrial hygienist	Never	Ever	Questionnaire	Never-low	Medium-heavy	7

NOS: the Newcastle-Ottawa quality assessment Scale; **S**: current smokers; **Y**: years.
C/D: cigarettes per day, **P.Y**: Pack.Year.

Table 5 Results of case-control studies included in the systematic review for the asbestos-smoking interaction

Ref.	Author (Year)	Cases	Controls	Recruitment period	NS /Exposed	S/Exposed	Interaction Estimation		Interpretation	
							Additive	Multiplicative	Additive	Multiplicative
(121)	Martischnig (1977)	M: 201	M: 201	1972-1973	RR=1.08	≥25 C/D: RR=3.26	NA	No heterogeneity of RRs X^2= 2.89; DF =2	NA	No
(122)	Blot (1978)	M: 458	M: 553	1970-1976	RR=1.3	RR=1.7 RR=2.4	NA	No heterogeneity of RRs P>0.10	NA	No
(123)	Jöckel (1998)	M: 839 F: 165	M: 839 F: 165	1988-1993	OR=1.1	OR=6.5 OR=18	NA	IT P=0.73	NA	No
(124)	Gustavsson (2002)	M: 1038	M: 2359	1985-1990	RR=4.2 (1.6-11.1)	RR=28.6 (19.9-48.3)	S=1.15 (0.77-1.72)	IT OR=0.31 (0.11-0.86)	No	Negative
(125)	Carel (2007)	M: 2205	M: 2305	1998-2002	Not shown	Not shown	NA	No modification effect CEE: P=0.37 UK P=0.62.	NA	No
(36)	De Matteis (2012)	M: 1537	M: 1617	2002-2005	OR=2.47 (1.15-5.31)	OR=49.54 (28.18-87.08)	NA	LRT P=0.19	NA	No
(96)	Villeneuve (2012)	M: 1681	M: 2053	1994-1997	OR=2.20 (0.42-11.41)	OR=38.59 (10.78-138.08)	NA	IT P=0.77	NA	No
(126)	Lacourt (2015)	M: 414	M: 321	St.1: 1979-1986 St.2: 1996-1998	OR=1.2 (0.7–2.2)	OR=1.1 (0.8–1.6)	NA	IT P=0.68	NA	No

M: Males, **F**: Females, **S**: Smokers, **NS**: Non-Smokers, **CEE:** Central and Eastern Europe, **St.:** Study.
S: Synergy Index, **LRT:** likelihood ratio test, **IT:** interaction term, **NA:** Not Available.

2.3.3.2.3 Previous meta-analyses and Reviews

In addition to the original studies included in the present systematic review, the statistical interaction between the occupational exposure to asbestos and tobacco smoking was well studied through previous meta-analyses and systematic reviews.

Six meta-analyses relating to the evaluation of statistical interaction between asbestos and smoking were published. The six meta-analyses represented four different groups of individual studies. (111, 127-131) The two studies of Liddell 2001 and Berry and Liddell 2004 included the same 25 original studies and it was the same scenario for the two meta-analyses of Wraith and Mengersen 2007 and 2008 where they included the same 18 studies. (111, 128, 130, 131) The meta-analyses of Liddell 2001 and Wraith and Mengersen 2008 led to the same results as the meta-analyses of Berry and Liddell 2004 and Wraith and Mengersen 2007, respectively.

In 1999, Erren *et al.* published a meta-analysis using 12 epidemiological studies. For each study, the additive interaction was assessed using three different indices: Rothman's Synergy index *(S)*, Relative Excess Risk due to Interaction (RERI), and the attributable proportion due to interaction (AP). In addition, a weighted average of *S* was calculated from 11 studies (one study was excluded); it was 1.66 [95% CI: 1.33-2.06], significantly greater than one, indicating the presence of a positive additive interaction. (127)

In 2004, Berry and Liddell published a meta-analysis to evaluate the multiplicative interaction using the Modified version of the relative asbestos effect (RAE_{m}). The best estimation of the combined RAE_{m} was equal to 3.19 [95% CI: 1.67-6.13], significantly greater than one, indicating a negative multiplicative interaction. (111)

In 2007, Wraith and Mengersen published a meta-analysis to evaluate the statistical interaction using a Bayesian approach. They revised articles from both literature reviews of Lee's (2001) (108) and Liddell's (2001) (128). For each study included, they calculated separately Rothman's Synergy index (*S*) and the multiplicativity index (*V*). Using the Bayesian multivariate analysis, the combined *S* and *V* were 1.94 [95% CI: 1.29-2.84] and 0.83 [95% CI: 0.46-1.40], respectively. The results indicated the presence of a positive additive interaction, and the absence of a multiplicative interaction. (131)

In 2015, Ngamwong et *al.* published a meta-analysis and systematic review to evaluate the statistical interaction between smoking and occupational exposure to asbestos. 7 cohort and 10 case-control studies were included in the analysis. *S* [1.44; 95% CI: 1.26–1.77] and *V* [0.91; 95% CI: 0.63–1.30] were calculated indicating a positive additive interaction, but absence of multiplicative interaction. Although that authors included a study of environmental exposure to asbestos (132), this study can be used to demonstrate the presence of a positive additive interaction between smoking and occupational exposure to asbestos. (129)

On the other hand, five literature reviews were published to examine the interaction between asbestos and tobacco smoking.

In 1977, Saracci published a literature review where he used three models to assess the statistical interaction in each study: cumulative model, additive model and multiplicative model. Seven studies were reviewed, and the author expressed that the multiplicative scale was shown to fit best. In addition, Saracci mentioned that the multiplicative scale seemed more plausible as it was also compatible with a multi-stage carcinogenic mechanism and with the results of the experiments on animals (rats). He declared that from biology and public health points of view, the presence of a multiplicative interaction meant that tobacco smoking and

asbestos were separately capable to induce lung cancer, and that they acted in synergy when intervening simultaneously.(133) In 1987, Saracci published another review where he concluded that the interaction was multiplicative rather than additive.(134)

In 1986, Steenland and Thun revised eight epidemiological studies that evaluated the statistical interaction between smoking and exposure to asbestos and the resulting effect on lung cancer. They considered that only four studies provided sufficient information to assess the statistical interaction, but the results were contradictory.(135)

In 1994, Vainio and Boffetta published a literature review to study the mechanisms of the combined effect between asbestos and smoking in the etiology of lung cancer. They identified the presence of a multiplicative interaction between tobacco smoking and exposure to asbestos.(136)

In 2001, Lee published a literature review of 23 studies reporting epidemiological data on lung cancer analyzing the effect of the statistical interaction between tobacco smoking and exposure to asbestos. For each study, they evaluated the additive and multiplicative interactions. This review showed that the exposure to asbestos increased the risk of lung cancer among non-smokers, and that the interaction between exposure to asbestos and tobacco smoking on lung cancer was multiplicative rather than additive.(108)

In general, the analysis of the original studies included in this thesis was consistent with the previous meta-analyses findings; there was absence of multiplicative statistical interaction between occupational asbestos exposure and tobacco smoking.

2.3.3.3 Smoking-Silica Interaction

2.3.3.3.1 Cohort and Nested Case-control Study

The characteristics and the results of the studies evaluating silica-smoking statistical interaction are presented in table 6 and 7.

One cohort and one nested case-control study were reviewed and included. In 2013, Liu et *al.* published an article where the authors evaluated the additive interaction between tobacco smoking and exposure to silica by calculating the RERI, and the multiplicative interaction by adding a cross-product term of tobacco smoking and exposure to silica to the Cox proportional hazard model. RERI was 0.98 [95% CI: 0.23-1.74], and the cross-product term was not statistically significant (p=0.25), indicating the absence of additive and multiplicative interactions.(57)

In the nested case-control study, the authors examined the multiplicative interaction by adding a cross-product term of silica exposure and smoking to the logistic regression. The cross-product term was not statistically significant (p=0.57), showing the absence of a multiplicative interaction.(137)

2.3.3.3.2 Case-control studies

Five case-control studies were reviewed to assess the silica-smoking statistical interaction presented in Table 6 and Table 7.

In 2007, Cassidy et *al.* published a multicenter case-control study in Europe of 2,852 newly diagnosed cases of lung cancer and 3,104 controls in 7 European countries. The ORs of silica

weren't heterogeneous across smoking categories, indicating the absence of multiplicative interaction (*p*=0.37).(94)

A publication of the EAGLE study (Italy) was published in 2012 by De Matteis et *al.*, where the multiplicative interaction between silica and smoking was evaluated. The *p* value of the LRT for the silica–smoking interaction (*p*=0.94) was not statistically significant, indicating the absence of multiplicative interaction.(36).

In 2014, Kachuri et *al.* conducted a population-based case-control study in eight Canadian provinces and they assessed the additive and the multiplicative interactions. They had *S* = 2.38 [95% CI: 1.35-4.21] and *V* = 3.59 [95% CI: 1.51-8.49], revealing positive additive and positive multiplicative interactions.(97).

In 2015, Consonni et *al.* published a pooled case-control study (SYNERGY study) to evaluate the additive interaction between bricklayers and smoking by calculating RERI (95% IC), and the multiplicative interaction by adding a cross-product term between bricklayers and smoking in the logistic regression. The RERI [6.80; 95% CI: 4.36-9.62] showed positive additive interaction. Otherwise, the ORs of the cross-product term [1.37; 95% CI: 0.76-2.45; *p*=0.28] was not statistically significant, indicating the absence of multiplicative interaction. (138)

A study published by Lacourt et *al.* in 2015, evaluated the multiplicative interaction between the exposure of construction workers to crystalline silica and smoking. The *p* value of the cross-product term was significant (*p*=0.02), and the effect of occupational exposure to crystalline silica was higher for non/light smokers than for medium/heavy smoker, indicated a negative multiplicative interaction.(126)

In conclusion, the cohort, the nested case-control, and the majority of case-control studies indicated the absence of multiplicative interaction between crystalline silica and tobacco smoking. There was limited evidence to conclude for additive interaction.

2.3.3.3.3 Previous Literature Review

In 2009, Brown published a literature review on the complex statistical interactions between exposure to crystalline silica, smoking, silicosis and lung cancer (41). Several studies showed that smokers who were exposed to crystalline silica dust developed more frequently silicosis than non-smokers exposed to the same dose. The author stated that statistical interaction between smoking and occupational exposure to silica was not clear. (139)

2.3.3.4 Smoking-Diesel Interaction

Only two articles assessed the diesel-smoking statistical interaction were included (Table 6 and Table 7).

2.3.3.4.1 Nested case-control study

In 2012, Silverman et *al.* published a nested case-control study within a cohort of 12,315 workers in eight non-metal mining facilities in the US. The *p* value for the cross-product term (*p*=0.08) between exposure to diesel and smoking indicated the absence of multiplicative interaction.(140)

2.3.3.4.2 Case-control Study

In 2012, Pintos et *al.* published a pooled case-control study, of two case-control studies in the general population, conducted in Montreal, Canada. The multiplicative interaction was examined by adding a cross-product term of diesel and smoking to the logistic regression model. The OR for the product term [1.15; 95% CI: 0.5-2.7] wasn't significantly greater than one, indicating the absence of multiplicative interaction.(141)

The results of the two studies evaluating the interaction between tobacco smoking and diesel engine exhaust emissions showed the absence of a multiplicative interaction.

Table 6 Description of silica-smoking and diesel-smoking interaction studies included in the systematic review

Ref.	Author (Year)	Study Design	Geographic Area	Industry type	Outcome identification	Silica				Smoking			NOS
						Data collection	Exposure Identification	Non exposed	Exposed	Data collection	Non-Smoker	Smoker	
Silica-smoking interaction studies													
(57)	Liu (2013)	Prospective cohort	China	Metal mines and pottery factories	-Hospital record -Death certificate	Employment record	Matrix	Never	Ever	Interview	Never	Ever	8
(137)	Fu (1994)	Nested case-control	Guangxi province(China)	Tin miners	Death Certificate	-Employment record -Questionnaire	Expert	Never	YUED	Questionnaire	Never	P.Y	7
(94)	Cassidy (2007)	Multicenter hospital-based case-control	Europe	Undetermined	Hospital	Questionnaire	Industrial hygienist	Never	Ever	Questionnaire	Never	-Former -Current	7
(36)	De Matteis (2012)	Population-based case-control	Italy	Undetermined	Hospital	-Questionnaire -Interview	Matrix	Never	Ever	-Questionnaire -Interview	Never	-Former -Current	6
(97)	Kachuri (2014)	Population-based case-control	Canada	Undetermined	Register	Self-reported questionnaire	Industrial hygienist	Never	≥ 30 Y	Self-reported questionnaire	< 10 P.Y	≥ 40 P.Y	8
(138)	Consonni (2015)	Pooled case-control	Europe, Canada, Hong Kong and New Zealand	Bricklayers	-Register -Hospital	Questionnaire	Matrix	Never bricklayers	Ever bricklayers	Questionnaire	Never	Ever	8
(126)	Lacourt (2015)	Pooled case-control	Montreal (Canada)	Construction	Hospital	Questionnaire	Expert	Never	Substantial	Questionnaire	Never-low	Medium-heavy	7
Diesel-smoking interaction studies													
(140)	Silverman (2012)	Nested case-control	USA	Non-metal mining facilities	-Register -Death certificate	Computer-assisted telephone interview	Measures	Never	Tertiles	Computer-assisted telephone interview	Never	≥ 2 P.D	8
(141)	Pintos (2012)	Pooled case-control	Canada	Wide range of occupations and industries	Incident case	Questionnaire	-Chemist -Industrial hygienist	Never	Substantial	Questionnaire	Never-low (0-15 P.Y)	Medium-heavy (> 15 P.Y)	7

NOS: the Newcastle-Ottawa quality assessment Scale; **S**: current smokers; **Y**: years.
YUED: Years of Underground Exposure to Dust, **P.Y**: Pack.Year;

Table 7 Results of silica-smoking and diesel-smoking interaction studies included in the systematic review

Ref.	Author (Year)	Subjects (cases)	Cases (controls)	Period*	NS/Exposed	S/Exposed	Interaction Estimation		Interpretation	
							Additive	Multiplicative	Additive	Multiplicative
Silica-smoking interaction studies										
(57)	Liu (2013)	34018	546	1960-2003	HR=1.10 (0.68-1.78)	HR=3.83 (2.48-5.90)	RERI=0.98 (0.23-1.74)	IT P = 0.25	No	No
(137)	Fu (1994)	M: 79	M: 188	1973-1989	NA	NA	NA	IT P = 0.57	NA	No
(94)	Cassidy (2007)	M: 2197 F: 655	M: 2295 F: 809	1998-2002	OR=1.41 (0.79 -2.49)	OR=1.41 (1.07-1.87)	NA	Test for Heterogeneity P = 0.37	NA	No
(36)	De Matteis (2012)	M: 1537	M: 1617	2002-2005	OR=1.41 (0.51-3.91)	OR=44.98 (27.15-74.52)	NA	LRT P=0.94	NA	No
(97)	Kachuri (2014)	M: 1681	M: 2053	1994-1997	OR=0.63 (0.26-1.52)	OR=42.53 (23.54-76.83)	S=2.38 (1.35-4.21)	V=3.59 (1.51-8.49)	Positive	Positive
(138)	Consonni (2015)	M: 15608	M: 18531	1985-2010	OR=1.18	OR=18.5	RERI=6.80 (4.36-9.62)	IT P= 0.28	Positive	No
(126)	Lacourt (2015)	M: 241	M: 196	St.1: 1979-1986 St.2: 1996-1998	OR=3.1 (1.0–9.6)	OR=1.4 (0.7–2.7)	NA	IT P=0.02	NA	Negative
Diesel-smoking interaction studies										
(140)	Silverman (2012)	M: 198	M: 562 Ma	1947-1977	OR=7.30 (1.46- 36.57)	OR=17.38 (3.48-86.73)	NA	IT P=0.086	NA	No
(141)	Pintos (2012)	St. I: M: 857 St. II: M: 736	St. I: M: 533 St. II: M: 894	St. I: 1979-1986 St. II: 1996-2001	OR=2.29 (1.1-4.6)	OR=9.84 (6.4-15.1)	NA	IT OR=1.15 (0.5-2.7)	NA	No

M: Males, **F**: Females, **S**: Smokers, **NS**: Non-Smokers.
S: Synergy Index, ***V:*** Multiplicativity Index, **RERI:** Relative Excess Risk due to Interaction, **LRT:** likelihood ratio test, **IT:** interaction term, **NA:** Not Available.
*****: Follow-up or recruitment period

2.3.4 Discussion

Overall, this review suggests the absence of a multiplicative statistical interaction between the three most frequent occupational lung carcinogens, asbestos, crystalline silica and diesel engine exhaust emissions and tobacco smoking. On the other side, there is no enough evidence from the literature to conclude on the additive statistical interaction.

Four meta-analyses were conducted to evaluate the asbestos-smoking statistical interaction; one demonstrated a negative multiplicative interaction (111), and three suggested the presence of a positive additive interaction (127, 129, 131). The most recent systematic review published in 2015 indicated the presence of a positive additive interaction and the absence of multiplicative interaction (129). The presence of a positive additive interaction is less clear in the present systematic review. Out of the five studies were included and evaluated the additive interaction, only one study showed a positive additive interaction. This discordance could mainly be attribute to methodological differences in each study. In the present systematic review, we only included and evaluated studies that reported both the interaction results on a specified scale (multiplicative or additive) and the significance of the results, either in terms of confidence intervals or p-value, while the previous meta-analysis included studies from which authors could calculated odds ratios or relative risks and then assessed the statistical interaction (129). In the present systematic review, we did not perform a meta-analysis since it was not the primary aim of this study to focus exclusively on the asbestos-smoking statistical interaction, but instead we aimed to assess the statistical interactions between the most frequent occupational lung carcinogen and tobacco-smoking. Despite the recent publication of a meta-analysis assessing the asbestos-smoking statistical interaction, performing a new one using more stringent inclusion criteria for studies should be considered.

The inconsistency of the statistical interaction results between studies may come from methodological differences adopted in each study. Every study has limitations that could be the source of opposite results on the interaction evaluation. In the studies that were included, occupational histories and smoking details were collected using employment records or questionnaires. The reliability of the data may have been affected by the quality of the documentation in the records and by the recall bias from the questionnaires used to collect retrospective data. Although the data collection could be complete and accurate, the methods used to identify and assess occupational exposures may also have been a source of bias. For example; the utilization of a job-exposure matrix (JEM) could introduce non-differential misclassifications leading to a large number of false-positives and false-negatives. In consequence, there is a risk of underestimated risks that could affect the evaluation of the interaction.(77, 142)

When evaluating interactions, the method and the scale used to examine the interaction should be reported to avoid confusion and ambiguity and facilitate the comparison between studies.(143) In fact, the best approach is to evaluate the statistical interaction on both additive and multiplicative scales.(114) The additive interaction is generally evaluated by using the difference of risk differences known as interaction contrast, while risk ratios are used to evaluate the multiplicative interactions. In cohort studies, risks and risk ratios can be easily generated, but in the case-control studies only the odds ratios can be estimated. Using odds ratios instead of risk ratios to evaluate the additive or the multiplicative interaction could mistakenly show the presence of a positive interaction, even if the outcome is rare.(144, 145) The majority of the reviewed case-control studies evaluated exclusively the multiplicative interaction by testing the significance of the interaction term introduced into the regression model. However, while rarely used, some authors have proposed various measures to assess the additive interaction from case-

control data using logistic regression models.(103, 104, 146, 147) Additionally, discrepancy between studies may be explained by the measures used to assess the statistical additive interaction as each measure has its own interpretation. Indeed, Rothman et *al.* and Kalilani et *al.* suggested to use simultaneously three measures of interaction to evaluate the additive interaction: the attributable proportion due to interaction (AP), the relative excess risk due to interaction (RERI), and the Rothman's synergy index (S).(102, 106) Although, the attributable proportion due to interaction (AP) is the most robust measure to evaluate the additive interaction when the odds ratios are used instead of the risk ratios in the equation.(102) Because of its more intuitive interpretation, the Rothman's synergy index (S) (148) was used in the majority of the included studies to evaluate the additive statistical interaction even when odds ratios were used instead of risk ratios. Specific measures of interaction have been proposed to assess the statistical multiplicative interaction between asbestos exposure and tobacco smoking. The RAE was proposed to evaluate the asbestos-smoking multiplicative interaction in cohort studies.(110) However it was shown that the RAE tended to be underestimated in studies with low level of asbestos exposure. Thus, a modified version of the RAE (RAEm) have been proposed to assess the asbestos-smoking multiplicative interaction in studies with low asbestos exposure level.(111)

In many of the reviewed articles, the conclusion regarding the statistical interaction was not always consistent with the results of the evaluation; authors suggested the presence of a positive interaction without evaluating the statistically significance of the measure, or conclude on both scales although the interaction was evaluated on one scale. The same findings was discussed by Liddell (2001); authors continue to suggest the presence of a positive multiplicative asbestos-smoking interaction without enough or strong evidence from their results or from the literature.(128)

Statistical interaction (whatever the model, multiplicative or additive) between two risk factors increases cancer risk compared to risk related to each factor acting independently. Two main impacts can be considered from a public health point of view. First, regarding primary prevention, reducing exposure to those two risk factors will induce a greater benefice (number of avoided incident cases) if there is a significant interaction between those two factors. Secondly, regarding targeted screening program (screening proposed to a selected population according to a specific risk threshold), the existence of an interaction will decrease the level of exposure of those two factors corresponding to the defined risk threshold. The same argument could be applied to individual imputability used in compensation system. Therefore, the knowledge of a statistical interaction between two risk factors is crucial and the knowledge of the interaction scale (i.e. multiplicative or additive) is important to conduct risk assessment and risk management. Besides, in the light of the current knowledge, the statistical interaction between two factors do not allow to infer strong hypothesis about biological mechanisms.

In the current review, our conclusions are based on strong evidence, as the majority of the reviewed studies conclude the absence of the multiplicative interaction. In addition, all precautions were taken to avoid missing papers; three different bibliographic databases were used and each reference list of all included studies was reviewed. Finally, we believe that the publication bias is limited as several papers with negative results were published.

Overall, the evidence from the literature on the association of the occupational exposures to asbestos and to crystalline silica with the phenotypes of lung cancer (histological type, tumor location and age at diagnosis) was very limited. Furthermore, studies evaluated the interaction between tobacco smoking and occupational exposures to asbestos and

crystalline silica according to the phenotypes of lung cancer were also limited. Thus, we conducted a study (CaProMat study) to increase the knowledge on this topic.

2.3.5 Article 1 (Accepted - BMC Public Health)

Absence of Multiplicative Interactions between Occupational Lung Carcinogens and Tobacco Smoking: A Systematic Review Involving Asbestos, Crystalline Silica and Diesel Engine Exhaust Emissions.

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Abstract:

Background: Tobacco smoking is the main cause of lung cancer, but it is not the sole causal factor. Significant proportions of workers are smokers and exposed to occupational lung carcinogens. This study aims to systematically review the statistical interaction between occupational lung carcinogens and tobacco smoking, in particular asbestos, crystalline silica and diesel engine exhaust emissions.
Methods: Articles were identified using Scopus, PubMed, and Web of Science, and were limited to those published in English or French, without limitation of time. The reference list of selected studies was reviewed to identify other relevant papers. One reviewer selected the articles based on the inclusion and exclusion criteria. Two reviewers checked the eligibility of articles to be included in the systematic review. Data were extracted by one reviewer and revised by two other reviewers. Cohorts and case-control studies were analyzed separately. The risk of bias was evaluated for each study based on the outcome. The results of the interaction between the tobacco smoking and each carcinogen was evaluated and reported separately.
Results: Fifteen original studies were included for asbestos-smoking interaction, seven for silica-smoking interaction and two for diesel-smoking interaction. The results suggested the absence of multiplicative interaction between the three occupational lung carcinogens and smoking. There is no enough evidence from the literature to conclude for the additive interaction. We believe there is a limited risk of publication bias as several studies reported negative results were published.
Conclusion: there are no multiplicative interactions between the tobacco smoking and occupational lung carcinogens, in particular asbestos, crystalline silica and diesel engine exhaust emissions. Even though, specific programs should be developed and promoted to reduce concomitantly the exposure to occupational lung carcinogens and tobacco smoking.
Keywords: Lung cancer, Interaction, Smoking, Occupational exposures.

INTRODUCTION

Lung cancer remains the leading cause of cancer deaths among males and females. [1, 2] In 1986, the International Agency for Research on Cancer (IARC) classified tobacco smoking as a lung carcinogen [3], it was identified as the main cause of lung cancer, and it was found to account for 80 to 90% of the cases [4, 5]. However tobacco smoking is not the sole causal factor of lung cancer. Indeed, lung cancer cases have been identified in non-smokers groups but exposed to different types of occupational exposures [6]. In the last update of IARC, almost 29 agents were classified as lung carcinogens with sufficient evidence in humans [7]. Many of them are found in occupational settings such as all forms of asbestos, crystalline silica and diesel engine exhaust emissions, which are among the top most frequent occupational exposures.[8-11]

The rate of smoking is higher among blue-collar workers than white-collar workers [12]. Thus a significant proportion of workers are concomitantly exposed to occupational lung carcinogens and to tobacco smoking. This brings into light the importance of studying the statistical interactions between the occupational exposures and tobacco smoking.

In fact, the statistical interaction between the occupational exposure to asbestos and tobacco smoking was well studied through systematic reviews and meta-analyses, indicating the presence of a positive additive statistical interaction.[13-15] In the other hand, no systematic reviews were conducted to evaluate the statistical interactions between occupational exposure to crystalline silica and tobacco smoking or between diesel engine exhaust emissions and tobacco smoking.

Determine the nature of the statistical interaction between the occupational exposures and tobacco smoking is of high interest from a public health perspective, in particular to develop prevention programs. Therefore, we conducted a review on the interaction between the three most important occupational lung carcinogens, namely asbestos, crystalline silica and diesel engine exhaust

emissions and tobacco smoking to define if the interaction nature is similar irrespective to the lung carcinogen, or if the interaction nature is specific for each carcinogen.

The objective of this study is to evaluate the statistical interactions between the occupational exposures and tobacco smoking, with limitation to the three principal lung carcinogens; asbestos, crystalline silica and diesel engine exhaust emissions, through a systematic review including cohort and case-control studies.

METHODS

This systematic review was reported based on the PRISMA checklist (2009) and the PRISMA-P for developing review protocols (2015).[16, 17]

Search Strategy

Articles reviewed in this paper were identified using three bibliographic databases: PubMed, Scopus and Web of Science. The selected studies were limited to those published in English or French, without limitation to time. The most recent research was conducted in June 30, 2016.

For asbestos-tobacco, silica-tobacco and diesel-tobacco statistical interactions, all records of the three bibliographic databases were searched using the following key words respectively: ["asbestos" and "lung cancer" and "smoking"], ["silica" and "lung cancer" and "smoking"], and ["diesel" and "lung cancer" and "smoking"].

Inclusion Criteria

Studies were included in this review if they met the following criteria: human studies, studies published in peer-reviewed journals, cohort or case-control studies, studies evaluating the statistical interaction between tobacco smoking and one of the three studied occupational exposures on lung cancer, studies reporting the occupational exposure assessment, studies reporting the smoking behavior assessment, studies reporting the statistical analysis performed to assess the statistical interaction, and studies reporting the results of the statistical interaction and their statistical significance (P-value or CI 95%). For studies analyzing the same population, the most recently published article evaluating the statistical interaction that met all of the previous criteria was included.

Exclusion Criteria

In general, studies not meeting the inclusion criteria were excluded: clinical trials, in vitro studies, animal studies, cross-sectional studies, systematic reviews, meta-analyses, case reports and case series. Articles studying the statistical interactions between environmental exposures to asbestos, crystalline silica and diesel engine exhaust emissions and tobacco smoking on lung cancer were also excluded. Finally, articles that investigated the statistical interactions between asbestosis, silicosis, and smoking without taking into consideration asbestos and crystalline silica exposures were also excluded.

Articles Selection Process

Records identified through the three bibliographic databases were checked for duplications. Duplicated records were removed, and the remaining records were screened to distinguish those met the inclusion criteria. The screening phase was done in three steps: 1) selection of articles that studied the association between one of the three occupational exposures and lung cancer, 2) selection of the articles that studied the interaction based on the title or the abstract, and 3) for the

remaining articles, the full-text was screened to select studies that evaluated the interaction between one of the three occupational exposures and smoking. The reference list of the selected articles was reviewed to identify other relevant articles. The full-text articles remained was assessed for eligibility to determine the final list of articles included in the qualitative synthesis.

Data Extraction

Data extraction was performed by one author (MZ), and reviewed by two other authors (FD and AL). The following data were extracted from each study included in the present review : first author, publication year, geographic area, study type (prospective cohort study, retrospective cohort study, nested case-control study, population-based case-control study, hospital-based case-control study), exposure type, industry type, total number of subjects (population and cases/cases and controls), the method to collect the occupational exposure and smoking status details, the definition of occupational exposure, the definition of smoking status, the outcome (lung cancer) classification, the methodology of the statistical interaction evaluation, and the results of the statistical interaction evaluation.

Statistical Interaction Concepts

Rothman et *al.* stated that "the concept of interaction is that the effect of an exposure, compared with a reference unexposed group, may depend on the presence of one or more other factors". In addition, they specified that the statistical interaction is potentially scale-dependent.[18] In epidemiologic studies, researchers examine the additive interaction or multiplicative interaction only for empirical reasons; and usually use the one that shows a better fit to the observations. In fact, statistical interactions are mostly evaluated on multiplicative scale, due to the statistical models used in the analyses (e.g. logistic regression), and that the models generate the multiplicative interaction result directly. If authors are interested in the evaluation of the statistical interaction, they should report results on additive and multiplicative scales.[19] The methods of the statistical interaction evaluation used in the original papers are described in more detail [see Additional file 1].

Quality Assessment and Risk of Bias

The Newcastle-Ottawa quality assessment scale (NOS) was used to assess the quality of the design and the conduction of the included studies at the outcome level.[20, 21]

RESULTS

Study selection

Using the methodology previously delineated, 2,302 articles were identified for the asbestos-smoking interaction: 1,061 from Scopus, 628 from PubMed, and 613 from Web of Science. In addition, two articles were added from the reference list of the selected articles. 1,028 articles were duplicated and excluded. From the remaining 1,276 articles, 1,250 papers were irrelevant; studies not meeting the inclusion criteria, or meeting the exclusion criteria. After screening phase, 26 full-text articles were assessed for eligibility; 11 articles were excluded because of duplicates population and 15 articles were retained including 6 cohorts, 1 case-cohort study, and 8 case-control studies (figure 1).

The same methodology was used for silica-smoking and diesel-smoking interactions. In the end, seven articles were included for silica-smoking interaction involving one cohort, one nested case-control study, and five case-control studies (figure 2). For diesel-smoking interaction, only two

articles were included involving one nested case-control study and one pooled case-control study (figure 3).

The different phases of the study selection for the interactions between the three different occupational exposures and smoking are presented using the PRISMA 2009 flow diagrams.[16]

Occupational Exposures and Tobacco Smoking Interactions

Asbestos-smoking statistical interaction

The characteristics and the results of the six cohort studies and the case-cohort study evaluating asbestos-smoking statistical interaction are presented in tables 1a and 1b. Out of the seven studies, six studies assessed the multiplicative interaction; Multiplicative interaction was evaluated for the chrysotile workers of Qinghai mine in China [22], the crocidolite workers of Wittenoom mine in Australia [23], and the asbestos factory workers of East London [24]. The relative asbestos effect (RAE) with 95% confidence interval was calculated in the three studies, indicating the absence of a multiplicative interaction [22-24]. Additive and multiplicative interactions were evaluated for asbestos workers cohort in Great Britain [25]. Results showed that there is a positive additive interaction, but an absence of multiplicative interaction [25]. Additive and multiplicative interactions were also examined for the birth cohort of Quebec chrysotile miners and millers by calculating Rothman's synergy index (S) and RAE, showing the absence of additive and multiplicative interactions [26]. The case-cohort study evaluated the interactions and showed the absence of additive and multiplicative interactions [27]. The additive interaction was assessed for a cohort of Chinese male asbestos plant workers by calculating S. The value of S was not significantly greater than one indicating the absence of additive interaction [28].

The characteristics and the results of the eight case-control studies evaluating asbestos-smoking statistical interaction are presented in tables 2a and 2b. Seven of those studies did not reveal any multiplicative interaction when they were assessed [6, 29-34]. One case-control study, conducted in Sweden, evaluated the additive and multiplicative interactions and showed the absence of an additive interaction, and the presence of a negative multiplicative interaction [35].

Silica-smoking statistical interaction

The characteristics and the results of the studies evaluating silica-smoking statistical interaction are presented in table 3a and 3b. One cohort and one nested case-control study were reviewed and included. The cohort study, published in 2013, evaluated the additive and the multiplicative silica-smoking statistical interaction. The results of this study indicated the absence of additive and multiplicative interactions [36]. The nested case-control study examined the multiplicative interaction by adding an interaction term of crystalline silica exposure and smoking to the logistic regression, and showing the absence of a multiplicative interaction [37].

Five case-control studies were reviewed in this study to assess the silica-smoking statistical interaction. Two studies, one conducted in several centers in Europe and the other in Italy, showed that there is no multiplicative interaction [6, 38]. A study published in 2015, evaluated the multiplicative interaction between the exposure of construction workers to crystalline silica and smoking. The study showed a negative multiplicative interaction; the effect of occupational exposure to crystalline silica was higher for non/light smokers than for medium/heavy smokers [34]. A population-based case-control study in eight Canadian provinces showed positive additive and positive multiplicative interactions [39]. Another pooled case-control study (SYNERGY study) showed positive additive interaction, but no multiplicative interaction [40].

Diesel-smoking statistical interaction

Only two articles assessed the diesel-smoking statistical interaction were included in our review (table 3a). These two studies presented a nested case-control study of the workers of eight non-metal mining facilities in United States [41] and a pooled case control study conducted in Montreal (Canada) [42].The results of these two studies (table 3b) showed the absence of a multiplicative interaction.[41, 42]

DISCUSSION

Overall, this review suggests the absence of a multiplicative statistical interaction between the three most frequent occupational lung carcinogens, asbestos, crystalline silica and diesel engine exhaust emissions and tobacco smoking. On the other side, there is no enough evidence from the literature to conclude on the additive statistical interaction.

Asbestos-smoking statistical interaction

Four meta-analyses were conducted to evaluate the asbestos-smoking statistical interaction; one demonstrated a negative multiplicative interaction [43], and three suggested the presence of a positive additive interaction [13-15]. The most recent systematic review published in 2015 indicated the presence of a positive additive interaction and the absence of multiplicative interaction [15]. While we agreed about the absence of a multiplicative interaction, from this systematic review, the presence of a positive additive interaction is less clear. Indeed, out of the five original studies included in this review, only one showed a significant positive additive interaction. This discordance is mainly attributable to selection criteria of original studies. While in the most recent meta-analysis, authors included all studies from which they could assess statistical interaction from odds ratios or relative risks reported in the original studies without any notion of statistical significance [15], in the present systematic review, we add more stringent inclusion criteria. Indeed, we only included and evaluated studies that reported both the interaction results on a specified scale (multiplicative or additive) and the significance of the results, either in terms of confidence intervals or p-value. However, conclusions from our study are based on a systematic review of the literature and we did not perform a meta-analysis since it was not the primary aim of this study to focus exclusively on the asbestos-smoking statistical interaction. Instead, the present study aimed at assessing the statistical interactions between the most frequent occupational lung carcinogen and tobacco-smoking. Despite the recent publication of a meta-analysis assessing the asbestos-smoking statistical interaction, performing a new one using more stringent inclusion criteria for studies should be considered.

Silica-smoking and diesel-smoking statistical interaction

Similarly to asbestos-smoking statistical interaction, for both silica-smoking as well as diesel-smoking statistical interaction, the absence of a multiplicative statistical interaction seems to be consensual. Regarding additive interaction, for both silica-smoking and diesel-smoking statistical interaction, it is impossible to conclude on the presence of a statistical interaction on the additive scale. Indeed, for silica-smoking interactions, it is impossible to conclude due to discrepancies between original studies whereas for diesel-smoking interaction, no studies included in the present systematic review have addressed this issue.

Methodological points in original studies

The inconsistency of the statistical interaction results between original studies may come from methodological differences in each study. Every study has limitations that could be the source of opposite results on the interaction evaluation. In the studies that were included, occupational histories and smoking details were collected using employment records or questionnaires. The reliability of the data may have been affected by the quality of the documentation in the records

and by the recall bias from the questionnaires used to collect retrospective data. Although the data collection could be complete and accurate, the methods used to identify and assess occupational exposures may also have been a source of bias. For example; the utilization of a job-exposure matrix (JEM) could introduce non-differential misclassifications leading to a large number of false-positives and false-negatives. In consequence, there is a risk of underestimated risks that could affect the evaluation of the interaction.[44, 45]

When evaluating interactions, the method and the scale used to examine the interaction should be reported to avoid confusion and ambiguity and facilitate the comparison between studies.[46] In fact, the best approach is to evaluate the statistical interaction on both additive and multiplicative scales.[19] The additive interaction is generally evaluated by using the difference of risk differences known as interaction contrast, while risk ratios are used to evaluate the multiplicative interactions. In cohort studies, risks and risk ratios can be easily generated, but in the case-control studies only the odds ratios can be estimated. Using odds ratios instead of risk ratios to evaluate the additive or the multiplicative interaction could mistakenly show the presence of a positive interaction, even if the outcome is rare.[47, 48] The majority of the reviewed case-control studies evaluated exclusively the multiplicative interaction by testing the significance of the interaction term introduced into the regression model. However, while rarely used, some authors have proposed various measures to assess the additive interaction from case-control data using logistic regression models.[49-52] Additionally, discrepancy between studies may be explained by the measures used to assess the statistical additive interaction as each measure has its own interpretation. Indeed, Rothman et *al.* and Kalilani et *al.* suggested to use simultaneously three measures of interaction to evaluate the additive interaction: the attributable proportion due to interaction (AP), the relative excess risk due to interaction (RERI), and the Rothman's synergy index (S).[53, 54] Although, the attributable proportion due to interaction (AP) is the most robust measure to evaluate the additive interaction when the odds ratios are used instead of the risk ratios in the equation.[54] Because of its more intuitive interpretation, the Rothman's synergy index (S) [55] was used in the majority of the included studies to evaluate the additive statistical interaction even when odds ratios were used instead of risk ratios. Indeed, both S and AP measure interaction as departure from additivity but only S is suitable under a negative additive interaction assumption. Specific measures of interaction have been proposed to assess the statistical multiplicative interaction between asbestos exposure and tobacco smoking. The RAE was proposed to evaluate the asbestos-smoking multiplicative interaction in cohort studies.[24] However it was shown that the RAE tended to be underestimated in studies with low level of asbestos exposure. Thus, a modified version of the RAE (RAEm) have been proposed to assess the asbestos-smoking multiplicative interaction in studies with low asbestos exposure level.[43]

In many of the reviewed articles, the conclusion regarding the statistical interaction was not always consistent with the results of our evaluation; authors suggested the presence of a positive interaction without evaluating the statistically significance of the measure, or conclude on both scales although the interaction was evaluated on one scale only. The same findings was discussed by Liddell (2001); authors continue to suggest the presence of a positive multiplicative asbestos-smoking interaction without enough or strong evidence from their results or from the literature.[56]

In the current review, our conclusions are based on strong evidence, as the majority of the reviewed studies conclude the absence of the multiplicative interaction. In addition, all precautions were taken to avoid missing papers; three different bibliographic databases were used and each reference list of all included studies was reviewed. Finally, we believe that the publication bias is limited as several papers with negative results were published.

Public health implications

Statistical interaction (whatever the model, multiplicative or additive) between two risk factors increases cancer risk compared to risk related to each factor acting independently.

Two main impacts can be considered from a public health point of view. First, regarding primary prevention, reducing exposure to those two risk factors will induce a greater benefice (number of avoided incident cases) if there is a significant interaction between those two factors. Secondly, regarding targeted screening program (screening proposed to a selected population according to a specific risk threshold), the existence of an interaction will decrease the level of exposure of those two factors corresponding to the defined risk threshold. The same argument could be applied to individual imputability used in compensation system. Therefore, the knowledge of a statistical interaction between two risk factors is crucial and the knowledge of the interaction scale (i.e. multiplicative or additive) is important to conduct risk assessment and risk management.

Besides, in the light of the current knowledge, the statistical interaction between two factors do not allow to infer strong hypothesis about biological mechanisms.

CONCLUSIONS

To our knowledge, this is the first systematic review conducted to evaluate the statistical interactions between occupational exposures to crystalline silica and diesel engine exhaust emissions and tobacco smoking. In general, there is no multiplicative interaction between the three most frequent occupational lung carcinogens and the tobacco smoking. Evidence found in the literature cannot be considered sufficient to conclude on the additive scale. To minimize the risk of lung cancer among workers, specific programs should be developed and promoted to reduce concomitantly the exposure to occupational lung carcinogens and tobacco smoking.

LIST OF ABBREVIATIONS

IARC: International Agency for Research on Cancer
NOS: The Newcastle-Ottawa quality assessment Scale
RAE: the Relative Asbestos Effect
RAE_m: the Modified version of the relative asbestos effect
AP: the attributable proportion due to interaction
RERI: Relative Excess Risk due to Interaction
***S*:** Rothman's Synergy index

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Relevant data are available within the manuscript and the additional file.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MZ conducted the literature review, the study selection process, the data extraction and prepared the first draft for all sections of this manuscript with the help and supervision of PS, PB and AL. FD reviewed the eligibility of the included studies and the accuracy of the extracted data and contributed to the interpretation and discussion of findings. IS contributed to the interpretation of the statistical interaction results of the original studies included in the systematic review. PB and PS contributed to interpretation and discussion of findings. AL supervised all aspects of this manuscript, from the study selection process to the interpretation and discussion of findings. All co-authors participated in the editing and correction of the final text, and they read and approved the final manuscript.

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3 Objectives of CaProMat Analyses

Very few studies have described the prevalence of occupational exposures to asbestos and crystalline silica according to the histological types of lung cancer. Furthermore, to our knowledge, the literature did not uncover studies that investigated the prevalence of occupational exposure to asbestos or crystalline silica according to age at diagnosis. Thus, the CaProMat study analyses were conducted to compare the prevalence of occupational exposure to asbestos and to crystalline silica according to phenotypes of lung cancer characterized by either histological types of lung cancer or age at diagnosis among a large population of French male cases.

On the other hand, few studies have addressed the statistical interaction between tobacco smoking and occupational exposure to asbestos and crystalline silica, particularly for phenotypes of lung cancer such as histological type and tumor location. To our knowledge, there is no data on age at diagnosis. Therefore, we proposed, as second objective, to evaluate the statistical interactions between occupational exposures (asbestos and crystalline silica) and tobacco smoking according to specific phenotypes of lung cancer (histological types, tumor location and age at diagnosis) among a large series of lung cancer cases recruited in France and Canada.

4 CaProMat Study

4.1 Introduction

The CaProMat study is the largest known case-only study conducted to evaluate the relations between phenotypes of lung cancer, tobacco smoking, and occupational exposures. It is a pooled retrospective case-only study consisting of seven original studies that were conducted between 1999 and 2011 in different areas in France, and one original study conducted between 1996 and 2001 in Montreal, Canada. This study was funded by the « Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail **(**ANSES) » (Grant : ANSES EST-2011/1/189).

The socio-demographic details, diagnosis, occupational exposure and smoking habits were available for all studies. In addition, two specific JEMs, developed as part of MATGENE program of InVS (Institut de Veille Sanitaire), were available to evaluate the occupational exposure to asbestos and crystalline silica. (12, 149, 150)

Nine teams participated in the phase of pooling cases, and the team of *Santé Travail Environnement* of Bordeaux was responsible for the general coordination of the study:

1. Equipe Santé Travail Environnement, Centre INSERM U897, Université de Bordeaux
2. Département Santé Travail, Institut de Veille Sanitaire (InVS)
3. Equipe épidémiologie environnementale du cancer, Centre INSERM U1018, Villejuif
4. Centre INSERM U955, Créteil
5. Centre INSERM U954, Nancy
6. Consultations de Pathologies Professionnelles de Caen
7. Consultations de Pathologies Professionnelles de Grenoble
8. Consultations de Pathologies Professionnelles du Havre
9. Environmental Epidemiology and Population Health Research Team, Montréal.

4.2 Methods

4.2.1 Study population

The CaProMat study is a pooled case-only study conducted in France and in Montreal, Canada. Subjects were recruited between 1996 and 2011 from: 1) six French university hospitals of Bordeaux, Caen, Créteil, Grenoble, Nancy and Rouen included in the French national occupational disease surveillance and prevention network (RNV3P, Réseau National de Vigilance et de Prévention des Pathologies Professionnelles) (151); 2) the French population-based case-control study called ICARE in Bas-Rhin, Haut-Rhin, Doubs, Isère, Hérault, Somme, Calvados, Manche, Loire Atlantique, and Vendée (152); and 3) a Canadian population-based case-control study (153). (Table 8)

Table 8 Description of the eight case-series included in CaProMat study.

Original Study	Geographic Area	Recruitment Period	Population	Male (7,256)		Female (2,367)		Total (9,623)	
				n	%	n	%	n	%
CBP-RNV3P Bordeaux	Bordeaux	2005-2011	Hospital-based	845	11.6	272	11.5	1,117	11.6
CBP-RNV3P Caen	Caen	2005-2009	Hospital-based	377	5.2	115	4.9	492	5.1
CBP-RNV3P Creteil	Creteil	1999-2011	Hospital-based	1,458	20.1	517	21.8	1,975	20.5
CBP-RNV3P Grenoble	Grenoble	2005-2009	Hospital-based	257	3.5	87	3.7	344	3.6
CBP-RNV3P Nancy	Nancy	2005-2009	Hospital-based	1,046	14.4	293	12.4	1,339	13.9
CBP-RNV3P Rouen	Rouen	2002-2006	Hospital-based	417	5.7	0	0.0	417	4.3
ICARE study	Bas-Rhin, Haut-Rhin, Doubs, Isère, Hérault, Somme, Calvados, Manche, Loire Atlantique, Vendée	2001-2006	Population-based	2,121	29.2	619	26.2	2,740	28.5
Canadian study	Montreal	1996-2001	Population-based	735	10.1	464	19.6	1,199	12.5

The hospital-based RNV3P cases consisted of all cases of lung cancer that were treated in thoracic surgery or respiratory medicine services in six French university hospitals and that were directed to the occupational diseases clinics of the university hospital regardless of the suspicion of occupational exposures. The population-based cases from the two case-control studies consisted of all lung cancer cases identified across all major hospitals (both public and private). All lung cancer cases were histologically confirmed, and all histological types of lung cancer were included.

The initial CaProMat study population consisted of 11,228 lung cancer cases. During pooling and cleaning of data, 966 cases were excluded due to missing data on the occupational history (n=836), missing medical records (n=87), inconsistent data (n=33), duplicated subjects (n=6), and death of subject before the start of the initial study (n=4). In addition, a specific series of 639 cases from Créteil were also excluded because they were highly selected since they consisted of subjects specifically referred for only surgery. Overall, a total of 1,605 cases were excluded from the study, and the final CaProMat study population consisted of 9,623 lung cancer cases (7,256 males and 2,367 females).

4.2.2 Data Collection

Histological type (squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma and other histological types), tumor location (upper lobe *versus* lower lobe), and age at diagnosis were collected from medical records.

Complementary data were collected through personal interviews with all subjects, with the exception of the French and the Canadian case-control studies where next-of-kin were interviewed when the subject was unable to respond. (152, 153) For hospital-based cases, a standardized occupational health questionnaire was administered by an occupational physician, while for population-based cases, a standardized questionnaire was administered by trained interviewers.(152, 153) The lifetime occupational history for all jobs held for at least for six months was collected.

In addition, socio-demographic details were also collected and included gender, birth year, educational level (unschooled, primary, secondary and post-secondary) and respondent status. The detailed lifetime tobacco smoking habits were collected and included smoking status (never smoker, current smoker and ex-smoker), total smoking duration, mean number of cigarettes smoked per day, and time since cessation of smoking when appropriate).

4.2.3 Data Management

4.2.3.1 Construction of the e-database

The CaProMat study includes several previous studies in which the databases were already established. Original databases were sent to the team of "*Bordeaux*" who directed the work of cleaning and standardization of the data. A common e-database, accessible to all teams working on the project was created via the Web (e-database) to allow to integrate and to merge all the original data of each series, and to complete the missing data for some variables. Variable by variable, the data format has been modified to make it compatible with that of the e-database. Some variables were not available for all case series. Therefore, a work to search and extract the information has been made for several variables. These data were collected from medical records via standardized entry slips at the e-database format, and it was entered later to the e-database.

The e-database was developed and included socio-demographic characteristics, medical information on the diagnosed tumor, smoking history, and occupational history. The team of "*Nancy*" has developed the e-base from a technical point of view; where an online platform was created allowing each team to have access to the study data.

4.2.3.2 Coding and Recoding of Occupational Histories

In the final database, the lifetime occupational history for all jobs held for at least for six months was collected. Overall, the CaProMat study gathered 38,937 occupations. Occupational histories were coded differently in original studies. Three different classifications were used for occupations: the International Standard Classification of Occupations (ISCO) of 1988 for hospital-based cases (154), the ISCO of 1968 for the French population-based cases (155), and the Canadian Classification and Dictionary of Occupations (CCDO) of 1971 for the Canadian population-based cases. (156) Two different classifications were used for industries: the French Nomenclature of Activities (NAF 2000) for hospital-based and the French population-based cases (157), while the Canadian Standard Industrial Classification (CSIC) of 1980 was used for the Canadian population-based cases (158). Jobs coding was harmonized according to the ISCO of 1968 for occupations and the International Standard Industrial Classification (ISIC) of 1975 for industries (159).

4.2.4 Exposures Assessment

4.2.4.1 Tobacco Smoking

Subjects were defined as never smokers if they smoked less than 100 cigarettes during their life, and ex-smokers if they stopped smoking for more than two years. The comprehensive smoking index (CSI) was calculated from smoking details reported in the questionnaire. The CSI aggregates various details on the individual smoking habits including smoking intensity, smoking duration and time since cessation.

It has been shown that the CSI is an appropriate aggregated index to adjust for lifetime smoking history in lung cancer studies. (160) We further categorized subjects into never-low smokers (subjects with CSI values below the 25th percentiles) and medium-high smokers (subjects with CSI values above the 25th percentiles).

4.2.4.2 Occupational Exposures

Occupational exposures to asbestos and crystalline silica were retrospectively assessed by JEMs in relation to asbestos and crystalline silica. The two JEMs have been developed by the group

"MATGENE" at the department of occupational health of the "Institut de Veille Sanitaire" (French Institute for Public Health Surveillance).(12, 149, 150) For each job held by subjects, the JEMs assigned automatically three semi-quantitative exposure parameters: the probability, frequency and intensity of exposure.(12) In the two JEMs, the intensity of exposure was expressed in equivalent f/ml for asbestos exposure or in equivalent mg/m^3 for crystalline silica since these exposure parameters are the results of an expert assessment.(13, 161)

The asbestos JEM includes all jobs potentially exposed to asbestos fibers. A job is the crossing of an occupation and an industry. The asbestos JEM traces the historical exposures to asbestos fibers from 1945 to 2007. It takes into consideration five periods of exposure depending on the differences on conditions and regulations by time. The crystalline silica JEM includes all jobs potentially exposed to respirable crystalline silica dust (diameter <5 µm). The crystalline silica JEM traces the exposures to crystalline silica from 1947 to 2007. It takes into account different periods of exposure depending on the sector of activity (industry) due to difference on regulations. A probability of exposure for either asbestos or crystalline silica was automatically assigned by the two JEMs for each job reported by the subjects. This probability of exposure was expressed on a 5-categories scale for asbestos (0-1, 1-5, 5-30, 30-70, >70) and on a continuous 10% scale for crystalline silica. (12, 13) (Table 9)

The utilization of a standard method (JEM) to assess the occupational exposures to asbestos and to crystalline silica across the eight case-series was of highly importance. Although JEMs introduce non-differential misclassifications that could lead to false-positives and false-negatives. In addition, the heterogeneity of the work situations of a given job title could lead to a misclassification. On the other hand, the occupational classifications used affect the quality of assessment of occupational exposure. Thus, only ISCO 1968, PCS 1994 and NAF 2000 should be used. (12, 13)

Table 9 Probability, frequency and intensity of occupational exposure to asbestos and crystalline silica assigned by the Job-Exposure Matrices (JEMs).

Agent	Probability of exposure (%)	Frequency of exposure (% of working time)	Intensity of exposure (f/ml)
Asbestos	0 : 0 - 1 (never exposed) 1 : 1 - 5 2 : 5 - 30 3 : 30 - 70 4 : > 70	0 : 0 - 1 (never exposed) 1 : 1 - 5 2 : 5 - 30 3 : 30 - 70 4 : ≥ 70	0 : 0 – 0.0001 (never exposed) 1 : 0.0001 – 0.01 2 : 0.01 – 0.1 3 : 0.1 - 1 4 : 1 - 10 5 : ≥ 10
	Probability of exposure (%)	**Frequency of exposure (% of working time)**	**Intensity of exposure (mg/m^3)**
Crystalline silica	0 : 0 - 1 (never exposed) 1 : > 1 - 10 2 : 10 - 20 3 : 20 - 30 4 : 30 - 40 5 : 40 - 50 6 : 50 - 60 7 : 60 - 70 8 : 70 - 80 9 : 80 - 90 10 : > 90	0 : 0 - 1 (never exposed) 1 : 1 - 5 2 : 5 - 30 3 : 30 - 70 4 : ≥ 70	0 : 0 - 0.02 (never exposed) 1 : 0.02 - 0.1 2 : 0.1 - 0.5 3 : 0.5 - 1 4 : ≥ 1

For each of asbestos and crystalline silica, a subject was defined as *ever exposed* if he had *held at least one job with a non-null probability of exposure*. Three exposure indicators were then derived for the two agents studied: the highest probability of exposure over the entire occupational career. The total duration of exposure (in years) corresponded to the sum of jobs durations with a non-null probability of exposure over the entire occupational career. The cumulative exposure index (CEI) corresponded to the sum of the product of the duration, probability, frequency and intensity of exposure for each exposed job over the entire career: $\text{CEI} = \sum_i Di \times Pi \times Fi \times Ii$ (Di: Total duration of exposure of job i; Pi: Highest probability of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i). CEI

was expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure.

4.2.5 Statistical Analysis

In general, the statistical analysis was conducted among male lung cancer cases only. The female lung cancer cases were excluded from the analysis as the occupational exposure to either asbestos (73.5% for men *vs* 19.8% for women) or crystalline silica (39.0% for men *vs* 3.3% for women) was significantly different from among males.

4.2.5.1 Exposures Prevalence and Phenotypes of Lung Cancer

4.2.5.1.1 Main Statistical Analysis

The purpose of this analysis was to describe the prevalence of occupational exposure to asbestos and to crystalline silica according to phenotypes of lung cancer. The characteristics of occupational exposure to asbestos were different between France and Canada; France imported and used different types of fiber while Canada produced exclusively chrysotile. Moreover, France used asbestos until it was banned in 1997 (162), while Canada produced raw asbestos until 2011 (96). To simplify the inferences, the present analysis was restricted to French male lung cancer cases (n=6,521).

To take into account the uncertainty of the exposure, we derived a weighted prevalence of occupational exposure to asbestos and crystalline silica. This *weighted prevalence (Pw)* of occupational exposure was equal to the sum of the highest probability of occupational exposure to the agent (asbestos or crystalline silica) for each subject divided by the total number of subjects:

$Pw = \frac{\sum_{i=1}^{n} Pi}{n}$ (Pi: highest probability of exposure of subject i; n: total number of subjects).

We estimated weighted prevalence of occupational exposure to asbestos and crystalline silica according to histological types (squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma and other lung cancer) and according to age at diagnosis (< 50 years, 50 - 59 years, 60 - 69 years, ≥ 70 years). Also, further stratification by smoking status (non-smoker, current smoker, and ex-smoker) was carried out.

4.2.5.1.2 Complementary Analyses

Two sets of analyses were conducted separately for hospital-based and population-based cases to examine if the results are similar to the main analysis.

To confirm our results, the statistical analysis was conducted for different definitions of exposed subjects: *ever exposed regardless of the highest probability of exposure during working life, categorization of subjects according to the highest probability of exposure during the working life, and categorization according to the tertiles of the CEI.* For the present analysis, the CEI corresponded to the sum of the product of the duration, frequency and intensity of exposure for each exposed job over the entire career: CEI $= \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i). CEI was expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure.

For asbestos exposure, the highest probability of exposure was categorized as 0-5, 5-30, 30-70, and >70%, while it was categorized as 0-10, 10-50, 50-90 and >90% for crystalline silica

exposure. The tertiles of asbestos exposure were 0-1.1, 1.1-16.5, and >16.5 f.ml/year, while they were 0-0.4, 0.4-2.2, and >2.2 mg/m^3-year for crystalline silica exposure.

The differences between the prevalence of occupational exposures to asbestos and crystalline silica (weighted prevalence or proportion of exposure according to the different definitions of exposed subjects) according to histological types and age at diagnosis were tested by Pearson chi-square test or Fisher exact test when appropriate.

4.2.5.2 Interaction between Smoking and Occupational Exposures on Phenotypes of Lung Cancer

4.2.5.2.1 Main Statistical Analysis

The purpose of this analysis was to evaluate the statistical interactions between occupational exposures (asbestos and crystalline silica) and tobacco smoking according to specific phenotypes of lung cancer. The statistical analysis was conducted among all male lung cancer cases recruited from France and Canada.

In the main analysis, subjects were defined as *exposed* to either asbestos or crystalline silica if they held at least one job with a probability of exposure greater than 30%. Exposure status was considered as uncertain for subjects with a non-null probability of exposure and a highest probability of exposure lower than 30%.

For histological type and tumor location as dependent variables, odds ratios (ORs) and their 95% CIs were estimated from unconditional logistic regression models. For histological types, four alternative definitions of the binary dependent variable were considered: 1) squamous cell carcinoma *versus* other histological types; 2) squamous cell carcinoma *versus* adenocarcinoma only; 3) small cell carcinoma *versus* other histological types; 4) small cell carcinomas *versus* adenocarcinoma only. Mean age at diagnosis (in years) was estimated from multiple linear regression models. The statistical interaction between tobacco smoking (medium-high smokers *versus* never-low smokers) and occupational exposure to either asbestos or crystalline silica (exposed *versus* non-exposed) was estimated by including a cross-product term of both variables in all regression models. All models were adjusted for potential confounders, namely asbestos or crystalline silica according to the occupational exposure of interest (exposed *versus* non-exposed), age at diagnosis (in years, for histological types and tumor location), histological type (for age at diagnosis and tumor location) and initial study.

For tumor location and age at diagnosis, we additionally tested whether there was a statistical interaction between tobacco smoking and histological types of lung cancer or not.

4.2.5.2.2 Complementary Analyses

We further conducted two complete sets of analyses by using different definitions of the exposed group: 1) we considered subjects who held at least one job with a non-null probability of exposure as exposed; and 2) we considered subjects with a highest probability of exposure lower than 30% as non-exposed.

In addition, to assess the impact of next-of-kin respondents on our results, a whole set of analyses was conducted exclusively among subjects who responded for themselves.

Data were analyzed using the statistical software SPSS (Statistical Package for Social Sciences), version 21.0 (Chicago, IL, USA). A *p*-value <0.05 was considered significant.

4.3 Results and Discussion

4.3.1 Description of the Study Population

The population of CaProMat study consisted of 9,623 subjects: 7,256 males and 2,367 females. Table 10 presents the main characteristics of the male's population. The male's population consisted of 4,400 subjects from RNV3P, 2,121 from ICARE, and 735 from the Canadian population-based study.

Table 10 Main characteristics of **male subjects** included in the CaProMat pooled case-only study.

	RNV3P (4,400)		**ICARE (2,121)**		**Canadian (735)**		**Male (7,256)**	
Characteristics	n	%	N	%	n	%	n	%
Histological type								
Squamous-cell carcinoma	1,362	31.0	762	35.9	260	35.4	2,384	32.9
Small cell lung cancer	599	13.6	302	14.2	125	17.0	1,026	14.1
Adenocarcinoma	1,686	38.3	760	35.8	241	32.8	2,687	37.0
Large cell carcinoma	503	11.4	231	10.9	71	9.7	805	11.1
Other lung cancer	250	5.7	66	3.1	38	5.2	354	4.9
Tumor location								
Upper lobe tumor	2,145	67.7	1,055	69.3	NA	NA	3,200	68.2
Lower lobe tumor	1,022	32.3	467	30.7	NA	NA	1,489	31.8
Age at diagnosis								
Age at diagnosis (years), mean (SD[a])	63.2 (10.5)		60.0 (9.0)		64.2 (7.9)		62.4 (10.0)	
Respondent status								
Self	4,400	100.0	2,063	97.3	442	60.1	6,905	95.2
Proxy	0	0.0	58	2.7	293	39.9	351	4.8
Smoking status								
Non-smokers	132	3.0	48	2.3	18	2.4	198	2.7
Current smokers	2,434	55.3	1,313	61.9	497	67.6	4,244	58.5
Ex-smokers	1,834	41.7	760	35.8	220	29.9	2,814	38.8
Educational level								
Unschooled	119	2.7	0	0.0	0	0.0	119	1.6
Primary	761	17.3	636	30.0	328	44.6	1,725	23.8
Secondary	1,516	34.5	998	47.1	315	42.9	2,829	39
Post-secondary	313	7.1	261	12.3	92	12.5	666	9.2
Unknown	1,691	38.4	226	10.7	0	0.0	1,917	26.4
Last job category (ISCO 1968)[b]								
Professional, technical and related workers	559	12.7	227	10.7	49	6.7	835	11.5
Administrative and managerial workers	237	5.4	119	5.6	49	6.7	405	5.6
Clerical and related workers	392	8.9	182	8.6	69	9.4	643	8.9
Sales workers	309	7.0	158	7.4	70	9.5	537	7.4
Service workers	354	8.0	160	7.5	123	16.7	637	8.8
Agricultural, animal husbandry and forestry workers, fishermen and hunters	177	4.0	159	7.5	10	1.4	346	4.8
Production and related workers, transport equipment operators and labourers	2370	53.9	1101	51.9	362	49.3	3,833	52.8
Unknown	2	0.0	15	0.7	3	0.4	20	0.3
Asbestos exposure								
Non-exposed	1,112	25.3	615	29.0	242	32.9	1,969	27.1
0% < P[c] ≤ 5%	332	7.5	198	9.3	45	6.1	575	7.9
5% < P ≤ 30%	613	13.9	332	15.7	155	21.1	1,100	15.2
30% < P ≤ 70%	1,589	36.1	660	31.1	189	25.7	2,438	33.6
P > 70%	754	17.1	316	14.9	104	14.1	1,174	16.2
Total duration of exposure (years), mean (SD)	18.6 (16.5)		18.1 (16.7)		15.8 (16.1)		17.5 (17.2)	
Cumulative exposure indexd (f/ml.year), mean (SD)	15.2 (28.5)		13.2 (30.0)		11.8 (23.9)		16.8 (30.5)	
Crystalline silica								
Non-exposed	2,711	61.6	1,270	59.9	526	71.6	4,507	62.1
0% < P ≤ 5%	21	0.5	99	4.7	0	0.0	120	1.7
5% < P ≤ 30%	166	3.8	77	3.6	28	3.8	271	3.7
30% < P ≤ 70%	671	15.3	327	15.4	109	14.8	1,107	15.3
P > 70%	831	18.9	348	16.4	72	9.8	1,251	17.2
Total duration of exposure (years), mean (SD)	7.3 (12.8)		7.5 (12.8)		5.5 (11.4)		7.4 (13.1)	
Cumulative exposure indexd (mg/m^3-year), mean (SD)	1.3 (5.0)		1.0 (3.3)		0.8 (2.7)		1.2 (4.2)	

[a] SD standard Deviation; NA Not available.
[b] ISCO 1968 International Standard Classification of Occupations, 1968, second edition.
[c] The highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[d] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).

Table 11 presents the main characteristics of the female's population. The female's population consisted of 1,284 subjects from RNV3P, 619 from ICARE, and 464 from the Canadian population-based study.

Table 11 Main characteristics of **female subjects** included in the CaProMat pooled case-only study.

	RNV3P (1,284)		**ICARE (619)**		**Canadian (464)**		**Female (2,367)**	
Characteristics	n	%	n	%	n	%	n	%
Histological type								
Squamous-cell carcinoma	173	13.5	99	16.0	91	19.6	363	15.3
Small cell lung cancer	171	13.3	83	13.4	80	17.2	334	14.1
Adenocarcinoma	708	55.1	351	56.7	216	46.6	1275	53.9
Large cell carcinoma	143	11.1	46	7.4	43	9.3	232	9.8
Other lung cancer	89	6.9	40	6.5	34	7.3	163	6.9
Tumor location								
Upper lobe tumor	630	70.2	305	70.1	NA	NA	935	70.2
Lower lobe tumor	267	29.8	130	29.9	NA	NA	397	29.8
Age at diagnosis								
Age at diagnosis (years), mean (SD[a])	60.4 (11.4)		57.2 (10.0)		61.5 (9.3)		59.8 (10.8)	
Respondent status								
Self	1,284	100.0	611	98.7	307	66.2	2,202	93.0
Proxy	0	0.0	8	1.3	157	33.8	165	7.0
Smoking status								
Non-smokers	324	25.2	183	29.6	32	6.9	539	22.8
Current smokers	690	53.7	327	52.8	342	73.7	1359	57.4
Ex-smokers	270	21.0	109	17.6	90	19.4	469	19.8
Educational level								
Unschooled	32	2.5	0	0.0	0	0.0	32	1.4
Primary	250	19.5	198	32.0	168	36.2	616	26.0
Secondary	489	38.1	268	43.3	239	51.5	996	42.1
Post-secondary	175	13.6	107	17.3	57	12.3	339	14.3
Unknown	338	26.3	46	7.4	0	0.0	384	16.2
Last job category (ISCO 1968)[b]								
Professional, technical and related workers	196	15.3	95	15.3	39	8.4	330	13.9
Administrative and managerial workers	46	3.6	12	1.9	9	1.9	67	2.8
Clerical and related workers	341	26.6	124	20.0	121	26.1	586	24.8
Sales workers	120	9.3	55	8.9	37	8.0	212	9.0
Service workers	344	26.8	198	32.0	121	26.1	663	28.0
Agricultural, animal husbandry and forestry workers, fishermen and hunters	23	1.8	11	1.8	1	0.2	35	1.5
Production and related workers, transport equipment operators and labourers	193	15.0	95	15.3	91	19.6	379	16.0
Unknown	21	1.6	29	4.7	45	9.7	95	4.0
Asbestos exposure								
Non-exposed	1,023	79.7	503	81.3	395	85.1	1,921	81.2
0% < P[c] ≤ 5%	81	6.3	30	4.8	11	2.4	122	5.2
5% < P ≤ 30%	88	6.9	37	6.0	23	5.0	148	6.3
30% < P ≤ 70%	73	5.7	36	5.8	24	5.2	133	5.6
P > 70%	19	1.5	13	2.1	11	2.4	43	1.8
Total duration of exposure (years), mean (SD)	2.6 (7.3)		2.4 (6.9)		1.1 (3.6)		2.2 (6.7)	
Cumulative exposure index[d] (f/ml.year), mean (SD)	1.8 (18.6)		0.7 (5.7)		0.2 (1.9)		1.2 (14.1)	
Crystalline silica								
Non-exposed	1,245	97.0	595	96.1	460	99.1	2,300	97.2
0% < P ≤ 5%	0	0.0	14	2.3	0	0.0	14	0.6
5% < P ≤ 30%	9	0.7	3	0.5	3	0.6	15	0.6
30% < P ≤ 70%	12	0.9	1	0.2	0	0.0	13	0.5
P > 70%	18	1.4	6	1.0	1	0.2	25	1.1
Total duration of exposure (years), mean (SD)	0.4 (3.1)		0.3 (1.7)		0.0 (0.4)		0.3 (2.4)	
Cumulative exposure index[d] (mg/m^3-year), mean (SD)	0.1 (2.1)		0.0 (0.1)		0.0 (0.1)		0.1 (1.5)	

[a] SD standard Deviation; NA Not available.
[b] ISCO 1968 International Standard Classification of Occupations, 1968, second edition.
[c] The highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[d] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).

4.3.2 Exposures Prevalence and Phenotypes of Lung Cancer

4.3.2.1 Main Results

The current analysis included 6,521 French male lung cancer cases corresponding to 28,385 jobs held for more than six months. The main characteristics of subjects were presented in Table 12. The two most frequent histological types were adenocarcinoma (37.5%) and squamous cell carcinoma (32.6%). The mean age at diagnosis was 62.2 (±10.1) years. According to smoking status, 2.8% of the cases were non-smokers, while 57.4% and 39.8% were current smokers and ex-smokers, respectively. Considering the last job held, half of the cases were blue-collar workers (*production and related workers, transport equipment operators and labourers* according to the ISCO of 1968). For asbestos, the proportion of subjects who held at least one job with a non-null probability of exposure was 73.5% and 16.4% had a highest probability of exposure greater than 70%. The proportion of subjects who held at least one job with a non-null probability of exposure to crystalline silica was 39.0% and 25.9% had a highest probability of exposure greater than 50%. Finally, the mean CEI was 14.6 (±29.0) f/ml.year for asbestos, and 1.2 (±4.5) mg/m^3-year for crystalline silica.

Table 12 Main characteristics of French subjects included in the CaProMat pooled case-only study.

Characteristics	Male (6,521) n	%
Histological type		
Squamous cell carcinoma	2,124	32.6
Small cell carcinoma	901	13.8
Adenocarcinoma	2,446	37.5
Large cell carcinoma	734	11.3
Other lung cancer	316	4.8
Age at diagnosis		
Age at diagnosis (years), mean (SD[a])	62.2 (10.1)	
Respondent status		
Self	6,463	99.1
Proxy	58	0.9
Smoking status		
Non-smokers	180	2.8
Current smokers	3,747	57.4
Ex-smokers	2,594	39.8
Educational level		
Unschooled	119	1.8
Primary	1,397	21.4
Secondary	2,514	38.6
Post-secondary	574	8.8
Unknown	1,917	29.4
Last job category (ISCO 1968)[b]		
Professional, technical and related workers	786	12.1
Administrative and managerial workers	356	5.5
Clerical and related workers	574	8.8
Sales workers	467	7.2
Service workers	514	7.9
Agricultural, animal husbandry and forestry workers, fishermen and hunters	336	5.2
Production and related workers, transport equipment operators and labourers	3,471	53.2
Unknown	17	0.3
Asbestos exposure		
Highest probability[c]		
P=0%	1,727	26.5
0% < P ≤ 5%	530	8.1
5% < P ≤ 30%	945	14.5
30% < P ≤ 70%	2,249	34.5
P > 70%	1,070	16.4
Total duration of exposure (years), mean (SD)	18.4 (16.6)	
Cumulative exposure index[d] (f/ml.year), mean (SD)	14.6 (29.0)	
Crystalline silica		
Highest probability		
P=0%	3,981	61.0
0% < P ≤ 10%	202	3.1
10% < P ≤ 50%	644	9.9
50% < P ≤ 90%	1,652	25.3
P > 90%	42	0.6
Total duration of exposure (years), mean (SD)	7.4 (12.8)	
Cumulative exposure index (mg/m^3-year), mean (SD)	1.2 (4.5)	

[a] SD standard Deviation.
[b] ISCO 1968 International Standard Classification of Occupations, 1968, second edition.
[c] Highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[d] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).

The weighted prevalence of occupational exposure to asbestos and crystalline silica according to histological types of lung cancer is presented in Table 13. The weighted prevalence of exposure to asbestos was 33.9% [95% CI: 32.8-35.1], while the weighted prevalence of exposure to crystalline silica was 25.7% [95% CI: 24.7-26.8]. For occupational asbestos exposure, there was no statistically significant difference in terms of weighted prevalence of exposure between histological types of lung cancer (p=0.13). Indeed, the maximum weighted prevalence of exposure was 35.0% [95% CI: 33.0-37.1] for the squamous cell carcinoma types, while it was at minimum 32.2%; [95% CI: 28.8-35.5] for the large cell carcinoma types. On the other hand, for crystalline silica, a borderline statistically significant difference was observed between histological types in terms of weighted prevalence of exposure (p=0.049). The maximum weighted prevalence of exposure to crystalline silica was 27.7% [95% CI: 25.8-29.6] for the squamous cell carcinoma types and the minimum weighted prevalence of exposure was 23.5% [95% CI: 18.8-28.2] for other lung cancer types.

Table 13 Occupational exposure to asbestos and crystalline silica by histological types among 6,521 French male lung cancer cases

	Histological types												
	Squamous cell carcinoma (2,124)		Small cell carcinoma (901)		Adenocarcinoma (2,446)		Large cell carcinoma (734)		Other lung cancer (316)		Total (6,521)		
	n (%)	Pw[a]% (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Asbestos													
Never (CEI[c]=0)	514 (24.2)	-	255 (28.3)	-	672 (27.5)	-	201 (27.4)	-	85 (26.9)	-	1,727 (26.5)	-	
Ever (CEI>0)	1,610 (75.8)	35.0 (33.0 - 37.1)	646 (71.7)	33.2 (30.1 - 36.2)	1,774 (72.5)	33.9 (32.1 - 35.8)	533 (72.6)	32.2 (28.8 - 35.5)	231 (73.1)	32.6 (27.4 - 37.8)	4,794 (73.5)	33.9 (32.8 - 35.1)	0.132
0<CEI≤1.1	519 (24.4)		210 (23.3)		605 (24.7)		191 (26.0)		77 (24.4)		1,602 (24.6)		
1.1<CEI≤16.5	531 (25.0)		201 (22.3)		608 (24.9)		171 (23.3)		83 (26.3)		1,594 (24.4)		
CEI>16.5	560 (26.4)		235 (26.1)		561 (22.9)		171 (23.3)		71 (22.5)		1,598 (24.5)		
Crystalline silica													
Never (CEI[c]=0)	1,240 (58.4)	-	546 (60.6)	-	1,533 (62.7)	-	461 (62.8)	-	201 (63.6)	-	3,981 (61.0)	-	
Ever (CEI>0)	884 (41.6)	27.7 (25.8 - 29.6)	355 (39.4)	25.7 (22.9 - 28.6)	913 (37.3)	24.6 (22.9 - 26.4)	273 (37.2)	24.5 (21.4 - 27.7)	115 (36.4)	23.5 (18.8 - 28.2)	2,540 (39.0)	25.7 (24.7 - 26.8)	0.049
0<CEI≤0.4	266 (12.5)		118 (13.1)		321 (13.1)		94 (12.8)		48 (15.2)		847 (13.0)		
0.4<CEI≤2.2	284 (13.4)		117 (13.0)		325 (13.3)		94 (12.8)		34 (10.8)		854 (13.1)		
CEI>2.2	334 (15.7)		120 (13.3)		267 (10.9)		85 (11.6)		33 (10.4)		839 (12.9)		

[a] Pw weighted prevalence equal to the sum of the highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects. Highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).

Table 14 presents the weighted prevalence of occupational exposure to asbestos according to histological types of lung cancer stratified by the smoking status. Regardless of the smoking status, there was no significant difference in terms of weighted prevalence of occupational asbestos exposure between the histological types of lung cancer. Among non-smokers, the maximum weighted prevalence of exposure to asbestos was observed for squamous cell carcinomas (30.2% [95% CI: 11.0-49.4]), while the minimum weighted prevalence of exposure was observed for small cell carcinomas (21.8% [95% CI: 0.0-52.4]). Among ex-smokers, the maximum weighted prevalence of exposure to asbestos was observed for squamous cell carcinomas (35.5% [95% CI: 32.4-38.6]), while the minimum weighted prevalence of exposure was observed for other lung cancer cases (31.2% [95% CI: 23.3-39.0]). Among current smokers, the maximum weighted prevalence of exposure to asbestos was observed for squamous cell carcinomas (34.8% [95% CI: 32.1-37.5]), while the minimum weighted prevalence of exposure was observed for large cell carcinomas (32.7% [95% CI: 28.3-37.2]).

Table 14 Occupational exposure to asbestos by histological types stratified by smoking status among 6,521 French male lung cancer cases

	Histological types												
	Squamous cell carcinoma (2,124)		Small cell carcinoma (901)		Adenocarcinoma (2,446)		Large cell carcinoma (734)		Other lung cancer (316)		Total (6,521)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Asbestos													
Non-smokers (180)													
Never (CEI[c]=0)	9 (40.9)	-	4 (57.1)	-	37 (33.3)	-	7 (41.2)	-	6 (26.1)	-	63 (35.0)	-	0.958
Ever (CEI>0)	13 (59.1)	30.2 (11.0 - 49.4)	3 (42.9)	21.8 (0.0 - 52.4)	74 (66.7)	28.1 (19.7 - 36.5)	10 (58.8)	25.1 (4.5 - 45.8)	17 (73.9)	27.1 (08.9 - 45.2)	117 (65.0)	27.7 (21.2 - 34.2)	
0<CEI≤1.1	2 (9.1)		1 (14.3)		28 (25.2)		4 (23.5)		8 (34.8)		43 (23.9)		
1.1<CEI≤16.5	6 (27.3)		0 (0.0)		23 (20.7)		4 (23.5)		6 (26.1)		39 (21.7)		
CEI>16.5	5 (22.7)		2 (28.6)		23 (20.7)		2 (11.8)		3 (13.0)		35 (19.4)		
Current smokers (3,747)													
Never (CEI=0)	292 (24.3)	-	179 (29.5)	-	379 (28.1)	-	106 (24.7)	-	46 (28.9)	-	1,002 (26.7)	-	0.292
Ever (CEI>0)	908 (75.7)	34.8 (32.1 - 37.5)	428 (70.5)	32.8 (29.0 - 36.5)	972 (71.9)	33.7 (31.2 - 36.2)	324 (75.3)	32.7 (28.3 - 37.2)	113 (71.1)	34.6 (27.2 - 42.0)	2,745 (73.3)	33.8 (32.3 - 35.4)	
0<CEI≤1.1	283 (23.6)		136 (22.4)		327 (24.2)		119 (27.7)		40 (25.2)		905 (24.2)		
1.1<CEI≤16.5	318 (26.5)		135 (22.2)		321 (23.8)		99 (23.0)		40 (25.2)		913 (24.4)		
CEI>16.5	307 (25.6)		157 (25.9)		324 (24.0)		106 (24.7)		33 (20.8)		927 (24.7)		
Ex-smokers[d] (2,594)													
Never (CEI=0)	213 (23.6)	-	72 (25.1)	-	256 (26.0)	-	88 (30.7)	-	33 (24.6)	-	662 (25.5)	-	0.315
Ever (CEI>0)	689 (76.4)	35.5 (32.4 - 38.6)	215 (74.9)	34.3 (28.8 - 39.8)	728 (74.0)	34.9 (31.9 - 37.9)	199 (69.3)	31.8 (26.4 - 37.1)	101 (75.4)	31.2 (23.3 - 39.0)	1,932 (74.5)	34.5 (32.7 - 36.3)	
0<CEI≤1.1	234 (25.9)		73 (25.4)		250 (25.4)		68 (23.7)		29 (21.6)		654 (25.2)		
1.1<CEI≤16.5	207 (22.9)		66 (23.0)		264 (26.8)		68 (23.7)		37 (27.6)		642 (24.7)		
CEI>16.5	248 (27.5)		76 (26.5)		214 (21.7)		63 (22.0)		35 (26.1)		636 (24.5)		

[a] Pw weighted prevalence equal to the sum of the highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects. Highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] Ex-smokers stopped smoking for more than two years.

Table 15 presents the weighted prevalence of occupational exposure to crystalline silica according to histological types of lung cancer stratified by smoking status. Regardless of the smoking status, there was no significant differences in terms of weighted prevalence of occupational exposure to crystalline silica, except for ex-smokers, where a borderline statistically significant difference was observed (p=0.045). Among ex-smokers, the maximum weighted prevalence of exposure to crystalline silica was observed for squamous cell carcinomas (27.9% [95% CI: 25.0-30.9]), while the minimum weighted prevalence of exposure was observed for other lung cancer cases (21.6% [95% CI: 14.6-28.6]). Among non-smokers, the maximum weighted prevalence of exposure to crystalline silica was observed for adenocarcinomas (21.1% [95% CI: 13.5-28.7]), while the minimum weighted prevalence of exposure was observed for small cell carcinomas (13.4% [95% CI: 0.0-27.6]). Among current smokers, the maximum weighted prevalence of exposure to crystalline silica was observed for squamous cell carcinomas (27.8% [95% CI: 25.3-30.4]), while the minimum weighted prevalence of exposure was observed for large cell carcinomas (25.5% [95% CI: 21.4-29.7]).

Table 15 Occupational exposure to crystalline silica by histological types stratified by smoking status among 6,521 French male lung cancer cases

	Histological types												
	Squamous cell carcinoma (2,124)		Small cell carcinoma (901)		Adenocarcinoma (2,446)		Large cell carcinoma (734)		Other lung cancer (316)		Total (6,521)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	p^b
Crystalline silica													
Non-smokers (180)													
Never (CEI[c]=0)	16 (72.7)	-	5 (71.4)	-	77 (69.4)	-	13 (76.5)	-	19 (82.6)	-	130 (72.2)	-	0.972
Ever (CEI>0)	6 (27.3)	13.4 (0.0 - 27.6)	2 (28.6)	14.3 (0.0 - 40.2)	34 (30.6)	21.1 (13.5 - 28.7)	4 (23.5)	14.7 (0.0 - 31.5)	4 (17.4)	15.7 (0.8 - 30.5)	50 (27.8)	18.6 (12.9 - 24.3)	
0<CEI≤0.4	4 (18.2)		0 (0.0)		14 (12.6)		1 (5.9)		2 (8.7)		21 (11.7)		
0.4<CEI≤2.2	0 (0.0)		2 (28.6)		9 (8.1)		2 (11.8)		1 (4.3)		14 (7.8)		
CEI>2.2	2 (9.1)		0 (0.0)		11 (9.9)		1 (5.9)		1 (4.3)		15 (8.3)		
Current smokers (3,747)													
Never (CEI=0)	709 (59.1)	-	366 (60.3)	-	818 (60.5)	-	263 (61.2)	-	92 (57.9)	-	2,248 (60.0)	-	0.785
Ever (CEI>0)	491 (40.9)	27.8 (25.3 - 30.4)	241 (39.7)	25.6 (22.1 - 29.1)	533 (39.5)	25.7 (23.4 - 28.1)	167 (38.8)	25.5 (21.4 - 29.7)	67 (42.1)	26.2 (19.4 - 33.0)	1,499 (40.0)	26.4 (25.0 - 27.8)	
0<CEI≤0.4	154 (12.8)		80 (13.2)		194 (14.4)		62 (14.4)		29 (18.2)		519 (13.9)		
0.4<CEI≤2.2	168 (14.0)		85 (14.0)		206 (15.2)		57 (13.3)		22 (13.8)		538 (14.4)		
CEI>2.2	169 (14.1)		76 (12.5)		133 (9.8)		48 (11.2)		16 (10.1)		442 (11.8)		
Ex-smokers[d] (2,594)													
Never (CEI=0)	515 (57.1)	-	175 (61.0)	-	638 (64.8)	-	185 (64.5)	-	90 (67.2)	-	1,603 (61.8)	-	**0.045**
Ever (CEI>0)	387 (42.9)	27.9 (25.0 - 30.9)	112 (39.0)	26.3 (21.2 - 31.3)	346 (35.2)	23.6 (20.9 - 26.2)	102 (35.5)	23.6 (18.7 - 28.5)	44 (32.8)	21.6 (14.6 - 28.6)	991 (38.2)	25.3 (23.6 - 27.0)	
0<CEI≤0.4	108 (12.0)		38 (13.2)		113 (11.5)		31 (10.8)		17 (12.7)		307 (11.8)		
0.4<CEI≤2.2	116 (12.9)		30 (10.5)		110 (11.2)		35 (12.2)		11 (8.2)		302 (11.6)		
CEI>2.2	163 (18.1)		44 (15.3)		123 (12.5)		36 (12.5)		16 (11.9)		382 (14.7)		

[a] Pw weighted prevalence equal to the sum of the highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects. Highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] Ex-smokers stopped smoking for more than two years.

The weighted prevalence of occupational exposure to asbestos and crystalline silica according to age at diagnosis is presented in Table 16. There was a statistically significant difference in terms of weighted prevalence of exposure between the categories of age at diagnosis for both occupational asbestos exposure (p=0.014) and occupational exposure to crystalline silica (p=0.018). The maximum weighted prevalence of exposure was observed in the subjects diagnosed between 50 to 59 years old for asbestos and younger than 50 years of age for crystalline silica (35.5% [95% CI: 33.4-37.6] and 27.6% [95% CI: 24.3-30.9], respectively), while the minimum weighted prevalence of exposure was observed in subjects diagnosed at 70 years of age or more for both agents (30.9% [95% CI: 28.7-33.1] and 23.5% [95% CI: 21.5-25.5], respectively).

Table 16 Occupational exposure to asbestos and crystalline silica by age at diagnosis among 6,521 French male lung cancer cases

	Age at diagnosis (years)										
	< 50 years (698)		50-59 years (1,981)		60-69 years (2,152)		≥ 70 years (1,690)		Total (6,521)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Asbestos											
Never (CEI[c]=0)	159 (22.8)	-	526 (26.6)	-	562 (26.1)	-	480 (28.4)	-	1,727 (26.5)	-	
Ever (CEI>0)	539 (77.2)	35.0 (31.4 - 38.5)	1,455 (73.4)	35.5 (33.4 - 37.6)	1,590 (73.9)	34.5 (32.5 - 36.5)	1,210 (71.6)	30.9 (28.7 - 33.1)	4,794 (73.5)	33.9 (32.8 – 35.1)	0.014
0<CEI≤1.1	195 (27.9)		465 (23.5)		525 (24.4)		417 (24.7)		1,602 (24.6)		
1.1<CEI≤16.5	222 (31.8)		497 (25.1)		473 (22.0)		402 (23.8)		1,594 (24.4)		
CEI>16.5	122 (17.5)		493 (24.9)		592 (27.5)		391 (23.1)		1,598 (24.5)		
Crystalline silica											
Never (CEI=0)	407 (58.3)	-	1,192 (60.2)	-	1,282 (59.6)	-	1,100 (65.1)	-	3,981 (61.0)	-	
Ever (CEI>0)	291 (41.7)	27.6 (24.3 - 30.9)	789 (39.8)	26.0 (24.0 - 27.9)	870 (40.4)	26.6 (24.8 - 28.5)	590 (34.9)	23.5 (21.5 - 25.5)	2,540 (39.0)	25.7 (24.7 – 26.8)	0.018
0<CEI≤0.4	130 (18.6)		293 (14.8)		255 (11.8)		169 (10.0)		847 (13.0)		
0.4<CEI≤2.2	114 (16.3)		292 (14.7)		287 (13.3)		161 (9.5)		854 (13.1)		
CEI>2.2	47 (6.7)		204 (10.3)		328 (15.2)		260 (15.4)		839 (12.9)		

[a] Pw weighted prevalence equal to the sum of the highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects. Highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).

Table 17 presents the weighted prevalence of occupational exposure to asbestos according to age at diagnosis stratified by the smoking status. Regardless of the smoking status, there was no significant differences in terms of the weighted prevalence of occupational exposure to asbestos, except for current smokers, where a statistically significant difference was observed (p=0.003). Among current smokers, the maximum weighted prevalence of exposure to asbestos was observed in the subjects diagnosed at younger than 50 years of age (35.7% [95% CI: 31.8 – 39.6]), while the minimum weighted prevalence of exposure was observed in subjects diagnosed at 70 years of age or more (29.2% [95% CI: 25.4 – 33.0]). Among non-smokers, the maximum weighted prevalence of exposure to asbestos was observed in the subjects diagnosed between 60 and 69 years old (34.3% [95% CI: 21.5-47.1]), while the minimum weighted prevalence of exposure was observed in subjects diagnosed at 70 years of age or more (23.9% [95% CI: 9.1-38.7]). Among ex-smokers, the maximum weighted prevalence of exposure to asbestos was observed in the subjects diagnosed between 50 and 59 years old (36.3% [95% CI: 32.1-40.4]), while the minimum weighted prevalence of exposure was observed in subjects diagnosed at 70 years of age or more (32.1% [95% CI: 29.4-34.9]).

Table 17 Occupational exposure to asbestos by age at diagnosis stratified by smoking status among 6,521 French male lung cancer cases

	Age at diagnosis (years)										
	< 50 years (698)		50-59 years (1,981)		60-69 years (2,152)		≥ 70 years (1,690)		Total (6,521)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Asbestos											
Non-smokers (180)											
Never (CEI[c]=0)	14 (43.8)	-	15 (44.1)	-	15 (28.3)	-	19 (31.1)	-	63 (35.0)	-	0.491
Ever (CEI>0)	18 (56.3)	23.9 (9.1 - 38.7)	19 (55.9)	25.8 (11.1 - 40.5)	38 (71.7)	34.3 (21.5 - 47.1)	42 (68.9)	25.0 (14.2 - 35.9)	117 (65.0)	27.7 (21.2 - 34.2)	
0<CEI≤1.1	7 (21.9)		3 (8.8)		14 (26.4)		19 (31.1)		43 (23.9)		
1.1<CEI≤16.5	9 (28.1)		4 (11.8)		14 (26.4)		12 (19.7)		39 (21.7)		
CEI>16.5	2 (6.3)		12 (35.3)		10 (18.9)		11 (18.0)		35 (19.4)		
Current smokers (3,747)											
Never (CEI=0)	125 (21.7)	-	370 (26.0)	-	343 (28.4)	-	164 (30.3)	-	1,002 (26.7)	-	**0.003**
Ever (CEI>0)	451 (78.3)	35.7 (31.8 - 39.6)	1,054 (74.0)	35.4 (32.9 - 37.9)	863 (71.6)	33.2 (30.5 - 35.8)	377 (69.7)	29.2 (25.4 - 33.0)	2,745 (73.3)	33.8 (32.3 - 35.4)	
0<CEI≤1.1	158 (27.4)		332 (23.3)		280 (23.2)		135 (25.0)		905 (24.2)		
1.1<CEI≤16.5	188 (32.6)		353 (24.8)		247 (20.5)		125 (23.1)		913 (24.4)		
CEI>16.5	105 (18.2)		369 (25.9)		336 (27.9)		117 (21.6)		927 (24.7)		
Ex-smokers[d] (2,594)											
Never (CEI=0)	20 (22.2)	-	141 (27.0)	-	204 (22.8)	-	297 (27.3)	-	662 (25.5)	-	0.089
Ever (CEI>0)	70 (77.8)	34.3 (24.4 - 44.1)	382 (73.0)	36.3 (32.1 - 40.4)	689 (77.2)	36.3 (33.2 - 39.5)	791 (72.7)	32.1 (29.4 - 34.9)	1,932 (74.5)	34.5 (32.7 - 36.3)	
0<CEI≤1.1	30 (33.3)		130 (24.9)		231 (25.9)		263 (24.2)		654 (25.2)		
1.1<CEI≤16.5	25 (27.8)		140 (26.8)		212 (23.7)		265 (24.4)		642 (24.7)		
CEI>16.5	15 (16.7)		112 (21.4)		246 (27.5)		263 (24.2)		636 (24.5)		

[a] Pw weighted prevalence equal to the sum of the highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects. Highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] Ex-smokers stopped smoking for more than two years.

Table 18 presents the weighted prevalence of occupational exposure to crystalline silica according to age at diagnosis, stratified by the smoking status. Here as well, regardless of the smoking status, there was no significant difference in terms of the weighted prevalence of occupational exposure to crystalline silica between the different categories of age at diagnosis. Among non-smokers, the maximum weighted prevalence of exposure to crystalline silica was observed in the subjects diagnosed between 50 and 59 years old (28.2% [95% CI: 13.1-43.4]), while the minimum weighted prevalence of exposure was observed in subjects diagnosed at 70 years of age or more (10.2% [95% CI: 2.6-17.7]). Among ex-smokers, the maximum weighted prevalence of exposure to crystalline silica was observed in the subjects diagnosed between 60 and 69 years old (26.8% [95% CI: 23.8-29.7]), while the minimum weighted prevalence of exposure was observed in subjects diagnosed at 70 years of age or more (24.2% [95% CI: 21.6-26.7]). Among current smokers, the maximum weighted prevalence of exposure to crystalline silica was observed in the subjects diagnosed younger than 50 years of age (28.4% [95% CI: 24.8-32.1]), while the minimum weighted prevalence of exposure was observed in subjects diagnosed at 70 years of age or more (23.7% [95% CI: 20.1-27.3]).

Table 18 Occupational exposure to crystalline silica by age at diagnosis stratified by smoking status among 6,521 French male lung cancer cases

	Age at diagnosis (years)										
	< 50 years (698)		50-59 years (1,981)		60-69 years (2,152)		≥ 70 years (1,690)		Total (6,521)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Crystalline silica											
Non-smokers (180)											
Never (CEI[c]=0)	24 (75.0)		21 (61.8)		35 (66.0)		50 (82.0%)		130 (72.2)		
Ever (CEI>0)	8 (25.0)	18.8 (5.2 - 32.3)	13 (38.2)	28.2 (13.1 - 43.4)	18 (34.0)	22.0 (10.8 - 33.1)	11 (18.0%)	10.2 (2.6 - 17.7)	50 (27.8)	18.6 (12.9 - 24.3)	0.086
0<CEI≤0.4	2 (6.3)		3 (8.8)		10 (18.9)		6 (9.8)		21 (11.7)		
0.4<CEI≤2.2	4 (12.5)		8 (23.5)		2 (3.8)		0 (0.0)		14 (7.8)		
CEI>2.2	2 (6.3)		2 (5.9)		6 (11.3)		5 (8.2)		15 (8.3)		
Current smokers (3,747)											
Never (CEI=0)	326 (56.6)		854 (60.0)		718 (59.5)		350 (64.7)		2,248 (60.0)		
Ever (CEI>0)	250 (43.4)	28.4 (24.8 - 32.1)	570 (40.0)	26.2 (24.0 - 28.5)	488 (40.5)	26.8 (24.3 - 29.3)	191 (35.3)	23.7 (20.1 - 27.3)	1,499 (40.0)	26.4 (25.0 - 27.8)	0.152
0<CEI≤0.4	116 (20.1)		208 (14.6)		142 (11.8)		53 (9.8)		519 (13.9)		
0.4<CEI≤2.2	96 (16.7)		220 (15.4)		161 (13.3)		61 (11.3)		538 (14.4)		
CEI>2.2	38 (6.6)		142 (10.0)		185 (15.3)		77 (14.2)		442 (11.8)		
Ex-smokers[d] (2,594)											
Never (CEI=0)	57 (63.3)		317 (60.6)		529 (59.2)		700 (64.3)		1,603 (61.8)		
Ever (CEI>0)	33 (36.7)	25.2 (16.2 - 34.1)	206 (39.4)	25.1 (21.4 - 28.8)	364 (40.8)	26.8 (23.8 - 29.7)	388 (35.7)	24.2 (21.6 - 26.7)	991 (38.2)	25.3 (23.6 - 27.0)	0.388
0<CEI≤0.4	12 (13.3)		82 (15.7)		103 (11.5)		110 (10.1)		307 (11.8)		
0.4<CEI≤2.2	14 (15.6)		64 (12.2)		124 (13.9)		100 (9.2)		302 (11.6)		
CEI>2.2	7 (7.8)		60 (11.5)		137 (15.3)		178 (16.4)		382 (14.7)		

[a] Pw weighted prevalence equal to the sum of the highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects. Highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] Ex-smokers stopped smoking for more than two years.

4.3.2.2 Complementary analyses

4.3.2.2.1 Comparison between Hospital-based and Population-based Results

The characteristics of hospital-based series and population-based series were compared. The hospital-based series consisted of 4,400 male lung cancer cases, while population-based series consisted of 2,121 male lung cancer cases. There was a significant difference between hospital-based and population-based according to histological types (squamous cell carcinoma: 31.0% *vs* 35.9%; adenocarcinoma: 38.3% *vs* 35.8%; $p<0.01$), to age at diagnosis (63.2 (±10.5) *vs* 60.0 (±9.0); $p<0.01$), to smoking status (current smokers: 55.3% *vs* 61.9%; $p<0.01$) to CEI for asbestos (15.2 (±28.5) *vs* 13.2 (±30.0) $p<0.01$), and to CEI for crystalline silica (1.3 (±5.0) vs 1.0 (±3.3), $p<0.01$). (Appendix B)

In addition, two sets of analyses were conducted separately for hospital-based and population-based cases; these analyses confirmed the absence of difference in terms of weighted prevalence for the occupational exposure to asbestos or crystalline silica according to histological types, with and without stratification by smoking status. For occupational asbestos exposure, there was no statistically significant difference in terms of weighted prevalence of exposure between histological types of lung cancer among either hospital-based cases ($p=0.22$) or population-based cases ($p=0.07$). On the other hand, for crystalline silica, there was no significant difference in terms of weighted prevalence of exposure between histological types of lung cancer among either hospital-based cases ($p=0.09$) or population-based cases ($p=0.51$). Whatever the smoking status, there was no significant differences in terms of weighted prevalence of occupational asbestos exposure between the histological types of lung cancer. The same findings were observed for crystalline silica. (Appendix C)

For age at diagnosis, there was a statistically significant difference in terms of weighted prevalence of exposure between the categories of age at diagnosis for both occupational asbestos exposure ($p=0.04$) and occupational exposure to crystalline silica ($p=0.03$) among hospital-based series. On the contrary, there was no significant difference in terms of the weighted prevalence of occupational exposure to either asbestos ($p=0.06$) or crystalline silica ($p=0.38$) among population-based series. Despite the non-statistically significant difference for population-based series, the same pattern of higher weighted prevalence of occupational exposures to asbestos and crystalline silica were observed among the category of subjects diagnosed at younger ages. Regardless of the smoking status, there was no significant difference in terms of weighted prevalence of occupational exposure to asbestos, except for current smokers, whereas a statistically significant difference was observed exclusively among hospital-based series ($p<0.01$). For crystalline silica, there was no significant difference in terms of weighted prevalence for smoking statuses. (Appendix C)

4.3.2.2.2 Results Based on Other Definitions of Exposure

The statistical analysis performed included 6,521 French male lung cancer cases was conducted for three different definitions of exposed subjects: *ever exposed regardless of the highest probability of exposure during working life, categorization of subjects according to the highest probability of exposure, and categorization according to the tertiles of the CEI.*

The definition of *ever exposed regardless of the highest probability of exposure during working life* showed the same findings of the main analysis based on the weighted prevalence. For occupational asbestos exposure, there was no statistically significant difference of proportion of

exposure between histological types of lung cancer (*p*=0.07). On the other hand, for crystalline silica, a statistically significant difference was observed between histological types in terms of proportion of exposure (*p*=0.03).

For asbestos exposure, the same results were observed for the two other definitions of exposure (*categorization of subjects according to the highest probability of exposure, and categorization according to the tertiles of the CEI*). For crystalline silica, same results were observed when subjects were categorized according to the highest probability of exposure, but not for the categorization according to the tertiles of the CEI (*p*=0.18). For whatever the smoking status was, there was no significant difference in terms of proportion of asbestos exposure, except for current smokers, and when subjects were categorized according to the tertiles of the CEI (*p*=0.02).

For crystalline silica, there was no significant difference in terms of proportion of exposure among non-smokers and current smokers for the three different exposed subjects. For ex-smokers, findings similar to the main analysis were observed; there was a statistically significant difference in terms of proportion of exposure among the histological types of lung cancer, with the exception for the subjects categorized according to the tertiles of the CEI (*p*=0.25). (Appendix D)

For age at diagnosis, there was a statistically significant difference in term of proportion of exposure between the categories of age at diagnosis for both occupational asbestos exposure and occupational exposure to crystalline silica for the three definitions of exposed subjects. For current smokers and ex-smokers, there was a statistically significant difference in terms of proportion of exposure to asbestos and to crystalline silica. Among non-smokers, there was no significant difference in terms of the proportion of occupational exposure to asbestos or to crystalline silica between the different categories of age at diagnosis.

In conclusion, the results were similar to the main analysis based on the weighted prevalence, especially for the two definitions of *ever exposed regardless of the highest probability of exposure during working life* and *categorization of subjects according to the highest probability of exposure*.

4.3.2.3 Discussion

There were major differences in the occupational exposures to asbestos and crystalline silica between males and females, in addition to the differences of occupational exposure characteristics between France and Canada. Thus, only the 6,521 French male lung cancer cases were included to test the association between different phenotypes of lung cancer (histological types and age at diagnosis) and occupational exposure to asbestos and crystalline silica.

In general, we did not identify a difference of weighted prevalence of occupational exposure to asbestos with and without stratification by smoking status. For crystalline silica, a borderline excess of weighted prevalence of exposure was observed for squamous cell carcinomas, confirmed among ex-smokers. Finally, the weighted prevalence of occupational exposure was maximized among lung cancer cases diagnosed between 50 and 59 years for asbestos and less than 50 years for crystalline silica. All those differences were minimal and of limited clinical importance.

Indeed, those results were confirmed by the additional analyses conducted with other definitions of exposure. Using two different definition of exposure, *ever exposed regardless of the highest probability of exposure during working life* and *categorization according to the tertiles of the CEI*, we did not identify a difference of prevalence of occupational exposure to asbestos with and without stratification by smoking status (*p*=0.067 and *p*=0.0115, respectively). In the contrary,

there was a statically significant difference of prevalence of occupational exposure to crystalline silica according to histological types (p=0.027 and p=0.002, respectively). After stratification by smoking status, there was no difference of prevalence of occupational exposure to crystalline silica among non-smokers and ex-smokers with the exception to ex-smokers (p=0.005 and p=0.042, respectively). (Appendix D)

For age at diagnosis, there was a statically significant difference of prevalence of occupational exposure to asbestos and to crystalline silica according to the different categories of age at diagnosis based on the three other definitions of exposures (*ever exposed regardless of the highest probability of exposure during working life, categorization of subjects according to the highest probability of exposure, and categorization according to the tertiles of the CEI*). Those results were confirmed among ex-smokers and current smokers. (Appendix D)

In order to increase the power of the study, seven different lung cancer series included in this analysis, both hospital-based and population-based, were pooled. This procedure allowed us to present a large number of cases with comparable investigations concerning diagnosis, occupational exposure and smoking habits. In order to test the representativeness of our study population, we verified the distribution of histological types with the results of a French study investigating the trend of histological types of lung cancer cases from 2000 to 2010. In this series, the percentage of squamous cell carcinomas decreased from 38.8% in 2000 to 26.3% in 2010, while the percentage of adenocarcinomas increased from 29.0% in 2000 to reach 45.4% in 2010. (163) The results were consistent with the evolution of the prevalence of histological types of lung cancer in industrial countries as the fraction of squamous cell carcinoma decreased with time while adenocarcinoma increased.(26)

Data from literature describing the prevalence of occupational exposures to either asbestos or crystalline silica according to histological types are sparse. Differences in methods reported in these studies (selection of lung cancer cases and assessment of occupational exposures) make comparisons difficult (Appendix E).

However, in each study, the same exposure assessment method was used across the different histological types of lung cancer. It was interesting to notice that for asbestos, results were similar to ours, and showing the same pattern of distribution of the prevalence of exposure between histological types.(36, 93, 95) In a case-only study conducted in France in 2010 (n=1,493), there was no significant difference of the prevalence of exposure between squamous cell carcinoma (35.8%), adenocarcinoma (34.4%), small cell carcinoma (33.1%), large cell carcinoma (27.2%), and other lung cancer types (33.7%) (p=0.39). (95) In a case-control study conducted in Italy (n=1,537), there was no statistically difference of the prevalence of exposure between squamous cell carcinoma (41.2%), adenocarcinoma (40.5%), and small cell carcinoma (45.9%) (p=0.48). (36) In addition, the same pattern was observed in a study conducted in Netherlands; squamous cell carcinoma (35.1%), adenocarcinoma (27.2%), small cell carcinoma (32.5%), and large cell carcinoma (34.6%) (p=0.2). (93) (Appendix E)

For occupational exposure to crystalline silica, the studies of De Matteis et *al*. and Vida et *al*. showed a higher prevalence of exposure among squamous cell carcinomas and small cell carcinomas, consistent with our findings. (36, 37) In the study of De Matteis et *al.*, the prevalence of exposure was 29.8% for squamous cell carcinoma, 29.3% for small cell carcinoma, while the prevalence of exposure was lower (17.5%) for adenocarcinoma (p<0.001). (36) In a Canadian study conducted in 2010, the prevalence of exposure was 30.0% for squamous cell carcinoma, 25.5% for

small cell carcinoma, while the prevalence of exposure was lower (20.6%) for adenocarcinoma (*p*=0.003). (37) In the study of Paris et *al*., the absence of statistical differences between histological types in terms of prevalence should be interpreted with caution, taking into account the very low level of prevalence of crystalline silica exposure, related to the method of exposure assessment used in this last study.(95) (Appendix E)

Occupational exposures to asbestos and crystalline silica were retrospectively assessed by two specific JEMs elaborated at the department of occupational health of the French Institute for Public Health Surveillance. (12, 149) Although several publications discussed the limitations of JEM compared to other methods (JEMs could lead to false-positives and false-negatives by introducing non-differential misclassifications (142)) (164-166), the utilization of JEMs allowed us to standardize the occupational exposure assessment across all subjects in order to compare the prevalence of occupational exposures according to histological types and age at diagnosis. Moreover, our results were confirmed whatever the definitions of exposed subjects: ever exposed regardless of the highest probability of exposure during working life, categorization of subjects according to the highest probability of exposure during the working life, or categorization according to the tertiles of CEI, indicating that the results were robust. (Appendix D)

The weighted prevalence of exposure estimated in our study was compared with the prevalence of exposures reported previously in the literature, and similar results were observed. Indeed, when a JEM was used to estimate the exposure, the prevalence of occupational exposure to asbestos was between 33.0% and 41.1% among males (36, 93, 123) On the other hand, the assessment of exposure to asbestos by experts showed a prevalence of occupational exposure between 31.2 % and 33.8%. (95, 167) For crystalline silica, the prevalence of occupational exposure found in the literature was similar to the weighted prevalence of the present study with a value between 21.8 % and 24.1% (36, 37, 167), with an exception to one study where the prevalence of exposure was higher (36.2%) (97).

Finally, the characteristics of hospital-based series and population-based series were compared. As expected, some differences were pointed out between the hospital-based cases and the population-based cases (squamous cell carcinoma: 31.0% *vs* 35.9%; adenocarcinoma: 38.3% *vs* 35.8%; age at diagnosis: 63.2 (±10.5) *vs* 60.0 (±9.0); current smokers: 55.3% *vs* 61.9%; cumulative exposure index for asbestos: 15.2 (±28.5) *vs* 13.2 (±30.0); cumulative exposure index for silica: 1.3 (±5.0) vs 1.0 (±3.3), respectively). (Appendix B) In addition, two sets of analyses were conducted separately for hospital-based and population-based cases; these analyses confirmed the absence of difference in terms of weighted prevalence for the occupational exposure to asbestos or crystalline silica according to histological types, with and without stratification by smoking status. For age at diagnosis, despite the non-statistically difference for population-based series, the same pattern of higher weighted prevalence of occupational exposures to asbestos and crystalline silica were observed among the category of subjects diagnosed at younger ages. (Appendix C) Therefore, we considered that pooling the two series of cases did not affect our results.

In addition to the prevalence of exposure to occupational exposures, we aimed to evaluate the statistical interactions between occupational exposures and tobacco smoking according to specific phenotypes of lung cancer (histological types, tumor location and age at diagnosis). The results of the interactions between tobacco smoking and occupational exposure to asbestos and crystalline silica are presented in the next section.

4.3.2.4 Article 2 (Minor revision - American Journal of Industrial Medicine)

Title: Prevalence of occupational exposure to asbestos and crystalline silica according to phenotypes of lung cancer from the CaProMat study: a case-only study.

Short title: Prevalence of occupational exposure to asbestos and crystalline silica according to phenotypes of lung cancer.

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Abstract

Background: The objective of the study was to compare the prevalence of occupational exposure to asbestos and crystalline silica according to histological types of lung cancer and age at diagnosis.
Methods: CaProMat study is a pooled case-only study conducted between 1996 and 2011. The current study consisted of 6,521 lung cancer cases. Occupational exposure to asbestos and crystalline silica was assessed by two Job-Exposure Matrices. A weighted prevalence of exposure was derived and compared according to histological types and age at diagnosis.
Results: There was no difference of weighted prevalence of exposure to asbestos and crystalline silica according to histological types of lung cancer. There was a statistically significant difference of weighted prevalence of exposure to asbestos and crystalline silica according to age at diagnosis.
Conclusions: The histological type and age at diagnosis cannot be used as an indicator for the occupational exposure to asbestos or crystalline silica.

Keywords: Lung cancer, Histological types, Smoking, Asbestos, Crystalline silica.

INTRODUCTION

Lung cancer continues to be the leading cause of cancer deaths among men with an estimation of 1.1 million deaths worldwide corresponding to 24% of all cancer deaths in 2012. [Ferlay, et al. 2014, Islami, et al. 2015, Torre, et al. 2015].

Smoking is the main cause of lung cancer accounting for 80% to 90% of the cases [IARC 1986, Pesch, et al. 2012] However, besides smoking, there are several other risk factors for lung cancer including many occupational exposures. [IARC 2016, Siemiatycki 2014] Among the identified occupational exposure agents, asbestos and crystalline silica represent two of the most prevalent agents' encountered in occupational settings. [IARC 2012, Peters, et al. 2015, Van Tongeren, et al. 2012]

A key concern of clinicians is to help the patient understand the etiology of the disease, which sometimes has legal consequences. In lung cancer, it is possible that patients at different ages and with different histological types have different etiologies and that would be manifested in different profiles of exposures.

It has been recognized that tobacco smoking was associated with all histological types of lung cancer. However, the squamous cell carcinoma and small cell carcinoma were the predominant histological types of lung cancer among male smokers [Khuder, et al. 1998, Pesch, et al. 2012, Read, et al. 2004], and adenocarcinoma was the predominant among non-smokers and women [Pesch, et al. 2012, Read, et al. 2004] resulting in changes in the distribution of histological types over time in France, United States, and other industrialized countries. [Locher, et al. 2013, Lortet-Tieulent, et al. 2014, Meza, et al. 2015]

Besides smoking, there was limited evidence concerning the association between asbestos or crystalline silica and specific histological types of lung cancer. Indeed, very few studies have described the prevalence of occupational exposures to asbestos and crystalline silica according to the histological types of lung cancer. [de Klerk, et al. 1996, De Matteis, et al. 2012, Lee, et al. 1998, Offermans, et al. 2014, Paris, et al. 2010, Vena, et al. 1985, Vida, et al. 2010] Furthermore, to our knowledge, the literature did not uncover studies that investigated the prevalence of occupational exposure to asbestos or crystalline silica according to age at diagnosis.

The objective of this study was to compare the prevalence of occupational exposure to asbestos and crystalline silica according to phenotypes of lung cancer characterized by either histological types of lung cancer or age at diagnosis among a large population of French male cases.

MATERIALS AND METHODS

The CaProMat Study

The CaProMat study is a pooled case-only study of eight original studies, conducted between 1996 and 2011 in different areas in France and in Montreal, Canada. The CaProMat study population consisted of lung cancer cases recruited from: 1) six French university hospitals of Bordeaux, Caen, Créteil, Grenoble, Nancy and Rouen included in the French national occupational disease surveillance and prevention network (RNV3P, Réseau National de Vigilance et de Prévention des Pathologies Professionnelles) [Bonneterre, et al. 2010]; 2) the French population-based case-control study called ICARE in Bas-Rhin, Haut-Rhin, Doubs, Isère, Hérault, Somme, Calvados, Manche, Loire Atlantique, and Vendée [Luce and Stucker 2011]; and 3) a Canadian population-based case-control study [Vallieres, et al. 2012] (See additional file 1).

The hospital-based RNV3P cases consisted of all cases of lung cancer that were treated in thoracic surgery or respiratory medicine services in six French university hospitals and that were addressed to the occupational diseases clinics of each university hospital regardless of the suspicion of occupational exposures. The population-based cases from the two case-control studies consisted of all lung cancer cases identified across all major hospitals (both public and private). All histological types of lung cancer were included in this study. All lung cancer cases were histologically confirmed, and for all of them the histological types and age at diagnosis were collected through medical records.

The initial CaProMat study population consisted of 11,228 lung cancer cases. During pooling and cleaning of data, 966 cases were excluded due to missing data on the occupational history (n=836), missing medical records (n=87), inconsistent data (n=33), duplicated subjects (n=6), and death of subject before the start of the initial study (n=4). In addition, a specific series of 639 cases from Créteil were also excluded because they were highly selected since they consisted of subjects specifically referred for only surgery. Overall, a total of 1,605 cases were excluded from the study, and the final CaProMat study population consisted of 9,623 lung cancer cases (7,256 males and 2,367 females) corresponding to 38,937 jobs.

The characteristics of occupational exposure to asbestos were different between France and Canada; France imported and used different types of fiber while Canada produced exclusively chrysotile. Moreover, France used asbestos until it was banned in 1997 [Allen 2001], while Canada produced raw asbestos until 2011 [Villeneuve, et al. 2012]. To simplify inferences, the study population in the present analysis was restricted to French male lung cancer cases (n=6,521).

Data Collection

In each initial study, data were collected from subjects themselves through face-to-face interviews, except for ICARE study where proxies were interviewed when subjects were too sick to respond.[Luce and Stucker 2011]

For hospital-based RNV3P cases, data were collected through standardized occupational health questionnaire administered by the occupational physician, whereas for the population-based cases (from the ICARE case-control study), data were collected by trained interviewers using standardized questionnaires.[Luce and Stucker 2011]

From the data collected in each individual study, socio-demographic characteristics could be standardized and included in the CaProMat study such as gender, date of birth, educational level, and respondent status. In addition, information about details of the smoking history was standardized including smoking status, total smoking duration, mean number of cigarettes smoked per day, and time since cessation of smoking when appropriate. For smoking status, subjects were categorized as non-smokers if they smoked less than 100 cigarettes lifelong, ex-smokers if they stopped smoking for more than two years, or current smokers. Finally, the details of the occupational history were also standardized and included any job held for more than six months.

In original studies, occupational histories were coded using different classifications for both occupations and industries. Occupational histories were coded according to the International Standard Classification of Occupations (ISCO) of 1988 for occupations [International Labour Organization (ILO) 1990], and to the French Nomenclature of Activities (NAF 2000) for industries for RNV3P cases [Insee 1999]; and according to ISCO of 1968 [International Labour Organization (ILO) 1968] for occupations and NAF 2000 for industries for French population-based cases .

In order to pool occupational histories, each job was re-coded by industrial hygienists according to the ISCO of 1968 for occupations.

Occupational exposure assessment

Occupational exposures to asbestos and crystalline silica were retrospectively assessed by Job-Exposure Matrices (JEM) related to asbestos and crystalline silica. [Fevotte, et al. 2011, Lacourt, et al. 2012] For each job held by subjects, the JEMs assigned automatically three semi-quantitative exposure parameters: the probability, frequency and intensity of exposure.[Fevotte, et al. 2011] In the two JEMs, the intensity of exposure was expressed in equivalent f/ml for asbestos exposure or in equivalent mg/m^3 for crystalline silica since these exposure parameters are the results of an expert assessment [Bouyer and Hemon 1993, Orlowski, et al. 2015] (See additional file 2 for exposure parameters definition).

For each of asbestos and crystalline silica, subject was defined as *ever exposed* if he had *held at least one job with a non-null probability of exposure*. Three exposure indicators were then derived for the two agents studied: the highest probability of exposure over the entire occupational career. The total duration of exposure (in years) corresponded to the sum of jobs durations with a non-null probability of exposure over the entire occupational career. The cumulative exposure index (CEI) corresponded to the sum of the product of the duration, frequency and intensity of exposure for each exposed jobs over the entire career: $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i). CEI was expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure.

Statistical Analysis

To take into account the highest probability of exposure of each of the subjects, we derived a weighted prevalence of occupational exposure to asbestos and crystalline silica. This *weighted prevalence (Pw)* of occupational exposure was equal to the sum of the highest probability of occupational exposure to the agent (asbestos or crystalline silica) for each subject divided by the total number of subjects:

$Pw = \frac{\sum_{i=1}^{n} Pi}{n}$ (Pi: highest probability of exposure of subject i; n: total number of subjects).

We estimated weighted prevalence of occupational exposure to asbestos and crystalline silica according to histological types (squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma and other lung cancer) and according to age at diagnosis (< 50 years, 50 - 59 years, 60 - 69 years, ≥ 70 years). Also, further stratification by smoking status (non-smoker, current smoker, and ex-smoker) was carried out.

The differences between the weighted prevalence of occupational exposures to asbestos and crystalline silica according to histological types and age at diagnosis were tested by Pearson chi-square test or Fisher exact test when appropriate. Data were analyzed using the statistical software SPSS (Statistical Package for Social Sciences), version 21.0 (Chicago, IL, USA). A *p*-value <0.05 was considered significant.

RESULTS

The current study included 6,521 French male lung cancer cases corresponding to 28,385 jobs held for more than six months. The main characteristics of the study subjects were presented in table I. The two most frequent histological types were adenocarcinoma (37.5%) and squamous cell carcinoma

(32.6%). The mean age at diagnosis was 62.2 (±10.1) years. According to smoking status, 2.8% of the cases were non-smokers, while 57.4% and 39.8% were current smokers and ex-smokers, respectively. Considering the last job held, half of the cases were blue-collar workers (*production and related workers, transport equipment operators and labourers* according to the ISCO of 1968). For asbestos, the proportion of subjects who held at least one job with a non-null probability of exposure was 73.5% and 16.4% had a highest probability of exposure greater than 70%. The proportion of subjects who held at least one job with a non-null probability of exposure to crystalline silica was 39.0% and 25.9% had a highest probability of exposure greater than 50%. Finally, the mean CEI was 14.6 (±29.0) f/ml.year for asbestos and 1.2 (±4.5) mg/m^3-year for crystalline silica.

Table II presented the weighted prevalence of occupational exposure to asbestos and crystalline silica according to histological types of lung cancer. The weighted prevalence of exposure to asbestos was 33.9% [95% CI: 32.8 - 35.1], while the weighted prevalence of exposure to crystalline silica was 25.7% [95% CI: 24.7 - 26.8]. For occupational asbestos exposure, there was no statistically significant difference in terms of weighted prevalence of exposure between histological types of lung cancer (p=0.13). Indeed, the maximum weighted prevalence of exposure was 35.0% [95% CI: 33.0 - 37.1] for the squamous cell carcinoma types, while it was at minimum 32.2%; [95% CI: 28.8 - 35.5] for the large cell carcinoma types. On the other hand, for crystalline silica, a borderline statistically significant difference was observed between histological types in terms of weighted prevalence of exposure (p=0.049). The maximum weighted prevalence of exposure to crystalline silica was 27.7% [95% CI: 25.8 - 29.6] for the squamous cell carcinoma types and the minimum weighted prevalence of exposure was 23.5% [95% CI: 18.8 - 28.2] for other lung cancer types.

Table III presented the weighted prevalence of occupational exposure to asbestos according to histological types of lung cancer stratified by the smoking status. Whatever the smoking status, there was no significant differences in terms of weighted prevalence of occupational asbestos exposure between the histological types of lung cancer.

Table IV presented the weighted prevalence of occupational exposure to crystalline silica according to histological types of lung cancer stratified by smoking status. Whatever the smoking status, there was no significant differences in terms of weighted prevalence of occupational exposure to crystalline silica, except for ex-smokers, where a borderline statistically significant difference was observed (p=0.045).

Table V presented the weighted prevalence of occupational exposure to asbestos and crystalline silica according to age at diagnosis. There was a statistically significant difference in terms of weighted prevalence of exposure between the categories of age at diagnosis for both occupational asbestos exposure (p=0.014) and occupational exposure to crystalline silica (p=0.018). The maximum weighted prevalence of exposure was observed in the subjects diagnosed between 50 to 59 years old for asbestos and younger than 50 years of age for crystalline silica (35.5% [95% CI: 33.4 - 37.6] and 27.6% [95% CI: 24.3 – 30.9], respectively), while the minimum weighted prevalence of exposure was observed in subjects diagnosed at 70 years of age or more for both agents (30.9% [95% CI: 28.7 – 33.1] and 23.5% [95% CI: 21.5 – 25.5], respectively).

Table VI presented the weighted prevalence of occupational exposure to asbestos according to age at diagnosis stratified by the smoking status. Regardless of the smoking status, there was no significant differences in terms of the weighted prevalence of occupational exposure to asbestos, except for current smokers, where a statistically significant difference was observed (p=0.003). Among current smokers, the maximum weighted prevalence of exposure to asbestos was observed in the subjects diagnosed younger than 50 years of age (35.7% [95% CI: 31.8 – 39.6]), while the minimum weighted

prevalence of exposure was observed in subjects diagnosed at 70 years of age or more (29.2% [95% CI: 25.4 – 33.0]).

Table VII presented the weighted prevalence of occupational exposure to crystalline silica according to age at diagnosis, stratified by the smoking status. Here as well, regardless of the smoking status, there was no significant difference in terms of the weighted prevalence of occupational exposure to crystalline silica between the different categories of age at diagnosis.

DISCUSSION

In this large study concerning 6,521 French male lung cancer cases, we had the opportunity to test the association between different phenotypes of lung cancer (histological types and age at diagnosis) and two occupational lung carcinogens, namely asbestos and crystalline silica. Globally, we did not identify a difference of weighted prevalence of occupational exposure to asbestos with and without stratification by smoking status. For crystalline silica, a borderline excess of weighted prevalence of exposure was observed for squamous cell carcinoma, confirmed among ex-smokers. Finally, the weighted prevalence of occupational exposure was maximized among lung cancer cases diagnosed between 50 and 59 years for asbestos and less than 50 years for crystalline silica. All those differences were minimal and of limited clinical importance.

Data from literature describing the prevalence of occupational exposures to either asbestos or crystalline silica according to histological types are sparse. Differences in methods reported in these studies (selection of lung cancer cases and assessment of occupational exposures) make comparisons difficult (see additional file 3). However, in each study, the same exposure assessment method was used across the different histological types of lung cancer. It was interesting to notice that for asbestos, results were similar to ours, and showing the same pattern of distribution of the prevalence of exposure between histological types.[De Matteis, et al. 2012, Offermans, et al. 2014, Paris, et al. 2010] For occupational exposure to crystalline silica, the studies of De Matteis et *al.* and Vida et *al.* showed a higher prevalence of exposure among squamous cell carcinomas and small cell carcinomas, consistent with our findings. [De Matteis, et al. 2012, Vida, et al. 2010] In the study of Paris et *al.*, the absence of statistical differences between histological types in terms of prevalence should be interpreted with caution, taking into account the very low level of prevalence of crystalline silica exposure, related to the method of exposure assessment used in this last study.[Paris, et al. 2010]

In the current study, occupational exposures to asbestos and crystalline silica were retrospectively assessed by two specific JEMs elaborated at the department of occupational health of the French Institute for Public Health Surveillance. [Fevotte, et al. 2011, Lacourt, et al. 2012] Although several publications discussed the limitations of JEM compared to other methods [Benke, et al. 2001, Nam, et al. 2005, Offermans, et al. 2012], the utilization of JEMs allowed us to standardize the occupational exposure assessment across all subjects in order to compare the prevalence of occupational exposures according to histological types and age at diagnosis. Moreover, our results were confirmed whatever the definitions of exposed subjects: ever exposed regardless of the highest probability of exposure during working life, categorization of subjects according to the highest probability of exposure during the working life, or categorization according to the tertiles of CEI, indicating that the results were robust (see additional file 4).

In addition, a weighted prevalence of exposure was derived to take into account the uncertainty of exposures by giving every subject a weight based on its highest probability to have been occupationally exposed over its entire occupational career. The weighted prevalence of exposure estimated in our study was compared with the prevalence of exposures reported previously in the literature, and similar

results were observed. Indeed, when a JEM was used to estimate the exposure, the prevalence of occupational exposure to asbestos was between 33.0 % and 41.1 % among males [De Matteis, et al. 2012, Jöckel, et al. 1998, Offermans, et al. 2014] On the other hand, the assessment of exposure to asbestos by experts showed a prevalence of occupational exposure between 31.2 % and 33.8 %. [Bruske-Hohlfeld, et al. 2000, Paris, et al. 2010] For crystalline silica, the prevalence of occupational exposure found in the literature was similar to the weighted prevalence of the present study with a value between 21.8 % and 24.1 % [Bruske-Hohlfeld, et al. 2000, De Matteis, et al. 2012, Vida, et al. 2010], with an exception to one study where the prevalence of exposure was higher (36.2 %) [Kachuri, et al. 2014].

In order to increase the power of the study, seven different lung cancer series included in this analysis, both hospital-based and population-based, were pooled. This procedure allowed us to present a large number of cases with comparable investigations concerning diagnosis, occupational exposure and smoking habits. In order to test the representativeness of our study population, we verified the distribution of histological types with the results of a French study investigating the trend of histological types of lung cancer cases from 2000 to 2010. In this series, the percentage of squamous cell carcinomas decreased from 38.8% in 2000 to 26.3% in 2010, while the percentage of adenocarcinomas increased from 29.0% in 2000 to reach 45.4% in 2010. [Locher, et al. 2013] The results were consistent with the evolution of the prevalence of histological types of lung cancer in industrial countries as the fraction of squamous cell carcinoma decreased with time while adenocarcinoma increased.[Lortet-Tieulent, et al. 2014]

Finally, the characteristics of hospital-based series and population-based series were compared. As expected, some differences were pointed out between the hospital-based cases and the population-based cases (squamous cell carcinoma: 31.0% *vs* 35.9%; adenocarcinoma: 38.3% *vs* 35.8%; age at diagnosis: 63.2 (±10.5) *vs* 60.0 (±9.0); current smokers: 55.3% *vs* 61.9%; cumulative exposure index for asbestos: 15.2 (±28.5) *vs* 13.2 (±30.0); cumulative exposure index for silica: 1.3 (±5.0) vs 1.0 (±3.3), respectively). (See additional file 5) In addition, two sets of analyses were conducted separately for hospital-based and population-based cases; these analyses confirmed the absence of difference in terms of weighted prevalence for the occupational exposure to asbestos or crystalline silica according to histological types, with and without stratification by smoking status. For age at diagnosis, despite the non-statistically difference for population-based series, the same pattern of higher weighted prevalence of occupational exposures to asbestos and crystalline silica were observed among the category of subjects diagnosed at younger ages.(See additional file 6) Therefore, we considered that pooling the two series of cases did not affect our results.

CONCLUSION

To our knowledge, this is the largest case-only study on lung cancer conducted to describe the prevalence of occupational exposure to asbestos and crystalline silica according to histological types and age at diagnosis. There was no major difference in the prevalence of occupational exposures to asbestos and crystalline silica according to histological types and age at diagnosis. As a result, the histological type of lung cancer and age at diagnosis cannot be used as an indicator for the occupational exposure to asbestos or to crystalline silica. Therefore, the occupational exposure investigation should be conducted to identify the exposure to suspected occupational carcinogenic agents whatever the histological type or age at diagnosis.

LIST OF ABBREVIATIONS

IARC: International Agency for Research on Cancer

JEM: Job-Exposure Matrix
RNV3P: Réseau National de Vigilance et de Prévention des Pathologies Professionnelles
ISCO: International Standard Classification of Occupations
NAF: French Nomenclature of Activities
CEI: Cumulative Exposure Index
Pw: Weighted Prevalence
p: p-value
CI: Confidence Interval

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4.3.3 Interaction between Smoking and Occupational Exposures on Phenotypes of Lung Cancer

4.3.3.1 Main Results

The population study consisted of 7,256 male lung cancer cases representing 31,332 jobs held for more than six months. Table 19 presents the main characteristics of the population. Squamous cell carcinomas and adenocarcinomas represented 69.9% of the histological types with 32.9% and 37.0%, respectively. The bronchial tumor location was available for 4,689 cases representing 64.6% of the study population. There was a predominance of upper lobe tumors with 68.2% of the 4,689 lung cancer cases. The mean age at diagnosis was 62.4 (±10.0). Non-smokers represented 2.7% of the population study, while 58.5% and 38.8% were current smokers and ex-smokers, respectively. For occupational exposure to asbestos, 27.1% were never exposed, 23.1% had an uncertain exposure status (at least one job with a highest probability of exposure less than 30%), and 49.8% were defined as exposed. For occupational exposure to crystalline silica, 62.1% of subjects were never exposed, 5.4% had an uncertain exposure status (at least one job with a highest probability of exposure less than 30%) and 32.5% were defined as exposed.

Table 19 Main characteristics of male subjects included in the CaProMat pooled case-only study.

Characteristics	Male (7,256) n	%
Histological type		
Squamous-cell carcinoma	2,384	32.9
Small cell lung cancer	1,026	14.1
Adenocarcinoma	2,687	37.0
Large cell carcinoma	805	11.1
Other lung cancer	354	4.9
Tumor location (4,689)		
Upper lobe tumor	3,200	68.2
Lower lobe tumor	1,489	31.8
Age at diagnosis		
Age at diagnosis (years), mean (SD[1])	62.4 (10.0)	
Respondent status		
Self	6,905	95.2
Proxy	351	4.8
Smoking status		
Non-smokers	198	2.7
Current smokers	4,244	58.5
Ex-smokers	2,814	38.8
Comprehensive Smoking Index (CSI) quartiles		
Mean (SD[1])	1.7 (0.7)	
CSI=0	198	2.7
0 < CSI ≤ 1.37	1,764	24.3
1.37 < CSI ≤ 1.84	1,765	24.3
1.84 < CSI ≤ 2.17	1,774	24.4
CSI > 2.17	1,755	24.2
Educational level		
Unschooled	119	1.6
Primary	1,725	23.8
Secondary	2,829	39.0
Post-secondary	666	9.2
Unknown	1,917	26.4
Last job category (ISCO 1968)[2]		
Professional, technical and related workers	835	11.5
Administrative and managerial workers	405	5.6
Clerical and related workers	643	8.9
Sales workers	537	7.4
Service workers	637	8.8
Agricultural, animal husbandry and forestry workers, fishermen and hunters	346	4.8
Production and related workers, transport equipment operators and labourers	3,833	52.8
Unknown	20	0.3
Asbestos exposure		
Non-exposed	1,970	27.1
Uncertain exposure[3]	1,674	23.1
Exposed		
30% < P[4] ≤ 70%	2,438	33.6
P > 70%	1,174	16.2
Total duration of exposure (years), mean (SD)	17.5 (17.2)	
Cumulative exposure index[5] (f/ml.year), mean (SD)	16.8 (30.5)	
Crystalline silica		
Non-exposed	4,508	62.1
Uncertain exposure[3]	391	5.4
Exposed		
30% < P[4] ≤ 70%	1,107	15.3
P > 70%	1,250	17.2
Total duration of exposure (years), mean (SD)	7.4 (13.1)	
Cumulative exposure index[5] (mg/m^3-year), mean (SD)	1.2 (4.2)	

[1]SD standard Deviation.
[2] ISCO 1968 International Standard Classification of Occupations, 1968, second edition.
[3] Uncertain exposure: 0%<P<30%
[4] The highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[5] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).

Table 20 presents the statistical interactions on a multiplicative scale between tobacco smoking and occupational exposure to asbestos according to histological type of lung cancer.

The results showed that among subjects non-exposed to asbestos, tobacco smoking was positively associated with squamous cell carcinomas compared to other histological types (OR = 1.52 [95% CI: 1.20-1.92]) or to adenocarcinomas only (OR = 1.89 [95% CI: 1.47-2.44]). Among subjects exposed to asbestos, the magnitude of the association was similar than expected (OR = 1.83 [95% CI: 1.45-2.32] and OR = 2.15 [95% CI: 1.67-2.78] respectively). Indeed there was no statistical interaction on a multiplicative scale between tobacco smoking and occupational exposure to asbestos (p=0.90 and p=0.46, respectively).

The results showed that among subjects non-exposed to asbestos, tobacco smoking was positively associated with small cell carcinomas compared to other histological types (OR = 2.05 [95% CI: 1.47-2.84]) or to adenocarcinomas only (OR = 2.61 [95% CI: 1.84-3.70]). Among subjects exposed to asbestos, the magnitude of the association was similar than expected (OR = 1.75 [95% CI: 1.25-2.44] and OR = 2.31 [95% CI: 1.62-3.30] respectively). Indeed there was no statistical interaction on a multiplicative scale between tobacco smoking and occupational exposure to asbestos (p=0.34 and p=0.21, respectively).

Table 20 Statistical interaction between tobacco smoking and asbestos exposure on histological types among male lung cancer cases.

Asbestos exposure	Smoking status				β for cross-product term	*p* for cross-product term
	Never-low smokers[1]		Medium-high smokers[2]			
	SQCC/Others	OR (95%CI)[3]	SQCC/Others	OR (95%CI)[3]		
Non-exposed (P=0%)	132/398	1.00[4]	438/950	1.52 (1.20-1.92)	-0.02	0.90
Exposed (P>30%)	262/625	1.23 (0.95-1.59)	876/1,598	1.83 (1.45-2.32)		
	SQCC/ADC	OR (95%CI)[3]	SQCC/ADC	OR (95%CI)[3]		
Non-exposed (P=0%)	132/254	1.00[4]	438/486	1.89 (1.47-2.44)	-0.12	0.46
Exposed (P>30%)	262/377	1.28 (0.96-1.70)	876/868	2.15 (1.67-2.78)		
	SCC/Others	OR (95%CI)[3]	SCC/Others	OR (95%CI)[3]		
Non-exposed (P=0%)	48/482	1.00[4]	240/1,148	2.05 (1.47-2.84)	-0.20	0.34
Exposed (P>30%)	84/803	1.05 (0.71-1.54)	384/2,090	1.75 (1.25-2.44)		
	SCC/ADC	OR (95%CI)[3]	SCC/ADC	OR (95%CI)[3]		
Non-exposed (P=0%)	48/254	1.00[4]	240/486	2.61 (1.84-3.70)	-0.28	0.21
Exposed (P>30%)	84/377	1.17 (0.78-1.75)	384/868	2.31 (1.62-3.30)		

SQCC: Squamous cell carcinoma; ADC: Adenocarcinoma; SCC: Small cell carcinoma; P: Highest probability of exposure.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to crystalline silica (non-exposed vs exposed), age at diagnosis (years), and initial study.
[4]: Reference category defined as never-low smokers and non-exposed to asbestos.

Table 21 presents the statistical interactions on a multiplicative scale between tobacco smoking and occupational exposure to crystalline silica according to histological type of lung cancer.

The results show that among subjects non-exposed to crystalline silica, tobacco smoking was positively associated with squamous cell carcinomas compared to other histological types (OR = 1.62 [95% CI: 1.36-1.93]) or to adenocarcinomas only (OR = 1.92 [95% CI: 1.58-2.33]). Among subjects exposed to crystalline silica, the magnitude of the association was similar than expected (OR = 1.72 [95% CI: 1.41-2.11] and OR = 2.15 [95% CI: 1.72-2.70] respectively). Indeed, there was no statistical interaction on a multiplicative scale between tobacco smoking and occupational exposure to crystalline silica (p=0.17 and p=0.12, respectively).

When considering small cell carcinomas versus either other histological types or adenocarcinomas only, similar findings were observed. The results show that among subjects non-exposed to crystalline silica, tobacco smoking was positively associated with small cell carcinomas compared to other histological types (OR = 1.82 [95% CI: 1.42-2.34]) or to adenocarcinomas only (OR = 2.30 [95% CI: 1.76-2.99]). Among subjects exposed to crystalline silica, the magnitude of the association was similar than expected (OR = 1.96 [95% CI: 1.48-2.60] and OR = 2.57 [95% CI: 1.89-3.50] respectively). Indeed, there was no statistical interaction on a multiplicative scale between tobacco smoking and occupational exposure to crystalline silica (p=0.90 and p=0.59, respectively).

Table 21 Statistical interaction between tobacco smoking and crystalline silica exposure on histological types among male lung cancer cases.

Crystalline silica exposure	**Smoking status**				**β for cross-product term**	***p* for cross-product term**
	Never-low smokers[1]		Medium-high smokers[2]			
	SQCC/Others	OR (95%CI)[3]	SQCC/Others	OR (95%CI)[3]		
Non-exposed (P=0%)	241/697	1.00[4]	797/1,616	1.62 (1.36-1.93)	-0.20	0.17
Exposed (P>30%)	153/326	1.30 (1.01-1.68)	517/932	1.72 (1.41-2.11)		
	SQCC/ADC	OR (95%CI)[3]	SQCC/ADC	OR (95%CI)[3]		
Non-exposed (P=0%)	241/438	1.00[4]	797/855	1.92 (1.58-2.33)	-0.25	0.12
Exposed (P>30%)	153/193	1.44 (1.08-1.91)	517/499	2.15 (1.72-2.70)		
	SCC/Others	OR (95%CI)[3]	SCC/Others	OR (95%CI)[3]		
Non-exposed (P=0%)	87/851	1.00[4]	392/2,021	1.82 (1.42-2.34)	-0.03	0.90
Exposed (P>30%)	45/434	1.10 (0.74-1.64)	232/1,217	1.96 (1.48-2.60)		
	SCC/ADC	OR (95%CI)[3]	SCC/ADC	OR (95%CI)[3]		
Non-exposed (P=0%)	87/438	1.00[4]	392/855	2.30 (1.76-2.99)	-0.12	0.59
Exposed (P>30%)	45/193	1.27 (0.84-1.93)	232/499	2.57 (1.89-3.50)		

SQCC: Squamous cell carcinoma; ADC: Adenocarcinoma; SCC: Small cell carcinoma; P: Highest probability of exposure.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to asbestos (non-exposed vs exposed), age at diagnosis (years), and initial study.
[4]: Reference category defined as never-low smokers and non-exposed to crystalline silica.

Table 22 presents the statistical interactions on a multiplicative scale between tobacco smoking and occupational exposure to asbestos and crystalline silica according to the bronchial tumor location There was neither association nor interaction between tobacco smoking and asbestos exposure (β=0.08; *p*=0.66]), or crystalline silica exposure (β=-0.02; *p*=0.91).

Table 22 Statistical interaction between tobacco smoking and exposure to either asbestos or crystalline silica on tumor location among male lung cancer cases.

	Smoking status				**β for cross-product term**	***p* for cross-product term**
	Never-low smokers[1]		Medium-high smokers[2]			
	Upper lobe/Lower lobe	OR (95%CI)[3]	Upper lobe/Lower lobe	OR (95%CI)[3]		
Asbestos exposure						
Non-exposed (P=0%)	243/110	1.00[4]	582/251	1.02 (0.78-1.35)	0.08	0.66
Exposed (P>30%)	382/198	0.91 (0.67-1.23)	1,171/495	1.01 (0.77-1.33)		
Crystalline silica exposure						
Non-exposed (P=0%)	414/202	1.00[4]	1,040/442	1.08 (0.88-1.33)	-0.02	0.91
Exposed (P>30%)	211/106	0.99 (0.73-1.35)	713/304	1.05 (0.83-1.34)		

P: Highest probability of exposure.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to either asbestos or crystalline silica (non-exposed vs exposed), age at diagnosis (years), histological types, and initial study.
[4]: Reference category defined as never-low smokers and non-exposed to either asbestos or crystalline silica.

Table 23 presents the statistical interaction on an additive scale between tobacco smoking and occupational exposure to asbestos according to age at diagnosis. Subjects that were medium-high smokers and exposed to asbestos were diagnosed earlier than never-low smokers and non-exposed subjects, without statistical interaction except for adenocarcinomas (*p* for cross-product term <0.01).

Table 23 Statistical interaction between tobacco smoking and asbestos exposure on age at diagnosis stratified by histological types.

	Smoking status				
	Never-low smokers[1]		Medium-high smokers[2]		
	n (%)	Age at diagnosis (95% CI)[3]	n (%)	Age at diagnosis (95% CI)[3]	*p* for cross-product term
Squamous cell carcinoma (1,708)					
Asbestos exposure					
Non-exposed (P=0%)	132 (7.7)	68.7 (66.5-70.9)	438 (25.6)	65.7 (61.8-69.7)	0.50
Exposed (P>30%)	262 (15.3)	67.9 (63.7-72.0)	876 (51.3)	64.1 (56.1-72.2)	
Small cell carcinoma (756)					
Asbestos exposure					
Non-exposed (P=0%)	48 (6.3)	68.4 (64.9-71.9)	240 (31.7)	64.7 (58.2-71.1)	0.95
Exposed (P>30%)	84 (11.1)	66.6 (59.7-73.6)	384 (50.8)	63.0 (49.5-76.6)	
Adenocarcinoma (1,985)					
Asbestos exposure					
Non-exposed (P=0%)	254 (12.8)	63.5 (61.8-65.2)	486 (24.5)	61.8 (58.7-64.9)	<0.01
Exposed (P>30%)	377 (19.0)	65.6 (62.4-68.9)	868 (43.7)	60.6 (54.1-67.2)	
Large cell carcinoma (577)					
Asbestos exposure					
Non-exposed (P=0%)	66 (11.4)	65.9 (61.7-70.1)	152 (26.3)	63.9 (56.6-71.1)	0.91
Exposed (P>30%)	108 (18.7)	66.2 (58.6-73.9)	251 (43.5)	64.0 (49.3-78.6)	
Others (253)					
Asbestos exposure					
Non-exposed (P=0%)	30 (11.9)	64.2 (57.0-71.4)	72 (28.5)	65.4 (53.4-77.4)	0.32
Exposed (P>30%)	56 (22.1)	66.5 (54.0-79.0)	95 (37.5)	64.6 (41.2-88.0)	

P: Highest probability of exposure.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to crystalline silica (non-exposed vs exposed), and initial study.

Table 24 presents the statistical interaction on an additive scale between tobacco smoking and occupational exposure to crystalline silica according to age at diagnosis. Subjects that were medium-high smokers and exposed to crystalline silica were diagnosed earlier than never-low smokers and non-exposed subjects, without statistical interaction on an additive scale among all histological types.

Table 24 Statistical interaction between tobacco smoking and crystalline silica exposure on age at diagnosis stratified by histological types.

	Smoking status				
	Never-low smokers[1]		Medium-high smokers[2]		
	n (%)	Age at diagnosis (95% CI)[3]	n (%)	Age at diagnosis (95% CI)[3]	*p* for cross-product term
Squamous cell carcinoma (1,708)					
Crystalline silica exposure					
Non-exposed (P=0%)	241 (14.1)	69.0 (67.1-71.0)	797 (46.7)	65.6 (62.4-68.9)	0.87
Exposed (P>30%)	153 (9.0)	69.0 (65.1-72.9)	517 (30.3)	65.5 (58.2-72.7)	
Small cell carcinoma (756)					
Crystalline silica exposure					
Non-exposed (P=0%)	87 (11.5)	68.3 (65.2-71.4)	392 (51.9)	64.7 (59.4-70.0)	0.96
Exposed (P>30%)	45 (6.0)	68.9 (62.3-75.6)	232 (30.7)	65.2 (52.6-77.8)	
Adenocarcinoma (1,985)					
Crystalline silica exposure					
Non-exposed (P=0%)	438 (22.1)	64.5 (62.9-66.1)	855 (43.1)	61.3 (58.7-64.0)	0.10
Exposed (P>30%)	193 (9.7)	64.4 (61.1-67.7)	499 (25.1)	59.6 (53.3-65.9)	
Large cell carcinoma (577)					
Crystalline silica exposure					
Non-exposed (P=0%)	113 (19.6)	66.4 (62.5-70.3)	257 (44.5)	63.6 (57.3-69.8)	0.39
Exposed (P>30%)	61 (10.6)	64.6 (57.2-72.0)	146 (25.3)	63.6 (49.8-77.3)	
Others (253)					
Crystalline silica exposure					
Non-exposed (P=0%)	59 (23.3)	65.6 (58.6-72.5)	112 (44.3)	64.6 (54.0-75.2)	0.83
Exposed (P>30%)	27 (10.7)	63.6 (51.3-75.9)	55 (21.7)	63.3 (41.0-85.7)	

P: Highest probability of exposure.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to asbestos (non-exposed vs exposed), and initial study.

4.3.3.2 Complementary Analyses

4.3.3.2.1 First Complementary Analysis

In the first complementary analysis, we considered subjects who held at least one job with a non-null probability of exposure as exposed. (Appendix F)

The statistical interactions on multiplicative scale between tobacco smoking and occupational exposure to asbestos according to histological types of lung cancer were examined. Results showed that among subjects non-exposed to asbestos, tobacco smoking was positively associated with squamous cell carcinomas compared to other histological types (OR = 1.46 [95% CI: 1.16-1.83]) or to adenocarcinomas only (OR = 1.82 [95% CI: 1.41-2.33]). Among subjects exposed to asbestos, the magnitude of the association was similar (OR = 1.72 [95% CI: 1.39-2.13] and OR = 2.08 [95% CI: 1.64-2.63] respectively). Indeed, there was no statistical interaction on multiplicative scale between tobacco smoking and occupational exposure to asbestos (p=0.92 and p=0.48, respectively). Similar findings were observed when looking at small cell carcinomas. Among subjects non-exposed to asbestos, tobacco smoking was positively associated with small cell carcinomas compared to other histological types (OR = 2.06 [95% CI: 1.49-2.84]) or to adenocarcinomas only (OR = 2.60 [95% CI: 1.84-3.66]). Among subjects exposed to asbestos, the magnitude of the association was similar (OR = 1.71 [95% CI: 1.25-2.34] and OR = 2.26 [95% CI: 1.62-3.16] respectively). Indeed there was no statistical interaction on multiplicative scale between tobacco smoking and occupational exposure to asbestos (p=0.23 and p=0.14, respectively).

The statistical interactions on multiplicative scale between tobacco smoking and occupational exposure to crystalline silica according to histological types of lung cancer were evaluated. Results showed that among subjects non-exposed to silica, tobacco smoking was positively associated with squamous cell carcinomas compared to other histological types (OR = 1.61 [1.38-1.87]) or to adenocarcinomas only (OR = 1.92 [95% CI: 1.63-2.27]). Among subjects exposed to silica, the magnitude of the association was lower than expected (OR = 1.71 [95% CI: 1.45-2.02] and OR = 2.05 [95% CI: 1.70-2.47], respectively). On the other hand, among never-low smokers, crystalline silica exposure was positively associated with squamous cell carcinomas compared to other histological types (OR = 1.41 [95% CI: 1.14-1.74]) or to adenocarcinomas only (OR = 1.52 [95% CI: 1.20-1.92]). As a matter of fact, there was a negative statistical interaction on multiplicative scale between tobacco smoking and occupational exposure to silica (p=0.02 and p=0.01, respectively). Among subjects non-exposed to crystalline silica, tobacco smoking was positively associated with small cell carcinomas compared to other histological types (OR = 1.84 [95% CI: 1.48-2.28]) or to adenocarcinomas only (OR = 2.33 [95% CI: 1.85-2.93]). Among subjects exposed to crystalline silica, the magnitude of the association was lower than expected (OR = 1.91 [95% CI: 1.51-2.42] and OR = 2.46 [95% CI: 1.90-3.17] respectively). Among never-low smokers, crystalline silica exposure was positively associated with small cell carcinomas (OR = 1.41 [95% CI: 1.01-1.98]). When considering small cell carcinomas versus either other histological types or adenocarcinomas only, there was no statistical interaction observed (p=0.42 and p=0.13, respectively).

The statistical interactions on multiplicative scale between tobacco smoking and occupational exposure to asbestos and crystalline silica according to the bronchial tumor location were examined. There was neither association nor any interaction between tobacco smoking and asbestos exposure (β=0.11; p=0.49]), or crystalline silica exposure (β=<0.01; p=0.99).

The statistical interaction on additive scale between tobacco smoking and occupational exposure to asbestos according to age at diagnosis was evaluated. Subjects medium-high smokers and exposed to asbestos were diagnosed earlier than never-low smokers and non-

exposed subjects, without statistical interaction except for adenocarcinomas (*p* for cross-product term < 0.01).

Also, the statistical interaction on additive scale between tobacco smoking and occupational exposure to crystalline silica according to age at diagnosis was tested. Medium-high smokers and exposed to crystalline silica were diagnosed earlier than never-low smokers and non-exposed subjects, without statistical interactions except for adenocarcinomas (*p* for cross-product term < 0.05). (Appendix F)

4.3.3.2.2 Second Complementary Analysis

In the second complementary analysis, we considered subjects with a highest probability of exposure lower than 30% as non-exposed. The results of the second complementary analysis show the same findings as the main statistical analyses. (Appendix G)

Among subjects non-exposed to asbestos, tobacco smoking was positively associated with squamous cell carcinomas compared to other histological types or to adenocarcinomas only. Among subjects exposed to asbestos, the magnitude of the association was similar. Indeed there was no statistical interaction on multiplicative scale between tobacco smoking and occupational exposure to asbestos. Similar findings were observed when looking for small cell carcinomas.

In addition, among subjects non-exposed to crystalline silica and those exposed to crystalline silica, tobacco smoking was positively associated with squamous cell carcinomas compared to other histological types or to adenocarcinomas only. Otherwise, among never-low smokers, crystalline silica exposure was positively associated with squamous cell carcinomas compared to other histological types or to adenocarcinomas only. Indeed, there was no statistical interaction on multiplicative scale between tobacco smoking and occupational exposure to crystalline silica. Among subjects non-exposed to crystalline silica, tobacco smoking was positively associated with small cell carcinomas compared to other histological types or to adenocarcinomas only. Among subjects exposed to crystalline silica, the magnitude of the association was lower than expected. There was no statistical interaction when considering small cell carcinomas versus either other histological types or adenocarcinomas only.

In general, there were absence of statistical interactions on multiplicative scale between tobacco smoking and occupational exposure to either asbestos or crystalline silica according to the bronchial tumor location.

Medium-high smokers and exposed to asbestos were diagnosed earlier than never-low smokers and non-exposed subjects, without additive statistical interaction except for adenocarcinomas. Medium-high smokers and exposed to crystalline silica were diagnosed earlier than never-low smokers and non-exposed subjects, without additive statistical interaction for all histological types. (Appendix G)

4.3.3.2.3 Third Complementary Analysis

The third complementary analysis was conducted exclusively among subjects who responded to assess the impact of next-of-kin respondents on our results. This set of analyses showed the same findings as the main statistical analyses. (Appendix H)

4.3.3.3 Discussion

Tobacco smoking exposure was the main factor related to histological type and age at diagnosis. Squamous cell carcinoma and small cell carcinoma occurred more frequently among smokers. Lung cancer cases were diagnosed earlier among smokers. Additional exposure to either

asbestos or crystalline silica did not modify the effect of tobacco smoking for both histological type and age at diagnosis. Finally, neither tobacco smoking nor occupational exposure to asbestos or crystalline silica seemed to influence tumor location (upper *versus* lower lobes).

First of all, regarding tobacco smoking, our results are consistent with the literature. Tobacco smoking seemed to be more prevalent among squamous cell carcinoma and small cell carcinoma cases compared to adenocarcinoma cases. (6, 16, 168, 169) When looking at tumor location, lung cancer appeared to be more frequent in upper lobes irrespective of tobacco smoking (27). Moreover, when comparing current smokers to non-smokers, this difference seemed to be more prevalent among smokers (28). This is contradictory with our results; however, the study of Lee et *al.* did not simultaneously take into account tobacco smoking and histological types (28).

Finally, regarding age at diagnosis, similarly to our results, data from six cohort studies, mostly US based, suggested that lung cancer occurred later among non-smokers than among smokers, with large differences from one study to another (170). The same trend was observed in a case-control study (171). However, a detection bias cannot be excluded among young smokers (172).

Previous case series from the general population have not demonstrated a predominant histological type among subjects exposed to asbestos (28, 36, 95, 173). In 1998, Lee et *al.* published a case-only study conducted in USA; the OR of other histological types of lung cancer *versus* adenocarcinomas was not statistically significant (OR=1.72 [95% CI: 0.95–3.12]).(28) Two other case-only studies showed the same findings.(95, 173) The study of Paris et *al.* published in 2010, including more than 1,450 lung cancer cases showed the absence of predominant histological type; the OR of adenocarcinomas *versus* other histological types is not statistically significant (OR=1.03 [95% CI: 0.82–1.30]).(95) In 2012, a case-control study, conducted in Italy among 1,537 men, shows the presence of an association between asbestos exposure and the three examined histological types when comparing to controls; OR of adenocarcinomas is 1.75 [95% CI: 1.37–2.23], OR of squamous cell carcinomas is 1.85 [95% CI: 1.40–2.43], and OR of small cell carcinomas is 2.04 [95% CI: 1.38-3.00].(36) Results are more conflicting in the Netherlands cohort study; asbestos exposure was associated with squamous cell carcinomas (OR=1.68 [95% CI: 1.36–2.06]) and small cell carcinomas (OR=1.56 [95% CI: 1.18–2.05)], but not with adenocarcinomas (OR=1.09 [95% CI: 0.84–1.42]).(93) Conversely, occupational cohort studies demonstrate a significant predominance of squamous cell carcinomas among crocidolite miners (174) or adenocarcinomas among asbestos cement workers (175). Discrepancies between occupational cohort studies may be explained by either exposure to different fibers type (crocidolite (174) versus mostly chrysotile (175)) or smoking adjustment.

Our results are consistent with previous studies indicating that crystalline silica was more frequently associated with squamous cell carcinomas and small cell carcinoma. Most studies were based on general population series. Although all studies demonstrated that lung cancer risk was associated with crystalline silica exposure, results were more conflicting according to histological type after smoking adjustment: ORs of the same magnitude across all histological types for Cassidy et *al.* (94), predominance of adenocarcinomas for Paris et *al.* (95) or elevated ORs for squamous cell carcinomas and small cell carcinomas compared to OR for adenocarcinomas for Vida et *al.* (37), Consonni et *al.* (176) or De Matteis et *al.* (36).

The association between asbestos exposure and tumor location was also conflicting. While a population-based case-only study suggested an upper lobe tumor location for subjects exposed to asbestos (OR of upper lobe tumor *versus* lower lobe tumor: 3.03 [95% CI: 1.28–7.18]) (28), two interesting but biased studies with very high exposure levels and presence of either asbestos-related radiological findings (pulmonary and/or pleural fibrosis) (173) or fiber pulmonary concentration (177) demonstrated an excess of lower lobe tumor location.

To the best of our knowledge, there is no literature related to the association between crystalline silica exposure and tumor location for upper lobe location *versus* lower lobe location, while one study reported that exposure to crystalline silica was significantly associated with peripheral tumors (OR=3.28 [95% CI: 1.50-7.17]) only for the highest level of exposure. (178) Finally, we were unable to find data from the literature on the association between occupational exposure to asbestos and crystalline silica and age at diagnosis.

Only three studies have looked at the statistical interaction between tobacco smoking and occupational exposure to asbestos according to histological type, and concluded on absence lack of multiplicative interaction (179-181). To the best of our knowledge, no study has looked neither at the statistical interaction between tobacco smoking and occupational exposure to crystalline silica according to histological type, nor at the statistical interaction between tobacco smoking and occupational exposure to either asbestos or crystalline silica according to tumor location or age at diagnosis.

In the present study, two different JEMs were used to assess occupational exposures to asbestos and crystalline silica (182, 183). Although JEMs could lead to false-positives and false-negatives by introducing non-differential misclassifications (142), they allowed us to standardize the occupational exposure assessment across the eight initial studies. In the presence of misclassifications, the estimation of the interaction term seems more likely to be underestimated (184). In order to evaluate the impact of those misclassifications on our results, two additional set of analyses were conducted to modify the sensitivity and the specificity of our definition of occupationally exposed subjects. In the first additional analysis, the group of subjects who held at least one job with a non-null probability of exposure was defined as exposed, while the group of subjects with a highest probability of exposure lower than 30% was defined as non-exposed in the second additional analysis. For histological type, results remained unchanged except for the statistical interaction between tobacco smoking and crystalline silica. Indeed, while it was non-significant in the main analysis, the statistical interaction became statistically significant when comparing squamous cell carcinomas to other histological types or to adenocarcinomas only. For age at diagnosis, while there was no statistically significant interaction between tobacco smoking and crystalline silica on an additive scale among all histological types, the statistical interaction became statistically significant for adenocarcinomas only. (Appendix F) Due to the multiple comparisons performed, those two discrepancies seem to be more likely due to chance.

The present study is one of the largest studies, describing 7,256 male lung cancer cases with histologically confirmed diagnosis, detailed smoking habits and complete job histories, reporting 31,332 jobs. Cases were pooled from different initial studies using similar procedures to collect disease-related data from medical records (histological type, tumor location and age at diagnosis) and exposure-related data from trained interviewers (smoking habits and detailed lifetime occupational career). Moreover, the assessment of occupational exposures to asbestos and crystalline silica was standardized using the same two JEMs. Additionally, since some data were collected from proxies' respondents for population-based cases (4.8% of cases), a complete set of analyses was thus performed among self-respondents only. Results were similar to those obtained in our main analyses. (Appendix H)

4.3.3.4 Article 3 (Submitted - European Respiratory Journal)

Phenotypes of Lung Cancer and Statistical Interactions between Tobacco Smoking and Occupational Exposure to Asbestos and Crystalline Silica from a Large Case-only Study: The CaProMat Study.

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Abstract

Background: The aim of this study was to assess the effect modification of the association between tobacco smoking and phenotypes of lung cancer (histological type, tumor location, and age at diagnosis) by occupational exposure to asbestos or to crystalline silica.
Methods: The CaProMat study is a pooled case-only study including 7,256 male lung cancer cases recruited between 1996 and 2011 in France and Canada. Two job-exposure matrices (JEMs) were used to assess occupational exposure to asbestos and crystalline silica. Statistical interactions between tobacco smoking and occupational exposure to asbestos or crystalline silica were assessed using unconditional logistic regression models for histological type and tumor location and linear regression models for age at diagnosis.
Results: Tobacco smoking was associated with squamous cell carcinoma and small cell carcinomas as well as an earlier age at diagnosis. Additional exposure to either asbestos or crystalline silica did not modify the effect of tobacco smoking for either histological type or age at diagnosis. Neither tobacco smoking nor occupational exposure to asbestos or crystalline silica influenced tumor location.
Conclusions: Tobacco smoking was the main factor related to histological type and age at diagnosis. Those associations were not modified by occupational exposure to asbestos or crystalline silica.
Keywords: Lung Cancer, Interaction, Tobacco smoking, Occupational Exposures, Asbestos, Crystalline Silica, Histological Types, Tumor Location, Age at Diagnosis.

Introduction

Lung cancer remains the primary cause of cancer deaths among men worldwide. [1] The most frequent histological types of lung cancer are respectively adenocarcinoma, squamous cell carcinoma, small cell carcinoma and large cell carcinoma. [2] Among men, the bronchial tumor is more frequently located in the upper lobe than in the lower lobe. [3] More than 80% of male lung cancer cases occur after the age of 60. [4] In France, the median age at diagnosis is 63 [5], while it is 70 in the United States (US) [6].

It is well known that the prognosis of lung cancer is associated with certain phenotypes, specifically histological types [7]. In Canada, the 5-year survival rate was 56% for adenocarcinomas versus 28% for stage I and II squamous cell carcinomas (TNM classification of lung cancer) for the period between 1994 and 2000. [8] In France, for the period between 2008 and 2013, and for stage I and II lung cancer cases at the time of diagnosis, the 5-year survival rate was 62% for adenocarcinomas versus 47% for squamous cell carcinomas among men. [9]

Those phenotypes of lung cancer are themselves associated with certain risk factors such as tobacco smoking. Indeed, in terms of histological types, squamous cell carcinomas and small cell carcinomas are more frequent than adenocarcinomas among smokers. [10] There is less data supporting this association for tumor location and age at diagnosis.

Subjects exposed to occupational lung carcinogens including asbestos and crystalline silica are mostly blue-collar workers. Moreover, blue-collar workers are also those who are most often smokers. [11-13] Therefore, regarding phenotypes of lung cancer, it is important to document a possible statistical interaction between tobacco smoking and occupational exposure to lung carcinogens. Few studies have addressed this statistical interaction, particularly for phenotypes of lung cancer such as histological type [14, 15] and tumor location [3, 16]. To our knowledge, there is no data on age at diagnosis.

In this large case-only study, we proposed to assess the effect modification of the association between tobacco smoking and histological type and tumor location by occupational exposure to asbestos or to crystalline silica. As secondary objective, we further characterized the same effect modification on age at diagnosis.

Materials and Methods

The CaProMat Study

The CaProMat study is a pooled case-only study conducted in France and in Montreal, Canada. Subjects were recruited between 1996 and 2011 from six French original hospital-based studies [17], one French population-based case-control study (ICARE) [18], and one Canadian population-based case-control study [19]. (Additional file 1.) All cases were histologically confirmed. The CaProMat study population consisted of 9,623 lung cancer cases (7,256 males and 2,367 females).

Data Collection

Histological type (squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma and other histological types), tumor location (upper lobe *versus* lower lobe), and age at diagnosis were collected from medical records.

Complementary data were collected through personal interviews with all subjects, with the exception of the French and Canadian case-control studies where next-of-kin were interviewed when the subject was unable to respond. [18, 19] For the hospital-based cases, a standardized occupational health questionnaire was administered by an occupational physician, while for the

population-based cases, a standardized questionnaire was administered by trained interviewers. [18, 19]

Socio-demographic details were collected and included gender, birth year, educational level (unschooled, primary, secondary and post-secondary) and respondent status. Detailed lifetime tobacco smoking habits were also collected and included smoking status (never smoker, current smoker and ex-smoker), total smoking duration, mean number of cigarettes smoked per day, and time since cessation of smoking when appropriate. Subjects were defined as never smokers if they had smoked less than 100 cigarettes in their life and ex-smokers if they had stopped smoking for more than two years. [18] From smoking details reported in the questionnaire, the comprehensive smoking index (CSI) was calculated. The CSI aggregates various details on individual smoking habits including smoking intensity, smoking duration and time since cessation. It has been shown that the CSI is an appropriate aggregated index to adjust for lifetime smoking history in lung cancer studies. [20] We further categorized subjects into never-low smokers (subjects with CSI values below the 25th percentiles) and medium-high smokers (subjects with CSI values above the 25th percentiles). [19]

The lifetime occupational history for all jobs held for at least for six months was also collected. Occupational histories were coded differently in the original studies. Three different classifications were used for occupations [17-19]: the International Standard Classification of Occupations (ISCO) of 1988 for hospital-based cases, the ISCO of 1968 for the French population-based cases, and the Canadian Classification and Dictionary of Occupations (CCDO) of 1971 for the Canadian population-based cases. Two different classification were used for industries: the French Classification of Activities (NAF 2000) for hospital-based and French population-based cases, while the Canadian Standard Industrial Classification (CSIC) of 1980 was used for the Canadian population-based cases. We thus harmonized jobs coding according to the ISCO of 1968 for occupations and the International Standard Industrial Classification (ISIC) of 1975 for industries.

Occupational exposure assessment

Two job-exposure matrices (JEMs) were used to retrospectively assess occupational exposure to asbestos and crystalline silica. A probability of exposure to either asbestos or crystalline silica was automatically assigned by the two JEMs for each job reported by subjects. This probability of exposure was expressed on a 5-category scale for asbestos and on a continuous 10% scale for crystalline silica. [21, 22] All parameters documented in the two JEMs are presented in additional file 2.

For each subject, we derived their highest probability of exposure across all jobs held during the entire occupational career and we further categorized subjects into 5 categories of probability of exposure: non-exposed (0%), >0 to 5%, >5 to 30%, >30 to 70%, and >70%. Subjects were defined as *exposed* to either asbestos or crystalline silica if they held at least one job with a probability of exposure greater than 30%. Exposure status was considered as uncertain for subjects with a non-null probability of exposure and a highest probability of exposure lower than 30%.

Statistical analysis

Main statistical analysis

The statistical analysis was conducted among male lung cancer cases only. For histological type and tumor location as dependent variables, odds ratios (ORs) and their 95% confidence intervals (95% CIs) were estimated from unconditional logistic regression models. For histological types, four alternative definitions of the binary dependent variable were considered: 1) squamous cell carcinoma *versus* other histological types; 2) squamous cell carcinoma *versus* adenocarcinoma only; 3) small cell carcinoma *versus* other histological types; 4) small cell carcinomas *versus* adenocarcinoma only. Mean age at diagnosis (in years) was estimated from multiple linear

regression models. The statistical interaction between tobacco smoking (medium-high smokers *versus* never-low smokers) and occupational exposure to either asbestos or crystalline silica (exposed *versus* non-exposed) was estimated by including a cross-product term of both variables in all regression models. All models were adjusted for potential confounders, namely asbestos or crystalline silica according to the occupational exposure of interest (exposed *versus* non-exposed), age at diagnosis (in years, for histological types and tumor location), histological type (for age at diagnosis and tumor location) and initial study.

For tumor location and age at diagnosis, we additionally tested whether there was a statistical interaction between tobacco smoking and histological types of lung cancer or not.

Complementary analyses

We further conducted two complete sets of analyses by using different definitions of the exposed group: 1) we considered subjects who held at least one job with a non-null probability of exposure as exposed; and 2) we considered subjects with a highest probability of exposure lower than 30% as non-exposed (Additional file 3.).

To assess the impact of next-of-kin respondents on our results, a whole series of analyses was conducted exclusively among subjects who responded for themselves (Additional file 4.).

All analyses were performed using the statistical software SPSS (Statistical Package for Social Sciences), version 21.0 (Chicago, IL, USA).

Results

The population study consisted of 7,256 male lung cancer cases representing 31,332 jobs held for more than six months. Table 1 presents the main characteristics of the study population. Squamous cell carcinomas and adenocarcinomas represented 69.9% of the histological types with 32.9% and 37.0%, respectively. The bronchial tumor location was available for 4,689 cases representing 64.6% of the study population. There was a predominance of upper lobe tumors with 68.2% of the 4,689 lung cancer cases. The mean age at diagnosis was 62.4 (±10.0). Non-smokers represented 2.7% of the population study, while 58.5% and 38.8% were current smokers and ex-smokers, respectively. For occupational exposure to asbestos, 27.1% were never exposed, 23.1% had an uncertain exposure status (at least one job with a highest probability of exposure less than 30%), and 49.8% were defined as exposed. For occupational exposure to crystalline silica, 62.1% of subjects were never exposed, 5.4% had an uncertain exposure status (at least one job with a highest probability of exposure less than 30%) and 32.5% were defined as exposed.

Table 2 presents the statistical interactions on a multiplicative scale between tobacco smoking and occupational exposure to asbestos according to histological type of lung cancer. The results showed that among subjects non-exposed to asbestos, tobacco smoking was positively associated with squamous cell carcinomas compared to other histological types (OR = 1.52 [1.20-1.92]) or to adenocarcinomas only (OR = 1.89 [1.47-2.44]). Among subjects exposed to asbestos, the magnitude of the association was similar than expected (OR = 1.83 [1.45-2.32] and OR = 2.15 [1.67-2.78] respectively). Indeed there was no statistical interaction on a multiplicative scale between tobacco smoking and occupational exposure to asbestos (p=0.90 and p=0.46, respectively). Similar findings were observed when looking for small cell carcinomas.

Table 3 presents the statistical interactions on a multiplicative scale between tobacco smoking and occupational exposure to crystalline silica according to histological type of lung cancer. The results show that among subjects non-exposed to crystalline silica, tobacco smoking was positively associated with squamous cell carcinomas compared to other histological types (OR = 1.62 [1.36-1.93]) or to adenocarcinomas only (OR = 1.92 [1.58-2.33]). Among subjects exposed to crystalline silica, the magnitude of the association was similar than expected (OR = 1.72 [1.41-2.11] and OR

= 2.15 [1.72-2.70] respectively). Indeed, there was no statistical interaction on a multiplicative scale between tobacco smoking and occupational exposure to crystalline silica (p=0.17 and p=0.12, respectively). When considering small cell carcinomas versus either other histological types or adenocarcinomas only, similar findings were observed (p=0.90 and p=0.59, respectively).

Table 4 presents the statistical interactions on a multiplicative scale between tobacco smoking and occupational exposure to asbestos and crystalline silica according to the bronchial tumor location There was neither association nor interaction between tobacco smoking and asbestos exposure (β=0.08; p=0.66]), or crystalline silica exposure (β=-0.02; p=0.91).

Table 5 presents the statistical interaction on an additive scale between tobacco smoking and occupational exposure to asbestos according to age at diagnosis. Subjects that were medium-high smokers and exposed to asbestos were diagnosed earlier than never-low smokers and non-exposed subjects, without statistical interaction except for adenocarcinomas. For crystalline silica, there was no statistical interaction on an additive scale among all histological types (table 6).

Discussion

Tobacco smoking exposure was the main factor related to histological type and age at diagnosis. Squamous cell carcinoma and small cell carcinoma occurred more frequently among smokers. Lung cancer cases were diagnosed earlier among smokers. Additional exposure to either asbestos or crystalline silica did not modify the effect of tobacco smoking for both histological type and age at diagnosis. Finally, neither tobacco smoking nor occupational exposure to asbestos or crystalline silica seemed to influence tumor location (upper *versus* lower lobes).

First of all, regarding tobacco smoking, our results are consistent with the literature. Tobacco smoking seemed to be more prevalent among squamous cell carcinoma and small cell carcinoma cases compared to adenocarcinoma cases. [10, 23-25] When looking at tumor location, lung cancer appeared to be more frequent in upper lobes irrespective of tobacco smoking [26]. Moreover, when comparing current smokers to non-smokers, this difference seemed to be more prevalent among smokers [3]. This is contradictory with our results; however, the study of Lee et *al.* did not simultaneously take into account tobacco smoking and histological types [3].

Finally, regarding age at diagnosis, similarly to our results, data from six cohort studies, mostly US based, suggested that lung cancer occurred later among non-smokers than among smokers, with large differences from one study to another [27]. The same trend was observed in a case-control study [28]. However, a detection bias cannot be excluded among young smokers [29].

Previous case series from the general population have not demonstrated a predominant histological type among subjects exposed to asbestos [3, 12, 30, 31]. Results are more conflicting in the Netherlands cohort study [11]. Conversely, occupational cohort studies demonstrate a significant predominance of squamous cell carcinomas among crocidolite miners [32] or adenocarcinomas among asbestos cement workers [33]. Discrepancies between occupational cohort studies may be explained by either exposure to different fibers type (crocidolite [32] versus mostly chrysotile [33]) or smoking adjustment.

Our results are consistent with previous studies indicating that crystalline silica was more frequently associated with squamous cell carcinomas and small cell carcinoma. Most studies were based on general population series. Although all studies demonstrated that lung cancer risk was associated with crystalline silica exposure, results were more conflicting according to histological type after smoking adjustment: ORs of the same magnitude across all histological types for Cassidy et *al.* [13], predominance of adenocarcinomas for Paris et *al.* [12] or elevated ORs for squamous cell carcinomas and small cell carcinomas compared to OR for adenocarcinomas for Vida et *al.* [34], Consonni et *al.* [35] or De Matteis et *al.* [31].

The association between asbestos exposure and tumor location was also conflicting. While a population-based case-only study suggested an upper lobe tumor location for subjects exposed to asbestos [3], two interesting but biased studies with very high exposure levels and presence of either asbestos-related radiological findings (pulmonary and/or pleural fibrosis) [30] or fiber pulmonary concentration [36] demonstrated an excess of lower lobe tumor location.

To the best of our knowledge, there is no literature related to the association between crystalline silica exposure and tumor location for upper lobe location *versus* lower lobe location, while one study reported that exposure to crystalline silica was significantly associated with peripheral tumors (OR=3.28, 95% CI: 1.50-7.17) only for the highest level of exposure. [37] Finally, we were unable to find data from the literature on the association between occupational exposure to asbestos and crystalline silica and age at diagnosis.

Only three studies have looked at the statistical interaction between tobacco smoking and occupational exposure to asbestos according to histological type, and concluded on absence lack of multiplicative interaction [14, 15, 38]. To the best of our knowledge, no study has looked at the statistical interaction between tobacco smoking and occupational exposure to crystalline silica according to histological type, nor at the statistical interaction between tobacco smoking and occupational exposure to either asbestos or crystalline silica according to tumor location or age at diagnosis.

In the present study, two different JEMs were used to assess occupational exposures to asbestos and crystalline silica [21, 22]. Although JEMs could lead to false-positives and false-negatives by introducing non-differential misclassifications [39], they allowed us to standardize the occupational exposure assessment across the eight initial studies. In the presence of misclassifications, the estimation of the interaction term seems more likely to be underestimated [40]. In order to evaluate the impact of those misclassifications on our results, two additional set of analyses were conducted to modify the sensitivity and the specificity of our definition of occupationally exposed subjects. In the first additional analysis, the group of subjects who held at least one job with a non-null probability of exposure were defined as exposed, while the group of subjects with a highest probability of exposure lower than 30% was defined as non-exposed in the second additional analysis. For histological type, results remained unchanged except for the statistical interaction between tobacco smoking and crystalline silica Indeed, while it was non-significant in the main analysis, the statistical interaction became statistically significant when comparing squamous cell carcinomas to other histological types or to adenocarcinomas only. For age at diagnosis, while there was no statistically significant interaction between tobacco smoking and crystalline silica on an additive scale among all histological types, the statistical interaction became statistically significant for adenocarcinomas only. (Additional file 3.) Due to the multiple comparisons performed, those two discrepancies seem to be more likely due to chance.

The present study is one of the largest studies, describing 7,256 male lung cancer cases with histologically confirmed diagnosis, detailed smoking habits and complete job histories, reporting 31,332 jobs. Cases were pooled from different initial studies using similar procedures to collect disease-related data from medical records (histological type, tumor location and age at diagnosis) and exposure-related data from trained interviewers (smoking habits and detailed lifetime occupational career). Moreover, the assessment of occupational exposures to asbestos and crystalline silica was standardized using the same two JEMs. Additionally, since some data were collected from proxies' respondents for population-based cases (4.8% of cases), a complete set of analyses was thus performed among self-respondents only. Results were similar to those obtained in our main analyses. (Additional file 4.)

Conclusion

To our knowledge, this is the largest pooled case-only study assessing the effect modification of the association between tobacco smoking and phenotypes of lung cancer by occupational exposure

to asbestos and crystalline silica. Tobacco smoking was associated with squamous cell carcinoma and small cell carcinomas as well as an earlier age at diagnosis. Those associations were not modified by occupational exposure to asbestos or crystalline silica. Such results emphasized the need to look systematically for occupational exposure to lung carcinogens, whatever the histological type or tumor location. Moreover, influence of both exposure to tobacco smoke and occupational lung carcinogens on age at diagnosis should be taken into account when discussing age period of any lung cancer screening programs.

List of Abbreviations

United States: US
Comprehensive Smoking Index: CSI
International Standard Classification of Occupations: ISCO
Canadian Classification and Dictionary of Occupations: CCDO
French Classification of Activities: NAF
Canadian Standard Industrial Classification: CSIC
International Standard Industrial Classification: ISIC
Job-Exposure Matrices: JEMs
Odds Ratio: OR
Confidence Interval: CI
p-value: *p*
Highest Probability of exposure: P

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5 General Discussion

This thesis presents one of the largest studies including 9,623 lung cancer cases recruited in France and Montreal (Canada). Eight different lung cancer series, both hospital-based and population-based, were pooled. All lung cancer cases were histologically confirmed, with detailed smoking habits and complete job histories. In addition, two pre-developed JEMs were available to assess the occupational exposure to asbestos and crystalline silica. In fact, the exposure level to asbestos and crystalline silica was different between men and women. Thus, the statistical analysis was restricted to men (n=7,256). Indeed, the prevalence of exposure was examined exclusively among French men, as the exposure characteristics are different between France and Canada.

In the present thesis, we aimed to study the prevalence of occupational exposure to asbestos and to crystalline silica according to the phenotypes of lung cancer. This analysis was conducted among the 6,521 French male lung cancer cases. For histological type, our results were similar to the findings from the literature; there was no difference of prevalence of occupational exposure to asbestos with and without stratification by smoking status. For crystalline silica, the prevalence of exposure was higher among squamous cell carcinomas and small cell carcinomas than adenocarcinomas. The difference observed for crystalline silica is minimal and of limited clinical importance. In general, histological type cannot be use as an indicator of the occupational exposure to asbestos or to crystalline silica. The inspection to determine the occupational exposure to asbestos or to crystalline silica in case of lung cancer is always required. For age at diagnosis, the prevalence of occupational exposure was maximized among lung cancer cases diagnosed between 50 and 59 years for asbestos and less than 50 years for crystalline silica. Practically, those differences were limited and cannot be used to confirm the occupational exposure to either asbestos or crystalline silica. Our findings were confirmed by different complementary analyses, including a comparison of the results between hospital-based and population-based case series.

In contrary to the occupational exposure to asbestos and crystalline silica, there is strong evidence from the literature that tobacco smoking is more associated with squamous cell carcinoma and small cell carcinoma than adenocarcinoma. For age at diagnosis, there was evidence from the literature that lung cancer occurred earlier among smokers than non-smokers. On the other hand, tobacco smoking is more associated with an upper lobe tumor location. Based on the findings from the literature, we were interested to evaluate the effect modification of the occupational exposure to asbestos and to crystalline silica on the association between tobacco smoking and the phenotypes of lung cancer; especially that it was not well studied in the literature. Thus, we evaluated the statistical multiplicative interaction between tobacco smoking and occupational exposure to asbestos and to crystalline silica on histological type and tumor location. The statistical interaction on age at diagnosis was evaluated on an additive scale.

For tobacco smoking, our results confirmed the findings from the literature according to histological type and age at diagnosis. When looking at tumor location, our results were contradictory to those of the literature; there was absence of association between tobacco smoking and a specific tumor location. The occupational exposures to asbestos and to crystalline silica didn’t change the influence of tobacco smoking on phenotypes of lung cancer. In general, there was absence of multiplicative interaction between tobacco smoking and occupational exposure to asbestos and to crystalline silica among histological type and tumor location. For age at diagnosis, the additive interaction between tobacco smoking and occupational exposure to asbestos and to crystalline silica was not observed. Our results were confirmed for different definitions of exposure to asbestos and to crystalline silica.

In this thesis, we had the opportunity to assess the occupational exposures to asbestos and crystalline silica for all cases by two specific JEMs. Although several publications discussed

the limitations of JEM compared to other methods (JEMs could lead to false-positives and false-negatives by introducing non-differential misclassifications), the utilization of JEMs allowed us to standardize the occupational exposure assessment across all subjects in order to compare the prevalence of occupational exposures according to histological types and age at diagnosis, and to estimate the interactions between smoking and occupational exposures on the phenotypes of lung cancer.

In the present thesis, the associations between occupational exposures to asbestos and to crystalline silica with the phenotypes of lung cancer were studied among males only. In addition, the interactions between the two occupational exposures (asbestos and crystalline silica) and tobacco smoking according to the phenotypes of lung cancer were also examined among males only. It is also of high interest to study those associations and interactions among females. Unfortunately, among the present study population, the number of exposed females and their levels of exposure were very low, preventing us from conducting the statistical analysis. On the other hand, further studies on the other occupational lung carcinogens and their impact according to the phenotypes of lung cancer should be conducted among males and females.

In general, we are confident that our results are consistent as they are confirmed by the complementary analyses and by the evidence from the literature. In addition, pooling the two series of cases (hospital-based and population-based cases) did not affect our results.

6 Conclusions

Our systematic review showed the absence of statistical interaction on multiplicative scale between tobacco smoking and three occupational exposures (asbestos, crystalline silica, and diesel engine exhaust emissions) on the risk of lung cancer. The evidence from the literature was not enough to conclude for the additive interaction.

To our knowledge, the CaProMat study is the largest pooled case-only study on lung cancer conducted to time to describe the prevalence of occupational exposure to asbestos and crystalline silica according to histological types and age at diagnosis, and to assess the effect modification of the association between tobacco smoking and phenotypes of lung cancer by occupational exposure to asbestos and crystalline silica.

In general, there was no major difference in the prevalence of occupational exposures to asbestos and crystalline silica according to histological types and age at diagnosis. Tobacco smoking was associated with squamous cell carcinomas and small cell carcinomas as with an earlier age at diagnosis. Those associations were not modified by occupational exposure to asbestos or crystalline silica. Tumor location was not influenced by neither tobacco smoking nor occupational exposure to asbestos or crystalline silica.

Thus, the histological type of lung cancer, the tumor location, and age at diagnosis cannot be used as an indicator for the occupational exposure to asbestos or to crystalline silica. Therefore, an occupational exposure investigation should be conducted to identify the exposure to suspected occupational carcinogenic agents regardless of the histological type, the tumor location, or age at diagnosis.

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Appendix A: PRISMA 2009 Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix B: Characteristics of hospital-based and population-based male French lung cancer cases of CaProMat.

Table 1. Main characteristics of hospital-based and population-based male French lung cancer cases of CaProMat

	Hospital based Male (4,400)		Population based Male (2,121)		
Characteristics	n	%	n	%	*p*
Histological type					
Squamous cell carcinoma	1,362	31.0	762	35.9	
Small cell carcinoma	599	13.6	302	14.2	
Adenocarcinoma	1,686	38.3	760	35.8	**<0.001**[a]
Large cell carcinoma	503	11.4	231	10.9	
Other lung cancer	250	5.7	66	3.1	
Age at diagnosis					
Age at diagnosis (years), mean (SD[b])	63.2 (10.5)		60.0 (9.0)		**< 0.001**[c]
Respondent status					
Self	4,400	100.0	2,063	97.3	**<0.001**[a]
Proxy	0	0.0	58	2.7	
Smoking status					
Non-smokers	132	3.0	48	2.3	
Current smokers	2,434	55.3	1,313	61.9	**< 0.001**[a]
Ex-smokers	1,834	41.7	760	35.8	
Educational level					
Unschooled	119	2.7	0	0.0	
Primary	761	17.3	636	30.0	
Secondary	1,516	34.5	998	47.1	**< 0.001**[d]
Post-secondary	313	7.1	261	12.3	
Unknown	1,691	38.4	226	10.7	
Last job category (ISCO 1968)[e]					
Scientific, technical, liberal and related workers	559	12.7	227	10.7	
Directors and senior administrators	237	5.4	119	5.6	
Clerical and Related Workers	392	8.9	182	8.6	
Commercial Workers and sellers	309	7.0	158	7.4	**< 0.001**[d]
Specialized workers	354	8.0	160	7.5	
Farmers, ranchers, foresters, fishermen and hunters	177	4.0	159	7.5	
Non-agricultural workers and drivers	2,370	53.9	1,101	51.9	
Unknown	2	0.0	15	0.7	
Asbestos exposure					
Highest probability[f]					
P=0%	1,112	25.3	615	29.0	
0% < P ≤ 5%	332	7.5	198	9.3	
5% < P ≤ 30%	613	13.9	332	15.7	**<0.001**[a]
30% < P ≤ 70%	1,589	36.1	660	31.1	
P > 70%	754	17.1	316	14.9	
Total duration of exposure (years)[g], mean (SD)	18.6 (16.5)		18.1 (16.7)		0.451[c]
Cumulative exposure index (f/ml.year), mean (SD)	15.2 (28.5)		13.2 (30.0)		**0.01**[c]
Crystalline silica					
Highest probability					
P=0%	2,711	61.6	1,270	59.9	
0 < P ≤ 10%	67	1.5	135	6.4	
10% < P ≤ 50%	434	9.9	210	9.9	**<0.001**[a]
50 < P ≤ 90%	1,158	26.3	494	23.3	
P > 90%	30	0.7	12	0.6	
Total duration of exposure (years), mean (SD)	7.3 (12.8)		7.5 (12.8)		0.463[c]
Cumulative exposure index (mg/m³-year), mean (SD)	1.3 (5.0)		1.0 (3.3)		**<0.001**[c]

[a] *p*-value estimated by Chi-Square; [b] SD standard Deviation; [c] p-value estimated by T-test; [d] p-value estimated by Chi-Square without unknown category.

[e] ISCO 1968 International Standard Classification of Occupations, 1968, second edition.

[f] The highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).

[g] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m³-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).

Appendix C: Two sets of analyses were conducted separately for hospital-based and population-based cases to examine if the results are similar to the main analysis.

Hospital-based cases

Table 1. Occupational exposure to asbestos and crystalline silica by histological types among 4,400 hospital-based French male lung cancer cases

	Histological types												
	Squamous cell carcinoma (1,362)		Small cell carcinoma (599)		Adenocarcinoma (1,686)		Large cell carcinoma (503)		Other lung cancer (250)		Total (4,400)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Asbestos													
Never (CEI[c]=0)	316 (23.2)	-	159 (26.5)	-	439 (26.0)	-	125 (24.9)	-	73 (29.2)	-	1,112 (25.3)	-	
Ever (CEI>0)	1,046 (76.8)	36.2 (33.6 - 38.7)	440 (73.5)	35.1 (31.3 - 38.9)	1247 (74.0)	35.5 (33.2 - 37.8)	378 (75.1)	34.4 (30.2 - 38.5)	177 (70.8)	30.6 (24.9 - 36.3)	3,288 (74.7)	35.2 (33.8 - 36.7)	0.218
0<CEI≤1.1	310 (22.8)		133 (22.2)		390 (23.1)		130 (25.8)		56 (22.4)		1,019 (23.2)		
1.1<CEI≤16.5	364 (26.7)		142 (23.7)		448 (26.6)		123 (24.5)		65 (26.0)		1,142 (26.0)		
CEI>16.5	372 (27.3)		165 (27.5)		409 (24.3)		125 (24.9)		56 (22.4)		1,127 (25.6)		
Crystalline silica													
Never (CEI=0)	799 (58.7)	-	369 (61.6)	-	1061 (62.9)	-	317 (63.0)	-	165 (66.0)	-	2,711 (61.6)	-	
Ever (CEI>0)	563 (41.3)	28.7 (26.3 - 31.1)	230 (38.4)	26.1 (22.6 - 29.6)	625 (37.1)	25.4 (23.4 - 27.5)	186 (37.0)	25.4 (21.6 - 29.2)	85 (34.0)	23.0 (17.7 - 28.2)	1,689 (38.4)	26.4 (25.1 - 27.7)	0.092
0<CEI≤0.4	152 (11.2)		77 (12.9)		199 (11.8)		58 (11.5)		32 (12.8)		518 (11.8)		
0.4<CEI≤2.2	182 (13.4)		70 (11.7)		229 (13.6)		68 (13.5)		23 (09.2)		572 (13.0)		
CEI>2.2	229 (16.8)		83 (13.9)		197 (11.7)		60 (11.9)		30 (12.0)		599 (13.6)		

[a] Pw weighted prevalence equal to the sum of the Highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects The Highest probability is the higher probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).

Table 2. Occupational exposure to asbestos by histological types stratified by smoking status among 4,400 hospital-based French male lung cancer cases

	Histological types												
	Squamous cell carcinoma (1,362)		Small cell carcinoma (599)		Adenocarcinoma (1,686)		Large cell carcinoma (503)		Other lung cancer (250)		Total (4,400)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Asbestos													
Non-smokers (132)													
Never (CEI[c]=0)	7 (43.8)	-	3 (60.0)	-	29 (35.8)	-	3 (27.3)	-	4 (21.1)	-	46 (34.8)	-	0.836
Ever (CEI>0)	9 (56.3)	33.9 (10.7 - 57.1)	2 (40.0)	13.5 (0.0 - 43.5)	52 (64.2)	27.4 (17.7 - 37.1)	8 (72.7)	26.6 (0.5 - 52.7)	15 (78.9)	29.2 (8.8 - 49.7)	86 (65.2)	27.8 (20.2 - 35.5)	
0<CEI≤1.1	1 (6.3)		1 (20.0)		18 (22.2)		4 (36.4)		7 (36.8)		31 (23.5)		
1.1<CEI≤16.5	5 (31.3)		0 (0.0)		19 (23.5)		3 (27.3)		5 (26.3)		32 (24.2)		
CEI>16.5	3 (18.8)		1 (20.0)		15 (18.5)		1 (9.1)		3 (15.8)		23 (17.4)		
Current smokers (2,434)													
Never (CEI=0)	173 (23.5)	-	110 (28.0)	-	238 (26.4)	-	68 (23.8)	-	40 (33.6)	-	629 (25.8)	-	0.347
Ever (CEI>0)	563 (76.5)	35.8 (32.3 - 39.2)	283 (72.0)	34.3 (29.6 - 39.0)	662 (73.6)	35.6 (32.5 - 38.8)	218 (76.2)	35.4 (29.8 - 40.9)	79 (66.4)	32.4 (24.0 - 40.8)	1,805 (74.2)	35.3 (33.4 - 37.2)	
0<CEI≤1.1	158 (21.5)		86 (21.9)		201 (22.3)		72 (25.2)		25 (21.0)		542 (22.3)		
1.1<CEI≤16.5	205 (27.9)		93 (23.7)		229 (25.4)		69 (24.1)		28 (23.5)		624 (25.6)		
CEI>16.5	200 (27.2)		104 (26.5)		232 (25.8)		77 (26.9)		26 (21.8)		639 (26.3)		
Ex-smokers[d] (1,834)													
Never (CEI=0)	136 (22.3)	-	46 (22.9)	-	172 (24.4)	-	54 (26.2)	-	29 (25.9)	-	437 (23.8)	-	0.53
Ever (CEI>0)	474 (77.7)	36.7 (32.9 - 40.5)	155 (77.1)	37.2 (30.5 - 43.9)	533 (75.6)	36.3 (32.7 - 39.8)	152 (73.8)	33.4 (26.9 - 39.8)	83 (74.1)	29.0 (20.6 - 37.4)	1,397 (76.2)	35.8 (33.6 - 37.9)	
0<CEI≤1.1	151 (24.8)		46 (22.9)		171 (24.3)		54 (26.2)		24 (21.4)		446 (24.3)		
1.1<CEI≤16.5	154 (25.2)		49 (24.4)		200 (28.4)		51 (24.8)		32 (28.6)		486 (26.5)		
CEI>16.5	169 (27.7)		60 (29.9)		162 (23.0)		47 (22.8)		27 (24.1)		465 (25.4)		

[a] Pw weighted prevalence equal to the sum of the Highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects The highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] Ex-smokers stopped smoking for more than two years.

Table 3. Occupational exposure to crystalline silica by histological types stratified by smoking status among 4,400 hospital-based French male lung cancer cases

	Histological types												
	Squamous cell carcinoma (1,362)		Small cell carcinoma (599)		Adenocarcinoma (1,686)		Large cell carcinoma (503)		Other lung cancer (250)		Total (4,400)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Crystalline silica													
Non-smokers (132)													
Never (CEI[c]=0)	11 (68.8)	-	4 (80.0)	-	59 (72.8)	-	10 (90.9)	-	16 (84.2)	-	100 (75.8)	-	
Ever (CEI>0)	5 (31.3)	14.7 (0.0 - 32.0)	1 (20.0)	10.0 (0.0 - 36.3)	22 (27.2)	19.0 (10.5 - 27.6)	1 (9.1)	4.5 (0.0 - 16.9)	3 (15.8)	14.2 (0.0 - 29.9)	32 (24.2)	16.3 (10.0 - 22.5)	0.972
0<CEI≤0.4	3 (18.8)		0 (0.0)		10 (12.3)		0 (0.0)		1 (5.3)		14 (10.6)		
0.4<CEI≤2.2	0 (0.0)		1 (20.0)		5 (6.2)		0 (0.0)		1 (5.3)		7 (5.3)		
CEI>2.2	2 (12.5)		0 (0.0)		7 (8.6)		1 (9.1)		1 (5.3)		11 (8.3)		
Current smokers (2,434)													
Never (CEI=0)	436 (59.2)	-	244 (62.1)	-	551 (61.2)	-	176 (61.5)	-	76 (63.9)	-	1,483 (60.9)	-	
Ever (CEI>0)	300 (40.8)	29.1 (25.9 - 32.4)	149 (37.9)	25.4 (21.1 - 29.8)	349 (38.8)	26.5 (23.6 - 29.4)	110 (38.5)	26.7 (21.6 - 31.8)	43 (36.1)	24.3 (16.6 - 32.0)	951 (39.1)	27.1 (25.3 - 28.8)	0.617
0<CEI≤0.4	88 (12.0)		53 (13.5)		110 (12.2)		37 (12.9)		16 (13.4)		304 (12.5)		
0.4<CEI≤2.2	101 (13.7)		48 (12.2)		144 (16.0)		42 (14.7)		13 (10.9)		348 (14.3)		
CEI>2.2	111 (15.1)		48 (12.2)		95 (10.6)		31 (10.8)		14 (11.8)		299 (12.3)		
Ex-smokers[d] (1,834)													
Never (CEI=0)	352 (57.7)	-	121 (60.2)	-	451 (64.0)	-	131 (63.6)	-	73 (65.2)	-	1,128 (61.5)	-	
Ever (CEI>0)	258 (42.3)	28.5 (24.9 - 32.1)	80 (39.8)	27.8 (21.6 - 34.0)	254 (36.0)	24.8 (21.6 - 28.0)	75 (36.4)	24.6 (18.7 - 30.5)	39 (34.8)	23.0 (15.2 - 30.8)	706 (38.5)	26.2 (24.2 - 28.2)	0.303
0<CEI≤0.4	61 (10.0)		24 (11.9)		79 (11.2)		21 (10.2)		15 (13.4)		200 (10.9)		
0.4<CEI≤2.2	81 (13.3)		21 (10.4)		80 (11.3)		26 (12.6)		9 (08.0)		217 (11.8)		
CEI>2.2	116 (19.0)		35 (17.4)		95 (13.5)		28 (13.6)		15 (13.4)		289 (15.8)		

[a] Pw weighted prevalence equal to the sum of the Highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] Ex-smokers stopped smoking for more than two years.

Table 4. Occupational exposure to asbestos and crystalline silica by age at diagnosis among 4,400 hospital-based French male lung cancer cases

	Age at diagnosis (years)										
	< 50 years (421)		50-59 years (1,265)		60-69 years (1,388)		≥ 70 years (1,326)		Total (4,400)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Asbestos											
Never (CEI[c]=0)	90 (21.4)	-	322 (25.5)	-	343 (24.7)	-	357 (26.9)	-	1,112 (25.3)	-	
Ever (CEI>0)	331 (78.6)	37.1 (32.5 - 41.7)	943 (74.5)	36.6 (33.9 - 39.2)	1,045 (75.3)	36.5 (33.9 - 39.0)	969 (73.1)	32.1 (29.6 - 34.6)	3,288 (74.7)	35.2 (33.8 - 36.7)	**0.041**
0<CEI≤1.1	103 (24.5)		283 (22.4)		304 (21.9)		329 (24.8)		1019 (23.2)		
1.1<CEI≤16.5	147 (34.9)		336 (26.6)		333 (24.0)		326 (24.6)		1142 (26.0)		
CEI>16.5	81 (19.2)		324 (25.6)		408 (29.4)		314 (23.7)		1127 (25.6)		
Crystalline silica											
Never (CEI=0)	252 (59.9)	-	775 (61.3)	-	822 (59.2)	-	862 (65.0)	-	2,711 (61.6)	-	
Ever (CEI>0)	169 (40.1)	28.1 (23.8 - 32.4)	490 (38.7)	26.9 (24.5 - 29.4)	566 (40.8)	27.8 (25.4 - 30.2)	464 (35.0)	23.8 (21.5 - 26.1)	1,689 (38.4)	26.4 (25.1 - 27.7)	**0.034**
0<CEI≤0.4	75 (17.8)		166 (13.1)		149 (10.7)		128 (09.7)		518 (11.8)		
0.4<CEI≤2.2	68 (16.2)		177 (14.0)		196 (14.1)		131 (09.9)		572 (13.0)		
CEI>2.2	26 (06.2)		147 (11.6)		221 (15.9)		205 (15.5)		599 (13.6)		

[a] Pw weighted prevalence equal to the sum of the Highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects The highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).

Table 5. Occupational exposure to asbestos by age at diagnosis stratified by smoking status among 4,400 hospital-based French male lung cancer cases

	Age at diagnosis (years)										
	< 50 years (421)		50-59 years (1,265)		60-69 years (1,388)		≥ 70 years (1,326)		Total (4,400)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Asbestos											
Non-smokers (132)											
Never (CEI[c]=0)	10 (50.0)	-	8 (47.1)	-	12 (28.6)	-	16 (30.2)	-	46 (34.8)	-	
Ever (CEI>0)	10 (50.0)	23.0 (4.6 - 41.4)	9 (52.9)	22.6 (0.0 - 42.5)	30 (71.4)	36.7 (22.1 - 51.3)	37 (69.8)	24.3 (12.7 - 35.8)	86 (65.2)	27.8 (20.2 - 35.5)	0.440
0<CEI≤1.1	3 (15.0)		1 (05.9)		11 (26.2)		16 (30.2)		31 (23.5)		
1.1<CEI≤16.5	7 (35.0)		2 (11.8)		11 (26.2)		12 (22.6)		32 (24.2)		
CEI>16.5	0 (0.0)		6 (35.3)		8 (19.0)		9 (17.0)		23 (17.4)		
Current smokers (2,434)											
Never (CEI=0)	65 (19.1)	-	227 (24.9)	-	213 (27.6)	-	124 (30.3)	-	629 (25.8)	-	
Ever (CEI>0)	275 (80.9)	38.5 (33.3 - 43.7)	686 (75.1)	36.4 (33.2 - 39.5)	559 (72.4)	35.1 (31.8 - 38.5)	285 (69.7)	30.4 (25.9 - 34.8)	1,805 (74.2)	35.3 (33.4 - 37.2)	**0.003**
0<CEI≤1.1	81 (23.8)		202 (22.1)		159 (20.6)		100 (24.4)		542 (22.3)		
1.1<CEI≤16.5	123 (36.2)		239 (26.2)		166 (21.5)		96 (23.5)		624 (25.6)		
CEI>16.5	71 (20.9)		245 (26.8)		234 (30.3)		89 (21.8)		639 (26.3)		
Ex-smokers[d] (1,834)											
Never (CEI=0)	15 (24.6)	-	87 (26.0)	-	118 (20.6)	-	217 (25.1)	-	437 (23.8)	-	
Ever (CEI>0)	46 (75.4)	33.9 (22.0 - 45.7)	248 (74.0)	37.8 (32.6 - 43.0)	456 (79.4)	38.2 (34.3 - 42.2)	647 (74.9)	33.4 (30.3 - 36.6)	1,397 (76.2)	35.8 (33.6 - 37.9)	0.149
0<CEI≤1.1	19 (31.1)		80 (23.9)		134 (23.3)		213 (24.7)		446 (24.3)		
1.1<CEI≤16.5	17 (27.9)		95 (28.4)		156 (27.2)		218 (25.2)		486 (26.5)		
CEI>16.5	10 (16.4)		73 (21.8)		166 (28.9)		216 (25.0)		465 (25.4)		

[a] Pw weighted prevalence equal to the sum of the Highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects The highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] Ex-smokers stopped smoking for more than two years.

Table 6. Occupational exposure to crystalline silica by age at diagnosis stratified by smoking status among 4,400 hospital-based French male lung cancer cases

	Age at diagnosis (years)										
	< 50 years (421)		50-59 years (1,265)		60-69 years (1,388)		≥ 70 years (1,326)		Total (4,400)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Crystalline silica											
Non-smokers (132)											
Never (CEI[c]=0)	16 (80.0)		11 (64.7)		29 (69.0)		44 (83.0)		100 (75.8)		
Ever (CEI>0)	4 (20.0)	16.0 (0.0 - 32.1)	6 (35.3)	27.1 (5.9 - 48.2)	13 (31.0)	20.1 (8.0 - 32.2)	9 (17.0)	9.8 (1.8 - 17.8)	32 (24.2)	16.3 (10.0 - 22.5)	0.211
0<CEI≤0.4	1 (5.0)		1 (05.9)		6 (14.3)		6 (11.3)		14 (10.6)		
0.4<CEI≤2.2	2 (10.0)		3 (17.6)		2 (04.8)		0 (0.0)		7 (05.3)		
CEI>2.2	1 (05.0)		2 (11.8)		5 (11.9)		3 (5.7)		11 (08.3)		
Current smokers (2,434)											
Never (CEI=0)	197 (57.9)		559 (61.2)		460 (59.6)		267 (65.3)		1,483 (60.9)		
Ever (CEI>0)	143 (42.1)	29.3 (24.5 - 34.1)	354 (38.8)	27.1 (24.2 - 30.0)	312 (40.4)	28.0 (24.9 - 31.2)	142 (34.7)	23.2 (19.1 - 27.3)	951 (39.1)	27.1 (25.3 - 28.8)	0.165
0<CEI≤0.4	65 (19.1)		120 (13.1)		79 (10.2)		40 (9.8)		304 (12.5)		
0.4<CEI≤2.2	57 (16.8)		134 (14.7)		109 (14.1)		48 (11.7)		348 (14.3)		
CEI>2.2	21 (06.2)		100 (11.0)		124 (16.1)		54 (13.2)		299 (12.3)		
Ex-smokers[d] (1,834)											
Never (CEI=0)	39 (63.9)		205 (61.2)		333 (58.0)		551 (63.8)		1,128 (61.5)		
Ever (CEI>0)	22 (36.1)	25.1 (14.2 - 36.0)	130 (38.8)	26.4 (21.7 - 31.1)	241 (42.0)	28.0 (24.4 - 31.7)	313 (36.2)	25.0 (22.1 - 27.9)	706 (38.5)	26.2 (24.2 - 28.2)	0.400
0<CEI≤0.4	9 (14.8)		45 (13.4)		64 (11.1)		82 (9.5)		200 (10.9)		
0.4<CEI≤2.2	9 (14.8)		40 (11.9)		85 (14.8)		83 (9.6)		217 (11.8)		
CEI>2.2	4 (6.6)		45 (13.4)		92 (16.0)		148 (17.1)		289 (15.8)		

[a] Pw weighted prevalence equal to the sum of the Highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects The highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] Ex-smokers stopped smoking for more than two years.

Population-based cases

Table 7. Occupational exposure to asbestos and crystalline silica by histological types among 2,121 population-based French male lung cancer cases

	Histological types												
	Squamous cell carcinoma (762)		Small cell carcinoma (302)		Adenocarcinoma (760)		Large cell carcinoma (231)		Other lung cancer (66)		Total (2,121)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Asbestos													
Never (CEI[c]=0)	198 (26.0)	-	96 (31.8)	-	233 (30.7)	-	76 (32.9)	-	12 (18.2)	-	615 (29.0)	-	
Ever (CEI>0)	564 (74.0)	33.0 (29.7 - 36.4)	206 (68.2)	29.3 (24.2 - 34.5)	527 (69.3)	30.5 (27.2 - 33.7)	155 (67.1)	27.4 (21.6 - 33.1)	54 (81.8)	40.2 (28.3 - 52.0)	1,506 (71.0)	31.2 (29.2 - 33.2)	0.069[d]
0<CEI≤1.1	209 (27.4)		77 (25.5)		215 (28.3)		61 (26.4)		21 (31.8)		583 (27.5)		
1.1<CEI≤16.5	167 (21.9)		59 (19.5)		160 (21.1)		48 (20.8)		18 (27.3)		452 (21.3)		
CEI>16.5	188 (24.7)		70 (23.2)		152 (20.0)		46 (19.9)		15 (22.7)		471 (22.2)		
Crystalline silica													
Never (CEI=0)	441 (57.9)	-	177 (58.6)	-	472 (62.1)	-	144 (62.3)	-	36 (54.5)	-	1,270 (59.9)	-	
Ever (CEI>0)	321 (42.1)	26.0 (22.9 - 29.2)	125 (41.4)	24.9 (20.1 - 29.8)	288 (37.9)	22.9 (19.9 - 25.9)	87 (37.7)	22.7 (17.3 - 28.2)	30 (45.5)	25.5 (14.9 - 36.0)	851 (40.1)	24.4 (22.6 - 26.2)	0.509
0<CEI≤0.4	114 (15.0)		41 (13.6)		122 (16.1)		36 (15.6)		16 (24.2)		329 (15.5)		
0.4<CEI≤2.2	102 (13.4)		47 (15.6)		96 (12.6)		26 (11.3)		11 (16.7)		282 (13.3)		
CEI>2.2	105 (13.8)		37 (12.3)		70 (09.2)		25 (10.8)		3 (04.5)		240 (11.3)		

[a] Pw weighted prevalence equal to the sum of the Highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] *p*-value estimated by excluding "other lung cancer", the estimated *p*-value with "other lung cancer" was 0.018.

Table 8. Occupational exposure to asbestos by histological types stratified by smoking status among 2,121 population-based French male lung cancer cases

	Histological types												
	Squamous cell carcinoma (762)		Small cell carcinoma (302)		Adenocarcinoma (760)		Large cell carcinoma (231)		Other lung cancer (66)		Total (2,121)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Asbestos													
Non-smokers (48)													
Never (CEI[c]=0)	2 (33.3)	-	1 (50.0)	-	8 (26.7)	-	4 (66.7)	-	2 (50.0)	-	17 (35.4)	-	
Ever (CEI>0)	4 (66.7)	20.4 (0.0 - 52.6)	1 (50.0)	42.5 (0.0 - 100.0)	22 (73.3)	30.1 (13.7 - 46.5)	2 (33.3)	22.5 (0.0 - 55.9)	2 (50.0)	16.9 (0.0 - 53.6)	31 (64.6)	27.3 (14.7 - 39.9)	0.82
0<CEI≤1.1	1 (16.7)		0 (0.0)		10 (33.3)		0 (0.0)		1 (25.0)		12 (25.0)		
1.1<CEI≤16.5	1 (16.7)		0 (0.0)		4 (13.3)		1 (16.7)		1 (25.0)		7 (14.6)		
CEI>16.5	2 (33.3)		1 (50.0)		8 (26.7)		1 (16.7)		0 (00.0)		12 (25.0)		
Current smokers (1,313)													
Never (CEI=0)	119 (25.6)	-	69 (32.2)	-	141 (31.3)	-	38 (26.4)	-	6 (15.0)	-	373 (28.4)	-	
Ever (CEI>0)	345 (74.4)	33.2 (29.0 - 37.5)	145 (67.8)	30.0 (23.8 - 36.1)	310 (68.7)	29.9 (25.7 - 34.2)	106 (73.6)	27.4 (20.1 - 34.7)	34 (85.0)	41.3 (26.1 - 56.6)	940 (71.6)	31.2 (28.7 - 33.7)	0.077
0<CEI≤1.1	125 (26.9)		50 (23.4)		126 (27.9)		47 (32.6)		15 (37.5)		363 (27.6)		
1.1<CEI≤16.5	113 (24.4)		42 (19.6)		92 (20.4)		30 (20.8)		12 (30.0)		289 (22.0)		
CEI>16.5	107 (23.1)		53 (24.8)		92 (20.4)		29 (20.1)		7 (17.5)		288 (21.9)		
Ex-smokers[d] (760)													
Never (CEI=0)	77 (26.4)	-	26 (30.2)	-	84 (30.1)	-	34 (42.0)	-	4 (18.2)	-	225 (29.6)	-	
Ever (CEI>0)	215 (73.6)	33.0 (27.6 - 38.4)	60 (69.8)	27.4 (18.0 - 36.9)	195 (69.9)	31.4 (25.9 - 36.8)	47 (58.0)	27.6 (17.9 - 37.3)	18 (81.8)	42.3 (21.6 - 62.9)	535 (70.4)	31.4 (28.1 - 34.7)	0.174
0<CEI≤1.1	83 (28.4)		27 (31.4)		79 (28.3)		14 (17.3)		5 (22.7)		208 (27.4)		
1.1<CEI≤16.5	53 (18.2)		17 (19.8)		64 (22.9)		17 (21.0)		5 (22.7)		156 (20.5)		
CEI>16.5	79 (27.1)		16 (18.6)		52 (18.6)		16 (19.8)		8 (36.4)		171 (22.5)		

[a] Pw weighted prevalence equal to the sum of the Highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects The highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] Ex-smokers stopped smoking for more than two years.

Table 9. Occupational exposure to crystalline silica by histological types stratified by smoking status among 2,121 population-based French male lung cancer cases

	Histological types												
	Squamous cell carcinoma (762)		Small cell carcinoma (302)		Adenocarcinoma (760)		Large cell carcinoma (231)		Other lung cancer (66)		Total (2,121)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Crystalline silica													
Non-smokers (48)													
Never (CEI[c]=0)	5 (83.3)	-	1 (50.0)	-	18 (60.0)	-	3 (50.0)	-	3 (75.0)	-	30 (62.5)	-	0.902
Ever (CEI>0)	1 (16.7)	10.0 (0.0 - 34.0)	1 (50.0)	25.0 (0.0 - 85.0)	12 (40.0)	26.7 (10.8 - 42.5)	3 (50.0)	33.3 (0.0 - 71.1)	1 (25.0)	22.5 (0.0 - 63.4)	18 (37.5)	25.0 (12.8 - 37.3)	
0<CEI≤0.4	1 (16.7)		0 (0.0)		4 (13.3)		1 (16.7)		1 (25.0)		7 (14.6)		
0.4<CEI≤2.2	0 (0.0)		1 (50.0)		4 (13.3)		2 (33.3)		0 (0.0)		7 (14.6)		
CEI>2.2	0 (0.0)		0 (0.0)		4 (13.3)		0 (0.0)		0 (0.0)		4 (08.3)		
Current smokers (1,313)													
Never (CEI=0)	273 (58.8)	-	122 (57.0)	-	267 (59.2)	-	87 (60.4)	-	16 (40.0)	-	765 (58.3)	-	0.447
Ever (CEI>0)	191 (41.2)	25.8 (21.8 - 29.7)	92 (43.0)	25.8 (20.0 - 31.7)	184 (40.8)	24.2 (20.2 - 28.1)	57 (39.6)	23.2 (16.3 - 30.1)	24 (60.0)	31.9 (17.4 - 46.3)	548 (41.7)	25.1 (22.8 - 27.5)	
0<CEI≤0.4	66 (14.2)		27 (12.6)		84 (18.6)		25 (17.4)		13 (32.5)		215 (16.4)		
0.4<CEI≤2.2	67 (14.4)		37 (17.3)		62 (13.7)		15 (10.4)		9 (22.5)		190 (14.5)		
CEI>2.2	58 (12.5)		28 (13.1)		38 (8.4)		17 (11.8)		2 (5.0)		143 (10.9)		
Ex-smokers[d] (760)													
Never (CEI=0)	163 (55.8)	-	54 (62.8)	-	187 (67.0)	-	54 (66.7)	-	17 (77.3)	-	475 (62.5)	-	0.138
Ever (CEI>0)	129 (44.2)	26.8 (21.7 - 31.9)	32 (37.2)	22.7 (13.8 - 31.5)	92 (33.0)	20.5 (15.7 - 25.2)	27 (33.3)	21.1 (12.2 - 30.0)	5 (22.7)	14.3 (0.0 - 29.0)	285 (37.5)	23.1 (20.1 - 26.0)	
0<CEI≤0.4	47 (16.1)		14 (16.3)		34 (12.2)		10 (12.3)		2 (9.1)		107 (14.1)		
0.4<CEI≤2.2	35 (12.0)		9 (10.5)		30 (10.8)		9 (11.1)		2 (9.1)		85 (11.2)		
CEI>2.2	47 (16.1)		9 (10.5)		28 (10.0)		8 (9.9)		1 (4.5)		93 (12.2)		

[a] Pw weighted prevalence equal to the sum of the Highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] Ex-smokers stopped smoking for more than two years.

Table 10. Occupational exposure to asbestos and crystalline silica by age at diagnosis among 2,121 population-based French male lung cancer cases

	Age at diagnosis (years)										
	< 50 years (277)		50-59 years (716)		60-69 years (764)		≥ 70 years (364)		Total (2,121)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	p[b]
Asbestos											
Never (CEI[c]=0)	69 (24.9)	-	204 (28.5)	-	219 (28.7)	-	123 (33.8)	-	615 (29.0)	-	0.063
Ever (CEI>0)	208 (75.1)	31.8 (26.3 - 37.3)	512 (71.5)	33.5 (30.1 - 37.0)	545 (71.3)	31.0 (27.7 - 34.2)	241 (66.2)	26.6 (22.1 - 31.2)	1,506 (71.0)	31.2 (29.2 - 33.2)	
0<CEI≤1.1	92 (33.2)		182 (25.4)		221 (28.9)		88 (24.2)		583 (27.5)		
1.1<CEI≤16.5	75 (27.1)		161 (22.5)		140 (18.3)		76 (20.9)		452 (21.3)		
CEI>16.5	41 (14.8)		169 (23.6)		184 (24.1)		77 (21.2)		471 (22.2)		
Crystalline silica											
Never (CEI=0)	155 (56.0)		417 (58.2)		460 (60.2)		238 (65.4)		1,270 (59.9)		0.384
Ever (CEI>0)	122 (44.0)	26.8 (21.6 - 32.0)	299 (41.8)	24.3 (21.1 - 27.4)	304 (39.8)	24.5 (21.5 - 27.6)	126 (34.6)	22.4 (18.1 - 26.7)	851 (40.1)	24.4 (22.6 - 26.2)	
0<CEI≤0.4	55 (19.9)		127 (17.7)		106 (13.9)		41 (11.3)		329 (15.5)		
0.4<CEI≤2.2	46 (16.6)		115 (16.1)		91 (11.9)		30 (8.2)		282 (13.3)		
CEI>2.2	21 (7.6)		57 (8.0)		107 (14.0)		55 (15.1)		240 (11.3)		

[a] Pw weighted prevalence equal to the sum of the Highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] p-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).

Table 11. Occupational exposure to asbestos by age at diagnosis stratified by smoking status among 2,121 population-based French male lung cancer cases

	Age at diagnosis (years)										
	< 50 years (277)		50-59 years (716)		60-69 years (764)		≥ 70 years (364)		Total (2,121)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Asbestos											
Non-smokers (48)											
Never (CEI[c]=0)	4 (33.3)		7 (41.2)		3 (27.3)		3 (37.5)		17 (35.4)		
Ever (CEI>0)	8 (66.7)	25.4 (0.8 - 50.1)	10 (58.8)	29.0 (0.0 - 50.5)	8 (72.7)	25.0 (0.0 - 50.6)	5 (62.5)	30.0 (0.0 - 61.7)	31 (64.6)	27.3 (14.7 - 39.9)	1
0<CEI≤1.1	4 (33.3)		2 (11.8)		3 (27.3)		3 (37.5)		12 (25.0)		
1.1<CEI≤16.5	2 (16.7)		2 (11.8)		3 (27.3)		0 (0.0)		7 (14.6)		
CEI>16.5	2 (16.7)		6 (35.3)		2 (18.2)		2 (25.0)		12 (25.0)		
Current smokers (1,313)											
Never (CEI=0)	60 (25.4)		143 (28.0)		130 (30.0)		40 (30.3)		373 (28.4)		
Ever (CEI>0)	176 (74.6)	31.7 (25.8 - 37.7)	368 (72.0)	33.7 (29.6 - 37.8)	304 (70.0)	29.7 (25.4 - 34.0)	92 (69.7)	25.5 (18.1 - 32.9)	940 (71.6)	31.2 (28.7 - 33.7)	0.379
0<CEI≤1.1	77 (32.6)		130 (25.4)		121 (27.9)		35 (26.5)		363 (27.6)		
1.1<CEI≤16.5	65 (27.5)		114 (22.3)		81 (18.7)		29 (22.0)		289 (22.0)		
CEI>16.5	34 (14.4)		124 (24.3)		102 (23.5)		28 (21.2)		288 (21.9)		
Ex-smokers[d] (760)											
Never (CEI=0)	5 (17.2)		54 (28.7)		86 (27.0)		80 (35.7)		225 (29.6)		
Ever (CEI>0)	24 (82.8)	35.1 (17.7 - 52.5)	134 (71.3)	33.5 (26.7 - 40.2)	233 (73.0)	32.9 (27.8 - 38.1)	144 (64.3)	27.2 (21.3 - 33.0)	535 (70.4)	31.4 (28.1 - 34.7)	0.094
0<CEI≤1.1	11 (37.9)		50 (26.6)		97 (30.4)		50 (22.3)		208 (27.4)		
1.1<CEI≤16.5	8 (27.6)		45 (23.9)		56 (17.6)		47 (21.0)		156 (20.5)		
CEI>16.5	5 (17.2)		39 (20.7)		80 (25.1)		47 (21.0)		171 (22.5)		

[a] Pw weighted prevalence equal to the sum of the Highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] Ex-smokers stopped smoking for more than two years.

Table 12. Occupational exposure to crystalline silica by age at diagnosis stratified by smoking status among 2,121 population-based French male lung cancer cases

	Age at diagnosis (years)										
	< 50 years (277)		50-59 years (716)		60-69 years (764)		≥ 70 years (364)		Total (2,121)		
	n (%)	Pw[a] % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	n (%)	Pw % (95 % CI)	*p*[b]
Crystalline silica											
Non-smokers (48)											
Never (CEI[c]=0)	8 (66.7)		10 (58.8)		6 (54.5)		6 (75.0)		30 (62.5)		
Ever (CEI>0)	4 (33.3)	23.3 (0.0 - 47.3)	7 (41.2)	29.4 (7.8 - 51.1)	5 (45.5)	29.1 (2.3 - 55.9)	2 (25.0)	12.5 (0.0 - 35.4)	18 (37.5)	25.0 (12.8 - 37.3)	0.899
0<CEI≤0.4	1 (8.3)		2 (11.8)		4 (36.4)		0 (0.0)		7 (14.6)		
0.4<CEI≤2.2	2 (16.7)		5 (29.4)		0 (0.0)		0 (0.0)		7 (14.6)		
CEI>2.2	1 (8.3)		0 (0.0)		1 (9.1)		2 (25.0)		4 (8.3)		
Current smokers (1,313)											
Never (CEI=0)	129 (54.7)		295 (57.7)		258 (59.4)		83 (62.9)		765 (58.3)		
Ever (CEI>0)	107 (45.3)	27.2 (21.5 - 32.9)	216 (42.3)	24.7 (20.9 - 28.4)	176 (40.6)	24.5 (20.4 - 28.5)	49 (37.1)	25.3 (17.9 - 32.7)	548 (41.7)	25.1 (22.8 - 27.5)	0.757
0<CEI≤0.4	51 (21.6)		88 (17.2)		63 (14.5)		13 (9.8)		215 (16.4)		
0.4<CEI≤2.2	39 (16.5)		86 (16.8)		52 (12.0)		13 (9.8)		190 (14.5)		
CEI>2.2	17 (7.2)		42 (8.2)		61 (14.1)		23 (17.4)		143 (10.9)		
Ex-smokers[d] (760)											
Never (CEI=0)	18 (62.1)		112 (59.6)		196 (61.4)		149 (66.5)		475 (62.5)		
Ever (CEI>0)	11 (37.9)	25.3 (9.5 - 41.2)	76 (40.4)	22.7 (16.7 - 28.7)	123 (38.6)	24.4 (19.7 - 29.2)	75 (33.5)	21.0 (15.7 - 26.4)	285 (37.5)	23.1 (20.1 - 26.0)	0.738
0<CEI≤0.4	3 (10.3)		37 (19.7)		39 (12.2)		28 (12.5)		107 (14.1)		
0.4<CEI≤2.2	5 (17.2)		24 (12.8)		39 (12.2)		17 (7.6)		85 (11.2)		
CEI>2.2	3 (10.3)		15 (8.0)		45 (14.1)		30 (13.4)		93 (12.2)		

[a] Pw weighted prevalence equal to the sum of the Highest probability of exposure to asbestos or crystalline silica for a group of subjects divided by the total number of subjects The highest probability of exposure between all jobs held by a subject for more than 6 months over the entire occupational career. The probability of exposure for each job is estimated by a job-exposure matrix (JEM).
[b] *p*-value for the distribution of weighted prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[c] Cumulative Exposure Index CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[d] Ex-smokers stopped smoking for more than two years.

Appendix D: Results based on other definitions of exposure

Table 1. Occupational exposure to asbestos and crystalline silica by histological types among 6,521 French male lung cancer cases

	Histological types						
Occupational exposure	Squamous cell carcinoma (2,124)	Small cell carcinoma (901)	Adenocarcinoma (2,446)	Large cell carcinoma (734)	Other lung cancer (316)	**Total (6,521)**	***p***[a]
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Asbestos							
Never exposed (CEI[b]=0)	514 (24.2)	255 (28.3)	672 (27.5)	201 (27.4)	85 (26.9)	1,727 (26.5)	0.067
Exposed (CEI>0)	1,610 (75.8)	646 (71.7)	1,774 (72.5)	533 (72.6)	231 (73.1)	4,794 (73.5)	
Tertiles of CEI							
0 < CEI ≤ 1.1	519 (24.4)	210 (23.3)	605 (24.7)	191 (26.0)	77 (24.4)	1,602 (24.6)	
1.1 <CEI ≤16.5	531 (25.0)	201 (22.3)	608 (24.9)	171 (23.3)	83 (26.3)	1,594 (24.4)	0.115
CEI > 16.5	560 (26.4)	235 (26.1)	561 (22.9)	171 (23.3)	71 (22.5)	1,598 (24.5)	
Highest probability							
0 % <P ≤ 5 %	199 (9.4)	60 (6.7)	178 (7.3)	62 (8.4)	31 (9.8)	530 (8.1)	
5 % <P ≤ 30 %	295 (13.9)	135 (15.0)	351 (14.3)	116 (15.8)	48 (15.2)	945 (14.5)	0.115
30 % < P ≤ 70 %	745 (35.1)	313 (34.7)	840 (34.3)	250 (34.1)	101 (32.0)	2,249 (34.5)	
P > 70 %	371 (17.5)	138 (15.3)	405 (16.6)	105 (14.3)	51 (16.1)	1,070 (16.4)	
Crystalline silica							
Never exposed (ICE=0)	1,240 (58.4)	546 (60.6)	1,533 (62.7)	461 (62.8)	201 (63.6)	3,981 (61.0)	**0.027**
Exposed (ICE>0)	884 (41.6)	355 (39.4)	913 (37.3%)	273 (37.2)	115 (36.4)	2,540 (39.0)	
Tertiles of CEI							
0 < CEI ≤ 0.4	266 (12.5)	118 (13.1)	321 (13.1)	94 (12.8)	48 (15.2)	847 (13.0)	
0.4 < CEI ≤ 2.2	284 (13.4)	117 (13.0)	325 (13.3)	94 (12.8)	34 (10.8)	854 (13.1)	**0.002**
CEI > 2.2	334 (15.7)	120 (13.3)	267 (10.9)	85 (11.6)	33 (10.4)	839 (12.9)	
Highest probability							
0 % <P ≤ 10 %	79 (3.7)	28 (3.1)	63 (2.6)	20 (2.7)	12 (3.8)	202 (3.1)	
10 % <P ≤ 50 %	201 (9.5)	99 (11.0)	249 (10.2)	69 (9.4)	26 (8.2)	644 (9.9)	0.179
50 % < P ≤ 90 %	588 (27.7)	222 (24.6)	586 (24.0)	181 (24.7)	75 (23.7)	1,652 (25.3)	
P > 90 %	16 (0.8)	6 (0.7)	15 (0.6)	3 (0.4)	2 (0.6)	42 (0.6)	

[a] *p*-value estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[b] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).

Table 2. Occupational exposure to asbestos by histological types stratified by smoking status among 6,521 French male lung cancer cases

	Histological types						
	Squamous cell carcinoma (2,124)	Small cell carcinoma (901)	Adenocarcinoma (2,446)	Large cell carcinoma (734)	Other lung cancer (316)	**Total (6,521)**	***p*[a]**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Asbestos exposure							
Non-smokers (180)							
Never exposed (CEI[b]=0)	9 (40.9)	4 (57.1)	37 (33.3)	7 (41.2)	6 (26.1)	63 (35.0)	0.536
Exposed (CEI>0)	13 (59.1)	3 (42.9)	74 (66.7)	10 (58.8)	17 (73.9)	117 (65.0)	
Tertiles of CEI							
0 < CEI ≤ 1.1	2 (9.1)	1 (14.3)	28 (25.2)	4 (23.5)	8 (34.8)	43 (23.9)	0.689
1.1 <CEI ≤16.5	6 (27.3)	0 (0.0)	23 (20.7)	4 (23.5)	6 (26.1)	39 (21.7)	
CEI > 16.5	5 (22.7)	2 (28.6)	23 (20.7)	2 (11.8)	3 (13.0)	35 (19.4)	
Highest probability							
0 % <P ≤ 5 %	2 (9.1)	0 (0.0)	8 (7.2)	3 (17.6)	5 (21.7)	18 (10.0)	0.321
5 % <P ≤ 30 %	2 (9.1)	1 (14.3)	18 (16.2)	0 (0.0)	4 (17.4)	25 (13.9)	
30 % < P ≤ 70 %	4 (18.2)	1 (14.3)	37 (33.3)	5 (29.4)	4 (17.4)	51 (28.3)	
P > 70 %	5 (22.7)	1 (14.3)	11 (9.9)	2 (11.8)	4 (17.4)	23 (12.8)	
Current smokers (3,747)							
Never exposed (CEI=0)	292 (24.3)	179 (29.5)	379 (28.1)	106 (24.7)	46 (28.9)	1,002 (26.7)	0.077
Exposed (CEI>0)	908 (75.7)	428 (70.5)	972 (71.9)	324 (75.3)	113 (71.1)	2,745 (73.3)	
Tertiles of CEI							
0 < CEI ≤ 1.1	283 (23.6)	136 (22.4)	327 (24.2)	119 (27.7)	40 (25.2)	905 (24.2)	0.225
1.1 <CEI ≤16.5	318 (26.5)	135 (22.2)	321 (23.8)	99 (23.0)	40 (25.2)	913 (24.4)	
CEI > 16.5	307 (25.6)	157 (25.9)	324 (24.0)	106 (24.7)	33 (20.8)	927 (24.7)	
Highest probability							
0 % <P ≤ 5 %	115 (9.6)	33 (5.4)	101 (7.5)	40 (9.3)	13 (8.2)	302 (8.1)	**0.025**
5 % <P ≤ 30 %	156 (13.0)	96 (15.8)	188 (13.9)	76 (17.7)	21 (13.2)	537 (14.3)	
30 % < P ≤ 70 %	440 (36.7)	208 (34.3)	458 (33.9)	144 (33.5)	46 (28.9)	1,296 (34.6)	
P > 70 %	197 (16.4)	91 (15.0)	225 (16.7)	64 (14.9)	33 (20.8)	610 (16.3)	
Ex-smokers[c] (2594)							
Never exposed (CEI=0)	213 (23.6)	72 (25.1)	256 (26.0)	88 (30.7)	33 (24.6)	662 (25.5)	0.205
Exposed (CEI>0)	689 (76.4)	215 (74.9)	728 (74.0)	199 (69.3)	101 (75.4)	1,932 (74.5)	
Tertiles of CEI							
0 < CEI ≤ 1.1	234 (25.9)	73 (25.4)	250 (25.4)	68 (23.7)	29 (21.6)	654 (25.2)	0.146
1.1 <CEI ≤16.5	207 (22.9)	66 (23.0)	264 (26.8)	68 (23.7)	37 (27.6)	642 (24.7)	
CEI > 16.5	248 (27.5)	76 (26.5)	214 (21.7)	63 (22.0)	35 (26.1)	636 (24.5)	
Highest probability							
0 % <P ≤ 5 %	82 (9.1)	27 (9.4)	69 (7.0)	19 (6.6)	13 (9.7)	210 (8.1)	0.308
5 % <P ≤ 30 %	137 (15.2)	38 (13.2)	145 (14.7)	40 (13.9)	23 (17.2)	383 (14.8)	
30 % < P ≤ 70 %	301 (33.4)	104 (36.2)	345 (35.1)	101 (35.2)	51 (38.1)	902 (34.8)	
P > 70 %	169 (18.7)	46 (16.0)	169 (17.2)	39 (13.6)	14 (10.4)	437 (16.8)	

[a] *p*-value estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[b] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) and expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[c] Ex-smokers stopped smoking for more than two years.

Table 3. Occupational exposure to crystalline silica by histological types stratified by smoking status among 6,521 French male lung cancer cases

	Histological types						
	Squamous cell carcinoma (2,124)	Small cell carcinoma (901)	Adenocarcinoma (2,446)	Large cell carcinoma (734)	Other lung cancer (316)	**Total (6,521)**	***p*[a]**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Crystalline silica exposure							
Non-smokers (180)							
Never exposed (ICE[b]=0)	16 (72.7)	5 (71.4)	77 (69.4)	13 (76.5)	19 (82.6)	130 (72.2)	0.785
Exposed (ICE>0)	6 (27.3)	2 (28.6)	34 (30.6)	4 (23.5)	4 (17.4)	50 (27.8)	
Tertiles of CEI							
0 < CEI ≤ 0.4	4 (18.2)	0 (0.0)	14 (12.6)	1 (5.9)	2 (8.7)	21 (11.7)	
0.4 < CEI ≤ 2.2	0 (0.0)	2 (28.6)	9 (8.1)	2 (11.8)	1 (4.3)	14 (7.8)	0.725
CEI > 2.2	2 (9.1)	0 (0.0)	11 (9.9)	1 (5.9)	1 (4.3)	15 (8.3)	
Highest probability							
0 % <P ≤ 10 %	1 (4.5)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	2 (1.1)	
10 % <P ≤ 50 %	2 (9.1)	2 (28.6)	10 (9.0)	2 (11.8)	0 (0.0)	16 (8.9)	0.638
50 % < P ≤ 90 %	3 (13.6)	0 (0.0)	22 (19.8)	2 (11.8)	4 (17.4)	31 (17.2)	
P > 90 %	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.6)	
Current smokers (3,747)							
Never exposed (ICE=0)	709 (59.1)	366 (60.3)	818 (60.5)	263 (61.2)	92 (57.9)	2,248 (60.0)	0.885
Exposed (ICE>0)	491 (40.9)	241 (39.7)	533 (39.5)	167 (38.8)	67 (42.1)	1,499 (40.0)	
Tertiles of CEI							
0 < CEI ≤ 0.4	154 (12.8)	80 (13.2)	194 (14.4)	62 (14.4)	29 (18.2)	519 (13.9)	
0.4 < CEI ≤ 2.2	168 (14.0)	85 (14.0)	206 (15.2)	57 (13.3)	22 (13.8)	538 (14.4)	0.195
CEI > 2.2	169 (14.1)	76 (12.5)	133 (9.8)	48 (11.2)	16 (10.1)	442 (11.8)	
Highest probability							
0 % <P ≤ 10 %	46 (3.8)	20 (3.3)	44 (3.3)	15 (3.5)	10 (6.3)	135 (3.6)	
10 % <P ≤ 50 %	92 (7.7)	69 (11.4)	142 (10.5)	37 (8.6)	14 (8.8)	354 (9.4)	0.210
50 % < P ≤ 90 %	346 (28.8)	149 (24.5)	341 (25.2)	115 (26.7)	42 (26.4)	993 (26.5)	
P > 90 %	7 (0.6)	3 (0.5)	6 (0.4)	0 (0.0)	1 (0.6)	17 (0.5)	
Ex-smokers[c] (2,594)							
Never exposed (ICE=0)	515 (57.1)	175 (61.0)	638 (64.8)	185 (64.5)	90 (67.2)	1,603 (61.8)	**0.005**
Exposed (ICE>0)	387 (42.9)	112 (39.0)	346 (35.2)	102 (35.5)	44 (32.8)	991 (38.2)	
Tertiles of CEI							
0 < CEI ≤ 0.4	108 (12.0)	38 (13.2)	113 (11.5)	31 (10.8)	17 (12.7)	307 (11.8)	
0.4 < CEI ≤ 2.2	116 (12.9)	30 (10.5)	110 (11.2)	35 (12.2)	11 (8.2)	302 (11.6)	**0.042**
CEI > 2.2	163 (18.1)	44 (15.3)	123 (12.5)	36 (12.5)	16 (11.9)	382 (14.7)	
Highest probability							
0 % <P ≤ 10 %	32 (3.5)	8 (2.8)	18 (1.8)	5 (1.7)	2 (1.5)	65 (2.5)	
10 % <P ≤ 50 %	107 (11.9)	28 (9.8)	97 (9.9)	30 (10.5)	12 (9.0)	274 (10.6)	0.254
50 % < P ≤ 90 %	239 (26.5)	73 (25.4)	223 (22.7)	64 (22.3)	29 (21.6)	628 (24.2)	
P > 90 %	9 (1.0)	3 (1.0)	8 (0.8)	3 (1.0)	1 (0.7)	24 (0.9)	

[a] *p*-value estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[b] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[c] Ex-smokers stopped smoking for more than two years.

Table 4. Occupational exposure to asbestos and crystalline silica by age at diagnosis among 6,521 French male lung cancer cases

Occupational exposure	Age at diagnosis (years) < 50 years (698)	50-59 years (1,981)	60-69 years (2,152)	≥ 70 years (1,690)	Total (6,521)	*p*[a]
	n (%)	n (%)	n (%)	n (%)	n (%)	
Asbestos						
Never exposed (CEI[b]=0)	159 (22.8)	526 (26.6)	562 (26.1)	480 (28.4)	1,727 (26.5)	**0.041**
Exposed (CEI>0)	539 (77.2)	1,455 (73.4)	1,590 (73.9)	1,210 (71.6)	4,794 (73.5)	
Tertiles of CEI						
0 < CEI ≤ 1.1	195 (27.9)	465 (23.5)	525 (24.4)	417 (24.7)	1,602 (24.6)	
1.1 <CEI ≤16.5	222 (31.8)	497 (25.1)	473 (22.0)	402 (23.8)	1,594 (24.4)	**< 0.001**
CEI > 16.5	122 (17.5)	493 (24.9)	592 (27.5)	391 (23.1)	1,598 (24.5)	
Highest probability						
0 % <P ≤ 5 %	50 (7.2)	134 (6.8)	172 (8.0)	174 (10.3)	530 (8.1)	
5 % <P ≤ 30 %	121 (17.3)	277 (14.0)	297 (13.8)	250 (14.8)	945 (14.5)	**< 0.001**
30 % < P ≤ 70 %	260 (37.2)	676 (34.1)	761 (35.4)	552 (32.7)	2,249 (34.5)	
P > 70 %	108 (15.5)	368 (18.6)	360 (16.7)	234 (13.8)	1,070 (16.4)	
Crystalline silica						
Never exposed (CEI=0)	407 (58.3)	1,192 (60.2)	1,282 (59.6)	1,100 (65.1)	3,981 (61.0)	**0.001**
Exposed (ICE>0)	291 (41.7)	789 (39.8)	870 (40.4)	590 (34.9)	2,540 (39.0)	
Tertiles of CEI						
0 < CEI ≤ 0.4	130 (18.6)	293 (14.8)	255 (11.8)	169 (10.0)	847 (13.0)	
0.4 < CEI ≤ 2.2	114 (16.3)	292 (14.7)	287 (13.3)	161 (9.5)	854 (13.1)	**< 0.001**
CEI > 2.2	47 (6.7)	204 (10.3)	328 (15.2)	260 (15.4)	839 (12.9)	
Highest probability						
0 % <P ≤ 10 %	29 (4.2)	72 (3.6)	64 (3.0)	37 (2.2)	202 (3.1)	
10 % <P ≤ 50 %	57 (8.2)	203 (10.2)	244 (11.3)	140 (8.3)	644 (9.9)	**< 0.001**
50 % < P ≤ 90 %	203 (29.1)	504 (25.4)	543 (25.2)	402 (23.8)	1,652 (25.3)	
P > 90 %	2 (0.3)	10 (0.5)	19 (0.9)	11 (0.7)	42 (0.6)	

[a] *p*-value estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.

[b] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$CEI=$\sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).

Table 5. Occupational exposure to crystalline silica by age at diagnosis stratified by smoking status among 6,521 French male lung cancer

	Age at diagnosis (years)					
	< 50 years (698)	50-59 years (1,981)	60-69 years (2,152)	≥ 70 years (1,690)	**Total (6,521)**	***p***[a]
	n (%)	n (%)	n (%)	n (%)	n (%)	
Asbestos exposure						
Non-smokers (180)						
Never exposed (CEI[b]=0)	14 (43.8)	15 (44.1)	15 (28.3)	19 (31.1)	63 (35.0)	0.288
Exposed (CEI>0)	18 (56.3)	19 (55.9)	38 (71.7)	42 (68.9)	117 (65.0)	
Tertiles of CEI						
0 < CEI ≤ 1.1	7 (21.9)	3 (8.8)	14 (26.4)	19 (31.1)	43 (23.9)	
1.1 <CEI ≤16.5	9 (28.1)	4 (11.8)	14 (26.4)	12 (19.7)	39 (21.7)	0.043
CEI > 16.5	2 (6.3)	12 (35.3)	10 (18.9)	11 (18.0)	35 (19.4)	
Highest probability						
0 % <P ≤ 5 %	1 (3.1)	1 (2.9)	5 (9.4)	11 (18.0)	18 (10.0)	
5 % <P ≤ 30 %	7 (21.9)	4 (11.8)	6 (11.3)	8 (13.1)	25 (13.9)	0.277
30 % < P ≤ 70 %	6 (18.8)	11 (32.4)	17 (32.1)	17 (27.9)	51 (28.3)	
P > 70 %	4 (12.5)	3 (08.8)	10 (18.9)	6 (09.8)	23 (12.8)	
Current smokers (3,747)						
Never exposed (CEI=0)	125 (21.7)	370 (26.0)	343 (28.4)	164 (30.3)	1,002 (26.7)	**0.004**
Exposed (CEI>0)	451 (78.3)	1054 (74.0)	863 (71.6)	377 (69.7)	2,745 (73.3)	
Tertiles of CEI						
0 < CEI ≤ 1.1	158 (27.4)	332 (23.3)	280 (23.2)	135 (25.0)	905 (24.2)	
1.1 <CEI ≤16.5	188 (32.6)	353 (24.8)	247 (20.5)	125 (23.1)	913 (24.4)	**< 0.001**
CEI > 16.5	105 (18.2)	369 (25.9)	336 (27.9)	117 (21.6)	927 (24.7)	
Highest probability						
0 % <P ≤ 5 %	43 (7.5)	94 (6.6)	103 (8.5)	62 (11.5)	302 (8.1)	
5 % <P ≤ 30 %	97 (16.8)	202 (14.2)	156 (12.9)	82 (15.2)	537 (14.3)	**< 0.001**
30 % < P ≤ 70 %	219 (38.0)	508 (35.7)	409 (33.9)	160 (29.6)	1,296 (34.6)	
P > 70 %	92 (16.0)	250 (17.6)	195 (16.2)	73 (13.5)	610 (16.3)	
Ex-smokers[c] (2,594)						
Never exposed (CEI=0)	20 (22.2)	141 (27.0)	204 (22.8)	297 (27.3)	662 (25.5)	0.1
Exposed (CEI>0)	70 (77.8)	382 (73.0)	689 (77.2)	791 (72.7)	1,932 (74.5)	
Tertiles of CEI						
0 < CEI ≤ 1.1	30 (33.3)	130 (24.9)	231 (25.9)	263 (24.2)	654 (25.2)	
1.1 <CEI ≤16.5	25 (27.8)	140 (26.8)	212 (23.7)	265 (24.4)	642 (24.7)	**0.049**
CEI > 16.5	15 (16.7)	112 (21.4)	246 (27.5)	263 (24.2)	636 (24.5)	
Highest probability						
0 % <P ≤ 5 %	6 (6.7)	39 (7.5)	64 (7.2)	101 (9.3)	210 (8.1)	
5 % <P ≤ 30 %	17 (18.9)	71 (13.6)	135 (15.1)	160 (14.7)	383 (14.8)	**0.004**
30 % < P ≤ 70 %	35 (38.9)	157 (30.0)	335 (37.5)	375 (34.5)	902 (34.8)	
P > 70 %	12 (13.3)	115 (22.0)	155 (17.4)	155 (14.2)	437 (16.8)	

[a] *p*-value estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[b] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[c] Ex-smokers stopped smoking for more than two years.

Table 6. Occupational exposure to asbestos by age at diagnosis stratified by smoking status among 6,521 French male lung cancer

	Age at diagnosis (years)					
	< 50 years (698)	50-59 years (1,981)	60-69 years (2,152)	≥ 70 years (1,690)	**Total (6,521)**	***p***[a]
	n (%)	n (%)	n (%)	n (%)	n (%)	
Crystalline silica exposure						
Non-smokers (180)						
Never exposed (CEI[b]=0)	24 (75.0)	21 (61.8)	35 (66.0)	50 (82.0)	130 (72.2)	0.118
Exposed (ICE>0)	8 (25.0)	13 (38.2)	18 (34.0)	11 (18.0)	50 (27.8)	
Tertiles of CEI						
0 < CEI ≤ 0.4	2 (6.3)	3 (8.8)	10 (18.9)	6 (9.8)	21 (11.7)	
0.4 < CEI ≤ 2.2	4 (12.5)	8 (23.5)	2 (3.8)	0 (0.0)	14 (7.8)	**0.005**
CEI > 2.2	2 (6.3)	2 (5.9)	6 (11.3)	5 (8.2)	15 (8.3)	
Highest probability						
0 % <P ≤ 10 %	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.6)	2 (1.1)	
10 % <P ≤ 50 %	2 (6.3)	3 (8.8)	6 (11.3)	5 (8.2)	16 (8.9)	0.330
50 % < P ≤ 90 %	6 (18.8)	10 (29.4)	10 (18.9)	5 (8.2)	31 (17.2)	
P > 90 %	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.6)	
Current smokers (3,747)						
Never exposed (ICE=0)	326 (56.6)	854 (60.0)	718 (59.5)	350 (64.7)	2,248 (60.0)	**0.049**
Exposed (ICE>0)	250 (43.4)	570 (40.0)	488 (40.5)	191 (35.3)	1,499 (40.0)	
Tertiles of CEI						
0 < CEI ≤ 0.4	116 (20.1)	208 (14.6)	142 (11.8)	53 (9.8)	519 (13.9)	
0.4 < CEI ≤ 2.2	96 (16.7)	220 (15.4)	161 (13.3)	61 (11.3)	538 (14.4)	**< 0.001**
CEI > 2.2	38 (6.6)	142 (10.0)	185 (15.3)	77 (14.2)	442 (11.8)	
Highest probability						
0 % <P ≤ 10 %	27 (4.7)	52 (3.7)	45 (3.7)	11 (2.0)	135 (3.6)	
10 % <P ≤ 50 %	47 (8.2)	141 (9.9)	118 (9.8)	48 (8.9)	354 (9.4)	0.171
50 % < P ≤ 90 %	174 (30.2)	372 (26.1)	318 (26.4)	129 (23.8)	993 (26.5)	
P > 90 %	2 (0.3)	5 (0.4)	7 (0.6)	3 (0.6)	17 (0.5)	
Ex-smokers[c] (2,594)						
Never exposed (ICE=0)	57 (63.3)	317 (60.6)	529 (59.2)	700 (64.3)	1,603 (61.8)	0.119
Exposed (ICE>0)	33 (36.7)	206 (39.4)	364 (40.8)	388 (35.7)	991 (38.2)	
Tertiles of CEI						
0 < CEI ≤ 0.4	12 (13.3)	82 (15.7)	103 (11.5)	110 (10.1)	307 (11.8)	
0.4 < CEI ≤ 2.2	14 (15.6)	64 (12.2)	124 (13.9)	100 (09.2)	302 (11.6)	**< 0.001**
CEI > 2.2	7 (7.8)	60 (11.5)	137 (15.3)	178 (16.4)	382 (14.7)	
Highest probability						
0 % <P ≤ 10 %	2 (2.2)	20 (3.8)	18 (2.0)	25 (2.3)	65 (2.5)	
10 % <P ≤ 50 %	8 (8.9)	59 (11.3)	120 (13.4)	87 (8.0)	274 (10.6)	**0.026**
50 % < P ≤ 90 %	23 (25.6)	122 (23.3)	215 (24.1)	268 (24.6)	628 (24.2)	
P > 90 %	0 (0.0)	5 (1.0)	11 (1.2)	8 (0.7)	24 (0.9)	

[a] *p*-value estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[b] Cumulative Exposure Index $\mathrm{CEI} = \sum_i Di \times Fi \times Ii$ (Di: Total duration of exposure of job i; Fi: Frequency of exposure of job i; Ii: Intensity of exposure of job i) expressed in equivalent f/ml.year for asbestos exposure, and equivalent mg/m^3-year for crystalline silica exposure. Variables used in the calculation of CEI are estimated by a job-exposure matrix (JEM).
[c] Ex-smokers stopped smoking for more than two years.

Appendix E: Selected studies evaluating occupational exposure to asbestos and to crystalline silica according to histological types.

Table 1. Selected studies evaluating occupational exposure to asbestos according to histological types

Author (Year)	Study design	Country	Cases	Recruitment period	Recruitment	Data collection	Asbestos: Exposure Identification	Asbestos: Exposure categories	Prevalence of exposure by histological types		*p*[1]
Paris (2010)	Case-only	France	M: 1,303 F: 190	1997-2006	Two Hospitals	Questionnaire	Experts	Never Ever[2]	SQCC: 35.8% ADC: 34.4% SCC: 33.1% LCC: 27.2% OLC: 33.7%		0.39
De Matteis (2012)	Case-control	Italy	M: 1,537	2002-2005	13 Hospitals	Questionnaire	Matrix (DOMJEM)	Never Ever[3]	SQCC: 41.2% ADC: 40.5% SCC: 45.9%		0.48
Offermans (2014)	Case-cohort	Netherlands	M: 2,107	1986-2003	Register	Questionnaire	Matrix (DOMJEM and FINJEM)	Never Ever[3]	**DOMJEM** SQCC: 33.2% ADC: 28.2% SCC: 32.2% LCC: 34.0%	**FINJEM** SQCC: 35.1% ADC: 27.2% SCC: 32.5% LCC: 34.6%	0.2[4] 0.20[5]
Current study	Case-only	France	M: 6,521	1999-2011	Hospitals and registers	Questionnaire	Matrix (Matgéné)	Never Ever[3]	SQCC: 75.8% ADC: 72.5% SCC: 71.7% LCC: 72.6% OLC: 73.1%		0.07

[1] *p*-value for the distribution of prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[2] exposure for at least one year with frequency of exposure ≥ 5% of total work time per year.
[3] Held at least one job with a non-null probability of exposure.
[4] *p*-value for the distribution of prevalence estimated by Pearson Chi-Square based on the assessment of exposure by DOMJEM.
[5] *p*-value for the distribution of prevalence estimated by Pearson Chi-Square based on the assessment of exposure BY FINJEM.
M: males; F: females.
ADC: adenocarcinoma; SQCC: squamous cell carcinoma; SCC: small cell carcinoma; LCC: large cell carcinoma; OLC: other lung cancer.

Table 2. Selected studies evaluating occupational exposure to crystalline silica according to histological types

Author (Year)	Study design	Country	Cases	Recruitment period	Recruitment	Data collection	Crystalline silica		Prevalence of exposure by histological types	*P*[1]
							Exposure Identification	Exposure categories		
Paris (2010)	Case-only	France	M: 1,303 F: 190	1997-2006	Two Hospitals	Questionnaire	Experts	Never Ever[2]	SQCC: 5.6% ADC: 6.1% SCC: 2.4% LCC: 3.8% OLC: 3.1%	0.15
Vida (2010)	Case-control	Canada (Montreal)	M: 1,598	1979-2001	18 hospitals	Questionnaire	Experts	Never Ever[3]	SQCC: 30.0% ADC: 20.6% SCC: 25.5%	**0.003**
De Matteis (2012)	Case-control	Italy	M: 1,537	2002-2005	13 Hospitals	Questionnaire	Matrix (DOMJEM)	Never Ever[4]	SQCC: 29.8% ADC: 17.5% SCC: 29.3%	**<0.001**
Current study	Case-only	France	M: 6,521	1999-2011	Hospitals and registers	Questionnaire	Matrix (Matgéné)	Never Ever[4]	SQCC: 41.6% ADC: 37.3% SCC: 39.4% LCC: 37.2% OLC: 36.4%	**0.03**

[1] *p*-value for the distribution of prevalence estimated by Pearson Chi-Square test or Fisher exact test when expected values are less than 5.
[2] exposure for at least one year with frequency of exposure ≥ 5% of total work time per year.
[3] Exposure more than that can be found in the general environment.
[4] Held at least one job with a non-null probability of exposure.
M: males; F: females.
ADC: adenocarcinoma; SQCC: squamous cell carcinoma; SCC: small cell carcinoma; LCC: large cell carcinoma; OLC: other lung cancer.

Appendix F: Statistical analyses where subjects held at least one job with a non-null probability of exposure considered as exposed

Table 1. Statistical interaction between tobacco smoking and asbestos exposure on histological types among male lung cancer cases.

Asbestos exposure	Smoking status				β for cross-product term	*p* for cross-product term
	Never-low smokers[1]		Medium-high smokers[2]			
	SQCC/Others	OR (95%CI)[3]	SQCC/Others	OR (95%CI)[3]		
Non-exposed	139/405	1.00[5]	450/976	1.46 (1.16-1.83)	-0.01	0.92
Exposed[4]	424/994	1.20 (0.95-1.51)	1,371/2,497	1.72 (1.39-2.13)		
	SQCC/ADC	OR (95%CI)[3]	SQCC/ADC	OR (95%CI)[3]		
Non-exposed	139/256	1.00[5]	450/498	1.82 (1.41-2.33)	-0.11	0.48
Exposed[4]	424/592	1.27 (0.98-1.64)	1,371/1,341	2.08 (1.64-2.63)		
	SCC/Others	OR (95%CI)[3]	SCC/Others	OR (95%CI)[3]		
Non-exposed	50/494	1.00[5]	249/1,177	2.06 (1.49-2.84)	-0.23	0.23
Exposed[4]	137/1,281	1.05 (0.74-1.48)	590/3,278	1.71 (1.25-2.34)		
	SCC/ADC	OR (95%CI)[3]	SCC/ADC	OR (95%CI)[3]		
Non-exposed	50/256	1.00[5]	249/498	2.60 (1.84-3.66)	-0.30	0.14
Exposed[4]	137/592	1.18 (0.82-1.70)	590/1,341	2.26 (1.62-3.16)		

SQCC: Squamous cell carcinoma; ADC: Adenocarcinoma; SCC: Small cell carcinoma.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to crystalline silica (non-exposed vs exposed), age at diagnosis (years), and initial study.
[4]: The highest probability of exposure > 0
[5]: Reference category defined as never-low smokers and non-exposed to asbestos.

Table 2. Statistical interaction between tobacco smoking and crystalline silica exposure on histological types among male lung cancer cases.

Crystalline silica exposure	Smoking status				β for cross-product term	*p* for cross-product term
	Never-low smokers[1]		Medium-high smokers[2]			
	SQCC/Others	OR (95%CI)[3]	SQCC/Others	OR (95%CI)[3]		
Non-exposed	328/938	1.00[5]	1,087/2,155	1.61 (1.38-1.87)	-0.28	0.02
Exposed[4]	235/461	1.41 (1.14-1.74)	734/1,318	1.71 (1.45-2.02)		
	SQCC/ADC	OR (95%CI)[3]	SQCC/ADC	OR (95%CI)[3]		
Non-exposed	328/582	1.00[5]	1,087/1,129	1.92 (1.63-2.27)	-0.35	0.01
Exposed[4]	235/266	1.52 (1.20-1.92)	734/710	2.05 (1.70-2.47)		
	SCC/Others	OR (95%CI)[3]	SCC/Others	OR (95%CI)[3]		
Non-exposed	116/1,150	1.00[5]	519/2,723	1.84 (1.48-2.28)	-0.14	0.42
Exposed[4]	71/625	1.20 (0.87-1.65)	320/1,732	1.91 (1.51-2.42)		
	SCC/ADC	OR (95%CI)[3]	SCC/ADC	OR (95%CI)[3]		
Non-exposed	116/582	1.00[5]	519/1,129	2.33 (1.85-2.93)	-0.29	0.13
Exposed[4]	71/266	1.41 (1.01-1.98)	320/710	2.46 (1.90-3.17)		

SQCC: Squamous cell carcinoma; ADC: Adenocarcinoma; SCC: Small cell carcinoma.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to asbestos (non-exposed vs exposed), age at diagnosis (years), and initial study.
[4]: The highest probability of exposure > 0
[5]: Reference category defined as never-low smokers and non-exposed to crystalline silica.

Table 3. Statistical interaction between tobacco smoking and exposure to either asbestos or crystalline silica on tumor location among male lung cancer cases.

	Smoking status				β for cross-product term	*p* for cross-product term
	Never-low smokers[1]		Medium-high smokers[2]			
	Upper lobe/Lower lobe	OR (95%CI)[3]	Upper lobe/Lower lobe	OR (95%CI)[3]		
Asbestos exposure						
Non-exposed	250/115	1.00[5]	602/255	1.07 (0.81-1.40)	0.11	0.49
Exposed[4]	599/346	0.83 (0.63-1.08)	1,749/773	0.98 (0.77-1.26)		
Crystalline silica exposure						
Non-exposed	550/293	1.00[5]	1,380/607	1.15 (0.97-1.38)	<0.01	0.99
Exposed[4]	299/168	1.01 (0.79-1.29)	971/421	1.17 (0.96-1.42)		

[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to either asbestos or crystalline silica (non-exposed vs exposed), age at diagnosis (years), histological types, and initial study.
[4]: The highest probability of exposure > 0
[5]: Reference category defined as never-low smokers and non-exposed to either asbestos or crystalline silica.

Table 4. Statistical interaction between tobacco smoking and asbestos exposure on age at diagnosis stratified by histological types

	Smoking status				
	Never-low smokers[1]		Medium-high smokers[2]		
	n (%)	Age at diagnosis (95% CI)[3]	n (%)	Age at diagnosis (95% CI)[3]	*p* for cross-product term
Squamous cell carcinoma (2384)					
Asbestos exposure					
Non-exposed	139 (5.8)	69.2 (67.1-71.2)	450 (18.9)	66.2 (62.4-69.9)	0.34
Exposed[4]	424 (17.8)	68.8 (65.0-72.6)	1,371 (57.5)	64.8 (57.4-72.3)	
Small cell carcinoma (1026)					
Asbestos exposure					
Non-exposed	50 (4.9)	68.1 (64.8-71.5)	249 (24.3)	64.4 (58.2-70.6)	0.54
Exposed[4]	137 (13.4)	66.5 (60.0-72.9)	590 (57.5)	63.8 (51.1-76.5)	
Adenocarcinoma (2687)					
Asbestos exposure					
Non-exposed	256 (9.5)	63.8 (62.2-65.4)	498 (18.5)	62.2 (59.2-65.3)	<0.01
Exposed[4]	592 (22.0)	65.1 (62.1-68.2)	1,341 (49.9)	60.9 (54.6-67.2)	
Large cell carcinoma (805)					
Asbestos exposure					
Non-exposed	69 (8.6)	65.6 (61.8-69.5)	157 (19.5)	63.9 (57.0-70.8)	0.88
Exposed[4]	170 (21.1)	66.4 (59.4-73.3)	409 (50.8)	64.4 (50.9-77.9)	
Others (354)					
Asbestos exposure					
Non-exposed	30 (8.5)	65.2 (58.5-71.8)	72 (20.3)	66.7 (55.2-78.2)	0.28
Exposed[4]	95 (26.8)	68.4 (57.0-79.8)	157 (44.4)	66.8 (44.9-88.7)	

[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to crystalline silica (non-exposed vs exposed), and initial study.
[4]: The highest probability of exposure > 0

Table 5. Statistical interaction between tobacco smoking and crystalline silica exposure on age at diagnosis stratified by histological types

	Smoking status				
	Never-low smokers[1]		Medium-high smokers[2]		
	n (%)	Age at diagnosis (95% CI)[3]	n (%)	Age at diagnosis (95% CI)[3]	*p* for cross-product term
Squamous cell carcinoma (2,384)					
Crystalline silica exposure					
Non-exposed	328 (13.8)	69.4 (67.7-71.2)	1,087 (45.6)	66.1 (63.2-68.9)	0.32
Exposed[4]	235 (9.9)	69.8 (66.5-73.2)	734 (30.8)	65.6 (59.5-71.8)	
Small cell carcinoma (1,026)					
Crystalline silica exposure					
Non-exposed	116 (11.3)	67.4 (64.6-70.2)	519 (50.6)	64.6 (59.8-69.3)	0.88
Exposed[4]	71 (6.9)	67.4 (61.7-73.0)	320 (31.2)	64.3 (53.6-75.0)	
Adenocarcinoma (2,687)					
Crystalline silica exposure					
Non-exposed	582 (21.7)	64.7 (63.3-66.1)	1,129 (42.0)	61.8 (59.4-64.2)	<0.05
Exposed[4]	266 (9.9)	65.3 (62.4-68.1)	710 (26.4)	60.7 (55.1-66.2)	
Large cell carcinoma (805)					
Crystalline silica exposure					
Non-exposed	154 (19.1)	66.3 (62.8-69.8)	362 (45.0)	63.5 (57.9-69.0)	0.14
Exposed[4]	85 (10.6)	63.0 (56.6-69.4)	204 (25.3)	62.7 (51.0-74.5)	
Others (354)					
Crystalline silica exposure					
Non-exposed	86 (24.3)	67.1 (61.0-73.3)	145 (41.0)	65.9 (56.6-75.1)	0.55
Exposed[4]	39 (11.0)	64.2 (53.7-74.7)	84 (23.7)	64.5 (45.6-83.5)	

[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to asbestos (non-exposed vs exposed), and initial study.
[4]: The highest probability of exposure > 0

Appendix G: Statistical analyses where subjects with a highest probability of exposure lower than 30% considered as non-exposed.

Table 1. Statistical interaction between tobacco smoking and asbestos exposure on histological types among male lung cancer cases.

Asbestos exposure	Smoking status				β for cross-product term	*p* for cross-product term
	Never-low smokers[1]		Medium-high smokers[2]			
	SQCC/Others	OR (95%CI)[3]	SQCC/Others	OR (95%CI)[3]		
Non-exposed[4]	274/737	1.00[5]	881/1,752	1.46 (1.24-1.72)	-0.03	0.80
Exposed	289/662	1.12 (0.92-1.38)	940/1,721	1.60 (1.34-1.90)		
	SQCC/ADC	OR (95%CI)[3]	SQCC/ADC	OR (95%CI)[3]		
Non-exposed[4]	274/450	1.00[5]	881/902	1.76 (1.46-2.11)	-0.09	0.49
Exposed	289/398	1.14 (0.91-1.42)	940/937	1.82 (1.51-2.21)		
	SCC/Others	OR (95%CI)[3]	SCC/Others	OR (95%CI)[3]		
Non-exposed[4]	96/915	1.00[5]	426/2,207	1.80 (1.42-2.27)	-0.06	0.73
Exposed	91/860	1.03 (0.75-1.40)	413/2,248	1.74 (1.36-2.22)		
	SCC/ADC	OR (95%CI)[3]	SCC/ADC	OR (95%CI)[3]		
Non-exposed[4]	96/450	1.00[5]	426/902	2.21 (1.72-2.85)	-0.11	0.56
Exposed	91/398	1.06 (0.77-1.48)	413/937	2.11 (1.62-2.75)		

SQCC: Squamous cell carcinoma; ADC: Adenocarcinoma; SCC: Small cell carcinoma.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to crystalline silica (non-exposed vs exposed), age at diagnosis (years), and initial study.
[4]: Subjects with a highest probability of exposure less than 30%.
[5]: Reference category defined as never-low smokers and non-exposed to asbestos.

Table 2. Statistical interaction between tobacco smoking and crystalline silica exposure on histological types among male lung cancer cases.

Crystalline silica exposure	Smoking status				β for cross-product term	*p* for cross-product term
	Never-low smokers[1]		Medium-high smokers[2]			
	SQCC/Others	OR (95%CI)[3]	SQCC/Others	OR (95%CI)[3]		
Non-exposed[4]	372/999	1.00[5]	1,183/2,345	1.51 (1.31-1.74)	-0.14	0.26
Exposed	191/400	1.29 (1.04-1.60)	638/1,128	1.69 (1.43-1.99)		
	SQCC/ADC	OR (95%CI)[3]	SQCC/ADC	OR (95%CI)[3]		
Non-exposed[4]	372/618	1.00[5]	1,183/1,230	1.80 (1.54-2.11)	-0.22	0.11
Exposed	191/230	1.42 (1.11-1.81)	638/609	2.05 (1.70-2.46)		
	SCC/Others	OR (95%CI)[3]	SCC/Others	OR (95%CI)[3]		
Non-exposed[4]	127/1,244	1.00[5]	566/2,962	1.83 (1.49-2.24)	-0.14	0.43
Exposed	60/531	1.14 (0.82-1.58)	273/1,493	1.80 (1.42-2.27)		
	SCC/ADC	OR (95%CI)[3]	SCC/ADC	OR (95%CI)[3]		
Non-exposed[4]	127/618	1.00[5]	566/1,230	2.28 (1.83-2.84)	-0.27	0.18
Exposed	60/230	1.36 (0.95-1.93)	273/609	2.37 (1.83-3.06)		

SQCC: Squamous cell carcinoma; ADC: Adenocarcinoma; SCC: Small cell carcinoma.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to asbestos (non-exposed vs exposed), age at diagnosis (years), and initial study.
[4]: Subjects with a highest probability of exposure less than 30%.
[5]: Reference category defined as never-low smokers and non-exposed to crystalline silica.

Table 3. Statistical interaction between tobacco smoking and exposure to either asbestos or crystalline silica on tumor location among male lung cancer cases.

	Smoking status				β for cross-product term	*p* for cross-product term
	Never-low smokers[1]		Medium-high smokers[2]			
	Upper lobe/Lower lobe	OR (95%CI)[3]	Upper lobe/Lower lobe	OR (95%CI)[3]		
Asbestos exposure						
Non-exposed[4]	439/243	1.00[5]	1,093/498	1.17 (0.96-1.42)	-0.03	0.85
Exposed	410/218	1.08 (0.85-1.37)	1,258/530	1.23 (1.01-1.51)		
Crystalline silica exposure						
Non-exposed[4]	592/329	1.00[5]	1,518/658	1.22 (1.03-1.44)	-0.16	0.28
Exposed	257/132	1.08 (0.83-1.40)	833/370	1.11 (0.91-1.35)		

[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to either asbestos or crystalline silica (non-exposed vs exposed), age at diagnosis (years), histological types, and initial study.
[4]: Subjects with a highest probability of exposure less than 30%.
[5]: Reference category defined as never-low smokers and non-exposed to either asbestos or crystalline silica.

Table 4. Statistical interaction between tobacco smoking and asbestos exposure on age at diagnosis stratified by histological types

	Smoking status				
	Never-low smokers[1]		Medium-high smokers[2]		
	n (%)	Age at diagnosis (95% CI)[3]	n (%)	Age at diagnosis (95% CI)[3]	*p* for cross-product term
Squamous cell carcinoma (2,384)					
Asbestos exposure					
Non-exposed[4]	274 (11.5)	69.3 (67.6-71.0)	881 (37.0)	65.7 (62.8-68.7)	0.75
Exposed	289 (12.1)	68.5 (65.2-71.7)	940 (39.4)	64.6 (58.4-70.8)	
Small cell carcinoma (1,026)					
Asbestos exposure					
Non-exposed[4]	96 (9.4)	67.1 (64.3-70.0)	426 (41.5)	65.0 (60.1-69.9)	0.30
Exposed	91 (8.9)	66.9 (61.3-72.4)	413 (40.3)	63.1 (52.5-73.8)	
Adenocarcinoma (2,687)					
Asbestos exposure					
Non-exposed[4]	450 (16.7)	63.9 (62.5-65.3)	902 (33.6)	62.0 (59.5-64.5)	<0.01
Exposed	398 (14.8)	66.0 (63.3-68.8)	937 (34.9)	60.9 (55.5-66.3)	
Large cell carcinoma (805)					
Asbestos exposure					
Non-exposed[4]	124 (15.4)	65.6 (62.1-69.2)	299 (37.1)	64.0 (58.3-69.8)	0.68
Exposed	115 (14.3)	66.4 (60.1-72.7)	267 (33.2)	64.1 (52.4-75.9)	
Others (354)					
Asbestos exposure					
Non-exposed[4]	67 (18.9)	68.0 (62.1-73.9)	125 (35.3)	67.6 (58.3-76.9)	0.68
Exposed	58 (16.4)	67.5 (57.4-77.5)	104 (29.4)	66.0 (47.5-84.5)	

[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to crystalline silica (non-exposed vs exposed), and initial study.
[4]: Subjects with a highest probability of exposure less than 30%.

Table 5. Statistical interaction between tobacco smoking and crystalline silica exposure on age at diagnosis stratified by histological types

	Smoking status				
	Never-low smokers[1]		Medium-high smokers[2]		
	n (%)	Age at diagnosis (95% CI)[3]	n (%)	Age at diagnosis (95% CI)[3]	*p* for cross-product term
Squamous cell carcinoma (2,384)					
Crystalline silica exposure					
Non-exposed[4]	372 (15.6)	69.2 (67.6-70.9)	1,183 (49.6)	65.7 (63.0-68.4)	0.56
Exposed	191 (8.0)	69.5 (66.3-72.8)	638 (26.8)	65.5 (59.4-71.6)	
Small cell carcinoma (1,026)					
Crystalline silica exposure					
Non-exposed[4]	127 (12.4)	67.8 (65.1-70.5)	566 (55.2)	64.8 (60.3-69.4)	0.91
Exposed	60 (5.8)	67.5 (61.9-73.2)	273 (26.6)	64.7 (54.1-75.4)	
Adenocarcinoma (2,687)					
Crystalline silica exposure					
Non-exposed[4]	618 (23.0)	64.6 (63.3-66.0)	1,230 (45.8)	61.6 (59.3-63.9)	0.11
Exposed	230 (8.6)	64.6 (61.7-67.5)	609 (22.7)	60.1 (54.5-65.7)	
Large cell carcinoma (805)					
Crystalline silica exposure					
Non-exposed[4]	165 (20.5)	66.2 (62.8-69.7)	391 (48.6)	63.7 (58.3-69.1)	0.27
Exposed	74 (9.2)	63.5 (57.1-69.9)	175 (21.7)	62.9 (51.1-74.7)	
Others (354)					
Crystalline silica exposure					
Non-exposed[4]	89 (25.1)	68.2 (62.3-74.1)	158 (44.6)	67.4 (58.6-76.3)	0.91
Exposed	36 (10.2)	67.1 (56.7-77.5)	71 (20.1)	66.0 (47.2-84.8)	

[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to asbestos (non-exposed vs exposed), and initial study.
[4]: Subjects with a highest probability of exposure less than 30%.

Appendix H: Statistical analyses conducted exclusively among subjects who responded for themselves by excluding proxy respondents.

Table 1. Statistical interaction between tobacco smoking and asbestos exposure on histological types among male lung cancer cases.

Asbestos exposure	Smoking status				β for cross-product term	*p* for cross-product term
	Never-low smokers[1]		Medium-high smokers[2]			
	SQCC/Others	OR (95%CI)[3]	SQCC/Others	OR (95%CI)[3]		
Non-exposed (P=0%)	126/389	1.00[4]	402/867	1.58 (1.24-2.00)	-0.04	0.80
Exposed (P>30%)	256/615	1.28 (0.98-1.66)	846/1,529	1.94 (1.53-2.46)		
	SQCC/ADC	OR (95%CI)[3]	SQCC/ADC	OR (95%CI)[3]		
Non-exposed (P=0%)	126/248	1.00[4]	402/449	1.96 (1.51-2.55)	-0.15	0.36
Exposed (P>30%)	256/371	1.33 (1.00-1.77)	846/844	2.24 (1.73-2.91)		
	SCC/Others	OR (95%CI)[3]	SCC/Others	OR (95%CI)[3]		
Non-exposed (P=0%)	47/468	1.00[4]	220/1,049	2.07 (1.48-2.89)	-0.23	0.27
Exposed (P>30%)	82/789	1.02 (0.69-1.50)	357/2,018	1.66 (1.18-2.34)		
	SCC/ADC	OR (95%CI)[3]	SCC/ADC	OR (95%CI)[3]		
Non-exposed (P=0%)	47/248	1.00[4]	220/449	2.64 (1.85-3.76)	-0.31	0.17
Exposed (P>30%)	82/371	1.15 (0.76-1.73)	357/844	2.22 (1.54-3.19)		

SQCC: Squamous cell carcinoma; ADC: Adenocarcinoma; SCC: Small cell carcinoma; P: Highest probability of exposure.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to crystalline silica (non-exposed vs exposed), age at diagnosis (years), and initial study.
[4]: Reference category defined as never-low smokers and non-exposed to asbestos.

Table 2. Statistical interaction between tobacco smoking and crystalline silica exposure on histological types among male lung cancer cases.

Crystalline silica exposure	Smoking status				β for cross-product term	*p* for cross-product term
	Never-low smokers[1]		Medium-high smokers[2]			
	SQCC/Others	OR (95%CI)[3]	SQCC/Others	OR (95%CI)[3]		
Non-exposed (P=0%)	234/683	1.00[4]	745/1,486	1.66 (1.39-1.99)	-0.22	0.14
Exposed (P>30%)	148/321	1.28 (0.99-1.66)	503/910	1.72 (1.40-2.11)		
	SQCC/ADC	OR (95%CI)[3]	SQCC/ADC	OR (95%CI)[3]		
Non-exposed (P=0%)	234/430	1.00[4]	745/797	1.97 (1.62-2.40)	-0.29	0.08
Exposed (P>30%)	148/189	1.43 (1.07-1.91)	503/496	2.12 (1.68-2.66)		
	SCC/Others	OR (95%CI)[3]	SCC/Others	OR (95%CI)[3]		
Non-exposed (P=0%)	84/833	1.00[4]	357/1,874	1.84 (1.43-2.38)	-0.09	0.68
Exposed (P>30%)	45/424	1.17 (0.79-1.75)	220/1,193	1.98 (1.48-2.65)		
	SCC/ADC	OR (95%CI)[3]	SCC/ADC	OR (95%CI)[3]		
Non-exposed (P=0%)	84/430	1.00[4]	357/797	2.33 (1.78-3.06)	-0.20	0.39
Exposed (P>30%)	45/189	1.34 (0.88-2.04)	220/496	2.56 (1.87-3.50)		

SQCC: Squamous cell carcinoma; ADC: Adenocarcinoma; SCC: Small cell carcinoma; P: Highest probability of exposure.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to asbestos (non-exposed vs exposed), age at diagnosis (years), and initial study.
[4]: Reference category defined as never-low smokers and non-exposed to crystalline silica.

Table 3. Statistical interaction between tobacco smoking and exposure to either asbestos or crystalline silica on tumor location among male lung cancer cases.

	Smoking status				β for cross-product term	*p* for cross-product term
	Never-low smokers[1]		Medium-high smokers[2]			
	Upper lobe/Lower lobe	OR (95%CI)[3]	Upper lobe/Lower lobe	OR (95%CI)[3]		
Asbestos exposure						
Non-exposed (P=0%)	243/110	1.00[4]	581/251	1.02 (0.78-1.35)	0.07	0.70
Exposed (P>30%)	380/196	0.92 (0.68-1.24)	1,164/495	1.01 (0.76-1.32)		
Crystalline silica exposure						
Non-exposed (P=0%)	412/202	1.00[4]	1,032/433	1.10 (0.90-1.36)	-0.06	0.73
Exposed (P>30%)	209/104	1.01 (0.74-1.37)	705/304	1.05 (0.82-1.33)		

P: Highest probability of exposure.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to either asbestos or crystalline silica (non-exposed vs exposed), age at diagnosis (years), histological types, and initial study.
[4]: Reference category defined as never-low smokers and non-exposed to either asbestos or crystalline silica.

Table 4. Statistical interaction between tobacco smoking and asbestos exposure on age at diagnosis stratified by histological types

	Smoking status				
	Never-low smokers[1]		Medium-high smokers[2]		
	n (%)	Age at diagnosis (95% CI)[3]	n (%)	Age at diagnosis (95% CI)[3]	*p* for cross-product term
Squamous cell carcinoma (1,630)					
Asbestos exposure					
Non-exposed (P=0%)	126 (7.7)	69.1 (66.9-71.3)	402 (24.7)	65.6 (61.6-69.7)	0.80
Exposed (P>30%)	256 (15.7)	67.8 (63.6-72.0)	846 (51.9)	64.1 (55.8-72.3)	
Small cell carcinoma (706)					
Asbestos exposure					
Non-exposed (P=0%)	47 (6.7)	68.4 (64.8-72.0)	220 (31.2)	65.0 (58.4-71.6)	0.86
Exposed (P>30%)	82 (11.6)	66.6 (59.4-73.7)	357 (50.6)	62.8 (48.9-76.8)	
Adenocarcinoma (1,912)					
Asbestos exposure					
Non-exposed (P=0%)	248 (13.0)	63.5 (61.8-65.2)	449 (23.5)	61.8 (58.6-65.0)	<0.01
Exposed (P>30%)	371 (19.4)	65.7 (62.4-69.0)	844 (44.1)	60.6 (53.9-67.3)	
Large cell carcinoma (544)					
Asbestos exposure					
Non-exposed (P=0%)	64 (11.8)	66.0 (61.8-70.3)	136 (25.0)	63.9 (56.4-71.4)	0.88
Exposed (P>30%)	108 (19.9)	66.2 (58.4-74.0)	236 (43.4)	63.7 (48.6-78.8)	
Others (238)					
Asbestos exposure					
Non-exposed (P=0%)	30 (12.6)	64.3 (56.9-71.7)	62 (26.1)	65.1 (52.8-77.4)	0.39
Exposed (P>30%)	54 (22.7)	66.7 (54.0-79.5)	92 (38.7)	64.8 (40.7-88.8)	

P: Highest probability of exposure.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to crystalline silica (non-exposed vs exposed), and initial study.

Table 5. Statistical interaction between tobacco smoking and crystalline silica exposure on age at diagnosis stratified by histological types

	Smoking status				
	Never-low smokers[1]		Medium-high smokers[2]		
	n (%)	Age at diagnosis (95% CI)[3]	n (%)	Age at diagnosis (95% CI)[3]	*p* for cross-product term
Squamous cell carcinoma (1,630)					
Crystalline silica exposure					
Non-exposed (P=0%)	234 (14.4)	69.3 (67.3-71.3)	745 (45.7)	65.6 (62.2-68.9)	0.79
Exposed (P>30%)	148 (9.1)	69.1 (65.1-73.0)	503 (30.9)	65.6 (58.2-73.0)	
Small cell carcinoma (706)					
Crystalline silica exposure					
Non-exposed (P=0%)	84 (11.9)	68.5 (65.3-71.7)	357 (50.6)	65.0 (59.6-70.5)	0.80
Exposed (P>30%)	45 (6.4)	69.5 (62.7-76.3)	220 (31.2)	65.6 (52.7-78.5)	
Adenocarcinoma (1,912)					
Crystalline silica exposure					
Non-exposed (P=0%)	430 (22.5)	64.5 (62.9-66.0)	797 (41.7)	61.3 (58.6-64.0)	0.07
Exposed (P>30%)	189 (9.9)	64.5 (61.2-67.8)	496 (25.9)	59.5 (53.1-65.9)	
Large cell carcinoma (544)					
Crystalline silica exposure					
Non-exposed (P=0%)	111 (20.4)	66.6 (62.6-70.6)	232 (42.6)	63.5 (57.1-70.0)	0.33
Exposed (P>30%)	61 (11.2)	64.9 (57.4-72.5)	140 (25.7)	63.9 (49.8-78.0)	
Others (238)					
Crystalline silica exposure					
Non-exposed (P=0%)	58 (24.4)	65.5 (58.4-72.6)	100 (42.0)	64.4 (53.6-75.2)	0.87
Exposed (P>30%)	26 (10.9)	63.3 (50.7-75.9)	54 (22.7)	62.8 (39.8-85.7)	

P: Highest probability of exposure.
[1]: Never smoker subjects and subjects with Comprehensive Smoking Index (CSI) < 25th percentile.
[2]: Subjects with CSI ≥ 25th percentile.
[3]: Adjusted for occupational exposure to asbestos (non-exposed vs exposed), and initial study.

Titre : Relations entre Phénotypes des cancers broncho-pulmonaires, expositions professionnelles aux particules inhalées et consommation tabagique.

Résumé :

Contexte : L'objectif de cette thèse est d'étudier l'association entre l'exposition professionnelle à l'amiante et à la silice cristalline avec les phénotypes du cancer broncho-pulmonaire. Un autre objectif est d'évaluer la modification de l'effet de l'association entre le tabagisme et le type histologique, la localisation de la tumeur, et l'âge au diagnostic par l'exposition professionnelle à l'amiante ou à la silice cristalline.
Méthodes : L'étude CaProMat est une étude « case-only » rétrospective qui inclut 9623 cas de cancer broncho-pulmonaire Français et Canadiens. Tous les cas de cancer broncho-pulmonaire ont été identifiés d'une façon histologique. Les données ont été collectées par des fichiers médicaux et par des questionnaires standardisés. Deux Matrices Emplois-Expositions (MEEs) ont été utilisées pour évaluer rétrospectivement l'exposition professionnelle à l'amiante et à la silice cristalline.
Résultats : Il n'y a pas de différence de prévalence de l'exposition professionnelle à l'amiante pour les types histologiques. Pour la silice cristalline, un excès limite de la prévalence de l'exposition a été observé pour le carcinome épidermoïde. La prévalence a été maximisée chez les cas diagnostiqués entre 50 et 59 ans pour l'amiante et moins de 50 ans pour la silice cristalline. Une exposition supplémentaire à l'amiante ou à la silice cristalline n'a pas modifié l'effet du tabagisme pour les types histologiques, la localisation de la tumeur ou l'âge au diagnostic.
Conclusion : Le type histologique, la localisation de la tumeur, et l'âge au diagnostic ne peuvent pas être utilisés comme indicateurs de l'exposition professionnelle à l'amiante ou à la silice cristalline.

Mots clés : Cancer Broncho-pulmonaire, Prévalence, Tabagisme, Expositions professionnelles, Amiante, Silice Cristalline, Types histologiques, Localisation de la tumeur, Age au diagnostic.

Title: Relationships between the phenotypes of lung cancer, occupational exposure to inhaled particles, and tobacco smoking.

Abstract:

Introduction: The objective of this thesis was to study the association between tobacco smoking and occupational exposure to asbestos and crystalline silica with the phenotypes of lung cancer. The second objective was to assess the effect modification of the association between tobacco smoking and the phenotypes of lung cancer by occupational exposure to asbestos or to crystalline silica.
Methods: The CaProMat study is a pooled retrospective case-only study consisted of 9,623 French and Canadian lung cancer cases. All lung cancer cases were histologically confirmed. Data were collected from medical records and through standardized questionnaires. Two job-exposure matrices (JEMs) were used to assess the occupational exposure to asbestos and to crystalline silica.
Results: We did not identify a difference of prevalence of occupational exposure to asbestos according to histological type. For crystalline silica, a borderline excess of

prevalence of exposure was observed for squamous cell carcinoma. The prevalence of occupational exposure was maximized among lung cancer cases diagnosed between 50 and 59 years for asbestos and less than 50 years for crystalline silica. Additional exposure to either asbestos or crystalline silica did not modify the effect of tobacco smoking for histological type, tumor location or age at diagnosis.
Conclusions: The histological type, tumor location, and age at diagnosis cannot be used as an indicator for the occupational exposure to asbestos or to crystalline silica.

Keywords: Lung cancer, Prevalence, Interaction, Tobacco smoking, Occupational Exposures, Asbestos, Crystalline Silica, Histological Types, Tumor Location, Age at Diagnosis.

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