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Occupational exposures and lung cancer risk – an analysis of the CARTaGENE study

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Occupational exposures and lung cancer risk – an analysis of the CARTaGENE study

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Résumé

Problématique. Le tabagisme est le facteur de risque le plus important de cancer du poumon, cependant, d'autres facteurs comme les combinaisons de prédispositions génétiques, d'expositions environnementales et d'autres facteurs liés au mode de vie peuvent également contribuer au risque. Cette étude vise à déterminer les associations entre les expositions professionnelles courantes et le risque de cancer du poumon.

Méthodes. Une étude cas-cohorte nichée dans l'étude CARTaGENE a été utilisée. Les cas comprenaient tous les participants avec un diagnostic incident de cancer du poumon de 2009 à 2016 (n= 147). Au départ, une sous-cohorte de 1 032 individus a été échantillonnée. La matrice d'exposition professionnelle du Canada (CANJEM) a été utilisée pour déterminer les expositions professionnelles de l'emploi occupé le plus longtemps par les participants. Vingt-huit agents avec ≥ 5 cas exposés ont été retenus pour les analyses. Différents modèles de régression logistique multivariée avec des estimateurs de variance robuste ont été utilisés pour estimer les ratios des côtes (RC) et les intervalles de confiance (IC) à 95% pour les associations entre chaque agent et le risque de cancer du poumon tout en contrôlant pour les facteurs de risque établis.

Résultats. Un risque accru de cancer du poumon a été observé chez les personnes exposées aux cendres (RC = 4.42; IC 95%: 1.75-11.15), au sulfate de calcium (RC = 4.13; IC 95%: 1.20-14.20), au chlorure d'hydrogène (RC = 3.79; 95% IC: 1.07-13.41), au formaldéhyde (RC = 3.73; IC 95%: 1.51-9.19), aux fumées de cuisson (RC = 2.92; IC 95%: 1.33-6.42), aux alcanes (RC = 4.33; IC 95%: 1.41-13.29), aux aldéhydes aliphatiques (RC = 3.94; IC 95%: 1.41-10.98) et aux agents de nettoyage (RC = 2.60; IC 95%: 1.50-4.52). Une diminution de l'incidence du cancer du poumon a été observée chez les participants exposés au monoxyde de carbone (RC = 0.29; IC 95%: 0.12-0.74) et aux hydrocarbures aromatiques polycycliques de pétrole (RC = 0.18; IC 95%: 0.05-0.60).

Conclusion. Nos résultats soutiennent le rôle de plusieurs agents professionnels, pour lesquels nous avons des connaissances limitées, dans la contribution au risque de cancer du poumon.

Mots-clés. Cancer du poumon ; exposition professionnelle ; facteur de risque

Abstract

Background. Smoking is the strongest risk factor for lung cancer; however, other factors like the combinations of genetic predisposition, environmental exposures, and other lifestyle factors may also contribute to risk. This study aims to determine associations between prevalent occupational exposures and lung cancer risk.

Methods. A case-cohort design was nested within the CARTaGENE study. Cases included all participants with an incident diagnosis of lung cancer from 2009-2016 (n=147). A sub-cohort of 1,032 individuals was sampled at baseline. The Canadian Job Exposure Matrix was used to determine occupational exposures in participants' longest-held job. Twenty-eight agents with ≥5 exposed cases were retained for analysis. Separate multivariable logistic regression models with robust variance estimators were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations between each agent and lung cancer risk while controlling for established risk factors.

Results. Increased lung cancer risk was found among those exposed to ashes (OR=4.42; 95% CI: 1.75-11.15), calcium sulfate (OR=4.13; 95% CI: 1.20-14.20), hydrogen chloride (OR=3.79; 95% CI: 1.07-13.41), formaldehyde (OR=3.73; 95% CI: 1.51-9.19), cooking fumes (OR=2.92; 95% CI: 1.33-6.42), alkanes (OR=4.33; 95% CI:1.41-13.29), aliphatic aldehydes (OR=3.94; 95% CI: 1.41-10.98), and cleaning agents (OR=2.60; 95% CI: 1.50-4.52). A decrease in lung cancer incidence was found among participants exposed to carbon monoxide (OR=0.29; 95% CI:0.12-0.74) and polycyclic aromatic hydrocarbons from petroleum (OR=0.18; 95% CI: 0.05-0.60).

Conclusion. Our findings support the role of several occupational agents, for which we have limited knowledge, in contributing to lung cancer risk.

Keywords Lung cancer; occupational exposure; risk factor

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List of acronyms

JEMs: Job Exposure Matrices

CANJEM: Canadian job-exposure-matrix

FINJEM: Finnish job-exposure-matrix

IARC: International Agency for Research on Cancer

ISCO: International Standard Classification

FWI: Frequency Weighted Intensity

OR: Odd Ratio

CI: Confidence interval

RR: Relative Risk

RR: Risk Ratio

PAR: Population Attributable Risk

ETS: Environmental Tobacco Smoke

CSI: Comprehensive Smoking Index

PAHs: Polycyclic Aromatic Hydrocarbons

DAG: Directed Acyclic Graphs

List of abbreviations

vs.: Versus

e.g.: From the Latin, Exempli gratia (For example)

i.e.: From the Latin, Id est (That is)

et al.: From the Latin, et alia (and others.)

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Chapter 1. Introduction

Despite a substantial drop in the lung cancer incidence rate in men over the past 30 years and evidence of a slower decrease in females, lung cancer still remains the most common cancer type in terms of incidence and the leading cause of cancer deaths worldwide (1). In Canada, lung cancer is the most commonly diagnosed cancer with one of the lowest net survival rates as a result of diagnosis at an advanced stage (2). Although cigarette smoking is the strongest risk factor for this cancer (3), lung cancer also occurs among individuals who have never smoked (4,5), suggesting that other factors such as the combinations of genetic predisposition, environmental factors like occupational exposures, and other lifestyle factors may contribute to lung cancer risk (6,7).

It has been established that certain occupational exposures such as asbestos are causally associated with the risk of developing lung cancer (8,9). In developed countries, exposure to workplace substances are suggested to be responsible for approximately 2% to 6% of cancer incidence and 2% to 8% of all cancer deaths, particularly for cancer of the lung (10–17). In Canada, it was estimated that 15.5 million workers, alive in 2011, had been exposed to at least one occupational carcinogen for a minimum of one year between 1961 and 2001, with an overall population attributable risk (PAR) estimate of 14.9% for occupational lung cancer (24.4% in men and 3.4% in women) (18).

Nevertheless, the carcinogenicity of many workplace exposures remains unclear due to the sparse epidemiologic evidence. This thesis investigated the contribution of occupational exposures in lung cancer etiology among male and female workers. Occupational agents that are prevalent, with suggestive or probable evidence in playing a role in contributing to lung cancer development were prioritized. This dissertation is composed of six main chapters. In Chapter 2, an overview of lung cancer etiology, highlighting the role of occupational exposures is presented. The objectives and an overview of the study methodology is presented in Chapter 3. Chapter 4 presents the manuscript that will be submitted to “the

Journal of Occupational and Environmental Medicine" and contains the main results of this dissertation. In Chapter 5, supplementary results from sensitivity analyses are presented. In Chapter 6, study findings are summarized, and the strengths and limitations as well as the implications of this research are further discussed.

Chapter 2. Literature review

2.1 Lung cancer descriptive epidemiology

Noncommunicable diseases are the leading cause of mortality worldwide with 41 million deaths occurring each year which accounts for 71% of all deaths globally (19). In 2016, cancer was the second leading cause of deaths due to noncommunicable diseases (20,21). Lung cancer is the most prevalent cancer internationally with the highest mortality rate among all cancers, accounting for 18% of cancer-related mortality worldwide (22). North America, East Asia, and parts of central and eastern Europe have the highest incidence rates (1). In most countries, the incidence rates in men have been in decline for the past decades, whereas, rates among women have generally been increasing (1). Differences in smoking behavior (uptake and cessation) in men and women have likely contributed to the difference in incidence trends (4).

In Canada, lung cancer is the most commonly diagnosed cancer, accounting for 1 in 14 men and 1 in 15 women diagnosed with lung cancer in their lifetime (23). However, it is projected that the age-standardized incidence rates will decrease for both men and women by 2042 (in men from 58.9/100,000 in 2013 to 36.3/100,000 in 2042; in women from 47.7/100,000 in 2013 to 39.6/100,000 by 2042) (24). Concerning mortality, this cancer is responsible for approximately 26% of all cancer deaths for both sexes (2). The mortality rate in males has been declining since 1991, while in females it had increased until 2006 and since then has been decreasing but at a slower rate in comparison with males (-0.8% per year for women vs. -2.8% per year for men) (2).

Overall, the most prevalent histological types of lung cancer are adenocarcinoma (representing approximately 40% of all lung cancer) and squamous cell carcinoma (representing

25% to 30% of all lung cancer cases) (5,25,26). However, evidence suggests that even within a subtype, these cancers are histologically and molecularly heterogeneous (27).

2.2 Non-occupational lung cancer risk factors

Lung cancer is a cancer with the highest fraction attributable to smoking (28). However, It is estimated that around 10-20% of diagnosed lung cancer cases occur among never smokers; in fact, lung cancer is the 7th leading cause of cancer deaths occurring among never smokers (29). This suggests that the combinations of other factors also play a predominant role in lung cancer etiology (4). The following presents an overview of lung cancer risk factors that are classified according to the level of evidence found in our comprehensive literature review.

2.2.1 Lung cancer risk factors with the strongest evidence

2.2.1.1 Tobacco smoking

Tobacco smoking is a well-established determinant in cancer etiology and mortality. In 2000, 21% of total global cancer deaths were attributable to smoking (30). About 80-90% of lung cancer cases are associated with tobacco smoking (first or second-hand smoking) (31). A systematic review and meta-analysis of 34 studies, showed that smokers had a considerably higher risk of developing lung cancer when compared with nonsmokers (Risk Ratio (RR)=10.92; 95% CI:8.28-14.40; I^2=95%) (32). Moreover, smoking was found to yield similar risks in women and men (33).

More than 60 compounds present in tobacco smoke have been classified as carcinogenic for humans (34). Long term exposure of the lung epithelium to these compounds could form DNA adducts that lead to oncogenic mutations (35). Smoking could also have other irreversible effects such as chronic lung inflammation, oxidative stress, and cell structure changes which induce lung

malignancy even years after smoking cessation (36). The risk of lung cancer among former smokers depends on their prior level of consumption; however, those who quit smoking for 35 years still experience a higher risk of lung cancer compared to never smokers (37).

Smoking behaviors are associated with socioeconomic factors (e.g. education, income) as well as other factors such as type of work (e.g. workplace culture, work type, and job stressors) (38–40). By occupations, blue-collar workers (e.g. craftsmen, transportation and non-transportation operatives and laborers) have been considered a high-risk group with smoking rates greater than two-fold as compared to white-collar workers (41). Data from the Canadian Community Health Survey showed that a significantly higher proportion of manual workers are current smokers (daily and occasionally) as compared to other workers in the province of Quebec (42).

2.2.1.2 Environmental tobacco smoke

Environmental tobacco smoke (ETS) (also known as passive or second-hand tobacco smoke or involuntary smoking) is classified as a human lung carcinogen (43). A recent meta-analysis of 13 studies, reported that exposure to passive smoke increased lung cancer risk in never smokers (RR=1.41; 95% CI: 1.21-1.65; $I^2 = 0\%$) (32).

Based on the World Cancer Report, 15% to 50% of the population in most countries are exposed to ETS (1). It is estimated that tracheal, bronchus, and lung cancer deaths caused by second-hand smoke increased from 78,000 in 2007 to 100,000 in 2017 globally (44). In the United States, ETS is responsible for about 3,000 lung cancer deaths in non-smokers every year (45). Worldwide, this exposure mostly occurs at home (1.5 billion adults) rather than at the workplace (392 million adults) (46). Similar to active smoking, occupational ETS exposure is also associated with types of occupations (e.g. manual workers and blue-collar jobs), income, education and even

race/ethnicity (40,42,47). Due to workplace smoking restrictions, exposure to ETS in the work environment has declined in many developed countries. In Canada, the number of ETS-exposed workers reduced by 20% in 10 years (3.1% in 2006 to 2.3% in 2016), however, certain jobs in the sector of "trades, transport and equipment operators" and workers in primary industry still experience exposure to ETS (48).

2.2.1.3 Sex

Historically, lung cancer incidence rates have been higher in men given that they started smoking earlier and more intensely than women (49). However, studies have showed that this trend has reversed and that the incidence rate is now higher among women than men, especially in developed countries (50–52). Sex differences in smoking behaviors cannot fully explain these disparities in lung cancer incidence trends. There exists a sex-difference in lung cancer incidence among never smokers with higher cancer incidence in never-smoking women than men (53–55). In the U.S. and Europe, around 20% of female lung cancer cases have never smoked compared with 2% to 6% of nonsmoking men (56). Results from the National Institutes of Health-AARP cohort showed higher age-standardized incidence rates of lung carcinoma in never-smoking women (Incidence rate=25.3 per 100 000 person-years; 95% CI: 21.3-29.3) than never-smoking men (Incidence rate=20.3; 95% CI:16.3-24.3) (57). It is not known if women are biologically more susceptible to lung carcinogens (e.g. ETS, workplace carcinogens) than men (9,45,53,54,56,58–60).

2.2.1.4 Age

Older age is associated with the development of various cancers, especially cancer of the lung (4). In most populations, lung cancer incidence is low before age 40 and increases up to age 75-80 years (61). In Canada, lung cancer is the most commonly diagnosed cancer after age 50 (2).

2.2.1.5 Family history of lung cancer

It has been established that having a family history of lung cancer is associated with an elevated risk of developing lung cancer (45). Although this phenomenon may be partially explained by shared smoking behaviors, epidemiological studies have also shown an increased risk of lung cancer associated with family history among never smokers. A systematic review and meta-analysis of 11 studies found a relative risk (RR) of 1.51 (95% CI:1.11-2.06) among nonsmokers with a family history of lung cancer in their first-degree relatives as compared to those without a family history (62).

2.2.1.6 Outdoor/indoor air pollution

Worldwide, air pollution is estimated to account for 29% of all lung cancer deaths in adults (20). Outdoor air pollution is a complex mixture consisting of several known carcinogens and has been classified as carcinogenic for humans (63). Particulate matter (PM) is the most consistent predictor of the carcinogenicity of air pollution and has been associated with lung cancer risk (63). In a recent systematic review and meta-analysis of six studies, exposures to $PM_{2.5}$ ($\leq$ 2.5 μm, or fine particles) was associated with an elevated risk of lung cancer among never-smokers (RR=1.18; 95% CI:1.00-1.39) (64). Occupations such as urban traffic police, professional drivers, street vendors are highly exposed to air pollution since they spent the majority of their working time outdoors in polluted environments (65).

Burning wood, coal (or other solid fuels), and fumes from high-temperature cooking using unrefined vegetable oils in insufficiently ventilated houses creates indoor air pollution (61). A pooled analysis of seven studies from the International Lung Cancer Consortium found an increased risk among never smokers who predominantly used solid-fuel (OR= 1.65; 95% CI: 1.41-1.93) and coal (OR= 5.39; 95% CI: 3.73–7.79) in Asia (66).

2.2.1.7 History of tuberculosis and pneumonia infections

Chronic inflammation caused by infections such as pulmonary tuberculosis and pneumonia has been associated with lung cancer risk (61,67). A systematic review and meta-analysis reported an elevated lung cancer risk in patients who had a history of tuberculosis (RR=1.76; 95% CI:1.49-2.08; 30 studies) which was further increased when restricted to never smokers (RR=1.90; 95% CI:1.45-2.50; 11 studies) (68). Concerning pneumonia, an RR of 1.36 (95% CI:1.10-1.69; 8 studies) was found for lung cancer risk among never smokers with a history of this infection (68).

2.2.2 Lung cancer risk factors with suggestive evidence

2.2.2.1 Dietary factors

There is some evidence for the protective effect of vegetable (particularly cruciferous vegetables) and fruit consumption against lung cancer development (61). Mechanistically, the nutrient and bioactive components from vegetables and fruits may inhibit DNA adduct formation caused by smoking and even promote DNA repair (69). Similarly, some studies have suggested tea consumption as a preventive factor for lung cancer, however, results remain inconsistent (70).

The consumption of alcoholic beverages has been associated with an elevated risk of lung cancer in several studies (71). However, given the strong correlation between alcohol consumption and smoking in most populations, it is difficult to elucidate the independent contribution of alcohol

in lung cancer etiology (72). Inconclusive findings have been reported in analyses conducted among nonsmokers only (61,71,73).

2.2.2.2 Body weight and physical activity

Studies have found an inverse association between body mass index (BMI) and lung cancer risk that may be partially confounded by smoking (61,74,75). A recent meta-analysis of 16 prospective cohorts found no association between BMI and lung cancer risk among never smokers (RR=0.96; 95% CI: 0.85-1.10) (76). While using waist circumference, Hidayat et al. found a positive association between greater waist circumference and lung cancer risk among never smokers (RR= 1.11; 95% CI: 1.00-1.23) (77).

Similarly, physical activity has been shown to decrease lung cancer risk (5). A meta-analysis of 27 studies reported a 24% decreased risk of lung cancer among individuals with the highest level of physical activity, but this association disappeared when restricted to never smokers (RR=0.96; 95% CI: 0.79-1.18) (78). A meta-analysis of lung cancer risk and types of physical activity (recreational and occupational) indicated a 15% higher lung cancer risk for male workers with a high level of occupational physical activity and no statistically significant higher risk for female workers (79).

2.3 Occupational lung cancer

Evidence from the literature suggests that between 2% to 6% of cancer incidence are attributable to exposure to workplace substances and lung cancer is the leading malignancy as the result of these exposures (10–15,17,18). Globally, it has been estimated that 969,000 disability-adjusted life years are caused by occupational lung cancer (80). In Canada, the estimated lung

cancer PAR for concurrent occupational exposures to 17 lung carcinogens was found to be 14.9% (24.4% in men and 3.4% in women) (18).

2.3.1 Assessing occupational exposure to agents occurring in the workplace

The ability to measure and characterize workplace exposures is an important consideration in studies investigating the role of occupational exposures in cancer etiology. Direct exposure measurement, either through the use of measurement tools placed in the workplace and/or via the measurement of biomarkers, is considered a valid occupational assessment method. However, direct measurements are often costly and may only represent recent exposures. For the study of chronic diseases with a long latency period like lung cancer, we often employ indirect exposure assessment methods to retrospectively assess exposure during a hypothesized etiologically relevant time period. Several indirect approaches can be used and include: 1) participants self-reporting exposure using a pre-established list of substances; 2) experts (comprising of chemists and occupational hygienists) assessment of occupational exposure based on details provided by the participants; 3) the use of pre-existing measurement databases such as job-exposure matrices (JEMs) (81).

Compared to self-assessments, experts assessment of occupational exposures has been shown to be a more valid approach (81–83). Indeed, the experts assessment approach can take into account the time period of exposure, local peculiarities of production processes or materials used, and particular tasks performed by the worker (84). However, the main drawback is that expert assessment is expensive to carry out (85,86) and thus, the use of JEMs in epidemiologic studies has been advocated (87,88). In essence, a JEM is a fixed set of rules for translating any job code into a list of exposures associated with the job (e.g., auxiliary nurses with a 0-72.10 job code are exposed to biocides, cleaning agents, isopropanol, and aliphatic alcohols). There are two types of

JEMs including study- or industry-specific JEMs and generic JEMs. Generic JEMs, in contrast to specific JEMs, provide estimates of exposure across a wide range of occupations/industries and agents, and are applicable to different settings (89). The Finnish job-exposure matrix (FINJEM) (90) and the Canadian Job Exposure Matrix (CANJEM) are examples of generic JEMs (91).

2.3.2 Occupational lung cancer risk factors

Exposure to asbestos in the workplace was estimated to be the most significant contributor to occupational lung cancer burden (PAR of 8%) in Canada followed by diesel engine exhaust (PAR of 2.4%) and crystalline silica (PAR of 2.4%) (18). Several other occupational agents have also been identified and classified as lung carcinogens by the International Agency for Research on Cancer (IARC); including arsenic, beryllium, cadmium, chloromethyl ethers, chromium VI, nickel compounds, radon, silica, soot, coal combustion products, coal tar and pitch, inorganic acids, and benzo[a]pyrene (9,65,92,93).

Although more than 1,000 agents have been critically reviewed by the IARC Working Groups in the last half-century, 400 agents still remained classified as Group 2A (probably carcinogenic to humans) or 2B (possibly carcinogenic to humans) and many other agents have not been evaluated due to the sparse epidemiologic evidence. In the next section, classes of substances that are commonly found in the workplace and which are of interest in this thesis, are reviewed in relation to lung cancer risk. Table 2.1 presents detailed information on the major industries associated with exposure to these prevalent agents, as well as IARC classifications if the agent was evaluated.

Dusts

Dusts are generally categorized into inorganic and organic depending on their origins. Inorganic dusts are derived from mineral sources rather than biological elements. Among this class, asbestos is the most widely known and established occupational cause of lung cancer (4,94). However, studies of lung cancer referring to exposure to other inorganic dusts are limited. In a case-control study using experts assessment of occupational exposures, Siemiatycki et al. reported associations between lung cancer risk and exposure to concrete dust (OR=2.5; 90% CI: 1.3-5.0) and suggestive elevated risks associated with exposure to abrasive dust (OR=1.4; 90% CI: 0.9-2.0) and calcium sulfate (OR=1.4; 90% CI: 0.8-2.4) in male workers (95). However, in a case-control study among construction male workers that used the same method of exposures assessment, no association was observed between lung cancer and concrete dust (OR=0.9; 95% CI: 0.5-1.5) and calcium carbonate (OR=1.2; 95% CI: 0.6-2.6); though a suggestive increased risk was observed for exposure to calcium sulfate (OR=1.5; 95% CI: 0.9-2.5) which disappeared when restricted to never-low smokers (96). Moreover, a two-fold increase in lung cancer risk was reported for workers who were exposed to ashes (OR=1.9; 90% CI:1.0-3.7) in a case-control study that used expert-based assessment to ascertain occupational exposures (97).

Organic dusts can be defined as complex mixtures derived from vegetable and animal sources. Wood dust is a type of organic dust that is generally composed of cellulose, hemicellulose, and lignin and has been classified by IARC as Group 1 (carcinogenic to humans) for the nasal cavities, paranasal sinuses, and nasopharyngeal cancer (98). Five case-control studies and one cohort study have investigated the association between occupational exposure to wood dust and lung cancer risk. Two of five case-control studies employed an expert assessment approach among male workers and reported conflicting results; one revealed an increased risk (OR=1.4; 90% CI:

1.1-1.9) (97) and the other reported no association (OR=0.8; 95% CI: 0.5-1.3) (96). Using self-report to ascertain occupational exposure to wood dust, two case-control studies in men found a suggestive elevated risk of lung cancer associated with wood dust (OR=1.6; 95% CI: 0.8-3.2 (99); OR=1.1; 95% CI 0.9-1.5 (100)). Similarly, another case-control study assessed occupational wood dust exposure by self-report as well as expert assessment and reported a suggestive increased risk for exposure to wood dust (OR=1.3; 95% CI: 0.9-2.1) (101). In a cohort study, FINJEM was employed and men exposed to low levels of wood dust experienced a significantly elevated standardized incidence ratio of lung cancer (SIR=1.1; 95% CI: 1.0-1.2), however, no association was observed in female workers (102).

Gases

Gases are classified into two main groups: inorganic and organic. Common inorganic gases include carbon monoxide, hydrogen chloride, and ammonia. Limited studies have examined exposure to inorganic gases in relation to the risk of developing lung cancer. Hydrogen chloride is a colourless gas and is heavier than air; it is an unwanted contaminant in certain operations such as plastic pyrolysis. In a case-control study using expert assessment of occupational exposure, hydrogen chloride was not found to be associated with lung cancer risk among male construction workers (OR=0.6; 95% CI: 0.2-1.6) (96).

Ammonia is a by-product of coal distillation and also generated by passing nitrogen, hydrogen, and a catalyst through an electric arc. Analysis of lung cancer risk in a case-control study using experts assessment revealed a suggestive increased risk in male workers who were substantially exposed to ammonia (OR=1.9; 90% CI: 0.9-4.2) (97). This association was not found among women in a population-based case-control study, using the same method of exposure assessment (OR=0.9; 95% CI: 0.5-1.5) (103).

Formaldehyde is an organic gas classified as carcinogenic to humans (Group 1) with sufficient evidence for nasopharynx, leukemia, and/or lymphoma cancer by IARC (104). For lung cancer, a recent systematic review and meta-analysis of 31 studies reported no association between occupational exposure to formaldehyde and lung cancer risk (risk estimate=1.04; 95% CI: 0.97-1.12), though considerable heterogeneity was found across pooled studies (105). Another common organic gas is aliphatic aldehydes; in a case-control study using expert assessment, a suggestive positive association with lung cancer risk was found among female workers (OR=1.2; 95% CI: 0.7-1.9) (103).

Inorganic fumes

Inorganic fumes consist of fumes produced during the joining, cutting, and high-temperature processes of metals. Soldering fumes are inorganic fumes generated during the joining of metal using a filler metal known as a solder. Little is known about the lung carcinogenicity of soldering fumes. In a case-control study using expert assessment of occupational exposures among male construction workers, no association was found between exposure to soldering fumes and lung cancer risk (OR=0.7; 95% CI: 0.3-1.5) (96).

Combustion fumes

Combustion fumes comprise of inorganic and organic exhaust gas and fumes. Diesel engine emission is the most recognized agent in this category with a strong association with lung cancer (106). However, lung carcinogenicity of other agents in this category has not been sufficiently investigated. Cooking fumes is a mixture of substances generated during the thermal degradation of fats and other food constituents. Analysis of lung cancer risk in a population-based

case-control study using expert assessment revealed a suggestive increased risk in female workers who were exposed to cooking fumes (OR=1.5; 95% CI: 0.8-2.6) (103).

Gasoline engine emissions are produced as a result of internal combustion in engines running on leaded or unleaded gasoline fuel. Due to inadequate evidence of lung carcinogenicity in humans, the IARC has classified this agent as possibly carcinogenic to humans (Group 2B) (106). A more recent analysis of lung cancer risk in a population-based case-control study using expert assessment showed no association between lung cancer risk and occupational exposure to leaded (OR=0.8; 95% CI: 0.7-1.0) or unleaded (OR=0.8; 95% CI: 0.6-1.0) gasoline engine emissions in male workers (107).

Organic liquids and vapors

The category of organic liquids and vapors encompasses over 60 substances with a variety of different origins and applications. Polycyclic aromatic hydrocarbons (PAHs) are the most widely known class of agents in this category that has been linked to occupational lung cancer risk (108). However, benzo(a)pyrene is the only specific PAH that is classified as carcinogenic for humans (109) and has been considered as a representative marker of PAHs (4). Since different materials may generate different specific PAHs, using one agent as an indicator of all other PAHs may be misleading (110). Therefore, in a case-control study of male workers, PAH exposure was defined according to source materials and included: PAHs from coal, PAHs from petroleum, PAHs from wood, PAHs from other sources, and PAHs from any source (97). PAHs from petroleum can be formed by thermal decomposition of crude oil and certain petroleum-derived substances (e.g., heavy fuel oil, asphalt). A population-based case-control study in male workers reported no association between lung cancer and exposure to PAH from petroleum (OR=1.0; 95% CI: 0.8-1.3) using expert-based exposures assessment (110). However, an elevated risk of lung cancer was

found in male workers who were exposed to PAH from petroleum (OR=1.2; 90% CI: 1.0-1.6) in another case-control study using the same exposure assessment method (97). Only one case-control study has investigated the association between PAHs from any source and lung cancer risk employing an expert assessment approach; no association was observed in male workers (OR=1.0; 90% CI: 0.7-1.4) (97).

Isopropanol is colourless and highly flammable alcohol; two studies have investigated the association of lung cancer risk and occupational exposure to isopropanol and report conflicting results. Specifically, in a case-control study using expert assessment, a suggestive increased lung cancer risk was found in male workers who were exposed to isopropanol (OR=2.7; 90% CI: 0.9-8.1) (97). Among women using the same method for assessing occupational exposure to isopropanol, no association was found (OR=0.6; 95% CI: 0.3-1.1) (103). Aliphatic alcohol is another common agent in this category. In a case-control study, occupational exposure to aliphatic alcohol was assessed by experts and found not associated with lung cancer (OR=0.7; 95% CI: 0.4-1.2) among female workers (103).

Synthetic adhesives are synthetic resins- and rubbers-based adhesives that are used in many industries, particularly in the furniture and shoe industries. Only one case-control study has investigated the association between synthetic adhesives and lung cancer risk using expert assessment; no association was found among female workers (OR=1.1; 95% CI: 0.5-2.4) (103).

Organic solvents are liquids used as paint thinners, spot removers, dry-cleaning agents, diluents, degreasers, and for many other purposes. Among female workers, a suggestive positive association with lung cancer risk (OR=1.2; 95% CI: 0.7-1.8) has been reported (103). Similarly, in a case-control study, male workers who were exposed to solvents were also found to have a higher risk of lung cancer (OR=1.3; 90 % CI: 1.1-1.7) (97).

Alkanes (C5-C17) are saturated hydrocarbons containing between 5 and 17 carbon atoms that are liquids at standard conditions. Two case-control studies have investigated the association between occupational exposure to alkanes and lung cancer risk separately in men and women using expert assessment; Siemiatycki et al. reported a significant positive association (OR=1.5; 90% CI: 1.2-2.0) in men (97). While a nonsignificant elevated risk was observed (OR=1.4; 95% CI: 0.7-2.9) in women (103).

Mononuclear aromatic hydrocarbons (MAHs) are hydrocarbons that possess the special properties associated with the benzene ring. Three case-control studies employing expert assessment approach found suggestive elevated lung cancer risks for exposure to MAHs; two studies among male workers (OR=1.2; 90% CI: 0.8-1.6 (97); OR=1.2; 95% CI: 0.7-1.9 (111)) and one study among female workers (OR=1.9; 95% CI: 0.8-4.6) (103).

Metallic compounds

Lead compounds are classified by the IARC as Group 2A, probably carcinogenic to humans based on limited evidence of carcinogenicity from studies in humans (112). Two case-control studies of lung cancer have been conducted in male workers using expert assessment of lead compounds including inorganic lead, organic lead, and lead in gasoline emissions since the IARC evaluation; no significant association was reported (113,114).

General categories

The agent called “other paints, varnishes” refers to paints used on surfaces other than metal, and varnishes used on surfaces other than wood. To our knowledge, no epidemiological study has investigated occupational exposure to this agent and lung cancer risk.

Cleaning agents are simple sulfonated fatty acids or complex synthetic materials with the main function to aid water in the cleaning process. In two case-control studies that used expert assessment, no excess risk was found among female workers who were exposed to cleaning agents (OR=1.1; 95% CI: 0.7-1.7) (103) while a statistically significant increased risk in male workers was found (OR=15.1; 95% CI: 1.3-170) (111).

Biocides comprise all products used to disinfect, deodorize, sterilize, and sanitize. Exposure to this agent has been found to be protective of lung cancer risk among female workers (OR=0.6; 95% CI: 0.3-1.0) who participated in a case-control study (103).

Table 2.1 Prevalent occupational agents' profile

Category	Occupational agent	IARC classification [a]	Major industries with occupational exposure to the agent in Canada [b]
Dusts	Abrasive dust	Not evaluated	Repair of motor vehicles and motorcycles, machinery and equipment, manufacture of engines and turbines, watch, clock and jewelry repair, manufacture of jewelry
	Concrete dust	Not evaluated	Construction, manufacture of non-metallic mineral products, manufacture of cement, lime and plaster, electric light and power, mining and quarrying
	Ashes	Not evaluated	Restaurants, cafés and other eating and drinking places, sanity and similar services, hotels, rooming houses, camps and other lodging places, supporting services to air transport
	Cosmetic talc	2B (Talc-based body powder)	Barber and beauty shops, medical, dental and other health services, manufacture of soap and cleaning preparations, perfumes, cosmetics and other toilet preparations
	Calcium sulfate	Not evaluated	Construction, supporting services to water transport, manufacture of cement, lime and plaster, manufacture of non-metallic mineral products, authors, and music composers
	Calcium carbonate	Not evaluated	Stone quarrying, clay and sand pits, education services, manufacture of cement, lime and plaster, non-ferrous ore mining
	Wood dust	1 (Nasopharynx, nasal cavity, and paranasal sinus cancer)	Building construction, speciality trade contractors (construction), sawmills and wood preservation, furniture and cabinet manufacturing, other wood product manufacturing
Gases	Carbon monoxide	Not evaluated	Repair of motor vehicles and motorcycles, other passenger land transport, non-ferrous ore mining, iron and steel basic industries, urban, suburban and inter-urban highway passenger transport
	Ammonia	Not evaluated	Barber and beauty shops, watch, clock and jewelry repair, photographic studios, including commercial photography, sanity and similar services, tobacco manufactures
	Hydrogen chloride	Not evaluated	Photographic studios, including commercial photography, electrical repair shops, manufacture of plastic products, research and scientific institutes
	Formaldehyde	1 (Nasopharynx, Leukaemia and/or lymphoma cancer)	Household and institutional furniture and kitchen cabinet manufacturing, hospitals, sawmills and wood preservation, building finishing contractors
	Anaesthetic gases	Not evaluated	Medical, dental and other health services, research and scientific institutes, manufacture of drugs and medicines, education services, agriculture and livestock production
	Aliphatic aldehydes	Not evaluated	Barber and beauty shops, restaurants, cafés and other eating and drinking places, manufacture of wearing apparel, fur dressing and dyeing industries, photographic studios
Inorganic fumes	Soldering fumes	Not evaluated	Electrical repair shops, watch, clock and jewelry repair, manufacture of radio, television and communication equipment, manufacture of professional and scientific, and measuring and controlling equipment

Combustion fumes	Cooking fumes	Not evaluated	Restaurants, cafés and other eating and drinking places, manufacture of bakery products, domestic services, hotels, rooming houses, camps and other lodging places
	Gasoline engine emissions	2B	General freight tracking, local, municipal and regional public administration, automotive repair and maintenance, specialized freight tracking, services to buildings and dwellings
Organic liquids and vapours	Isopropanol	3 (limited evidence on lung cancer)	Barber and beauty shops, sanity and similar services, medical, dental and other health services, research and scientific institutes, welfare institutions
	Synthetic adhesives	Not evaluated	Manufacture of footwear, repair of footwear and other leather goods, manufacture of products of leather and leather substitutes, manufacture of furniture and fixtures
	Organic solvents	Not evaluated	Manufacture of footwear, repair of footwear and other leather goods, electrical repair shops, watch, clock and jewelry repair, manufacture of paints, varnishes and lacquers
	Alkanes (C_5-C_{17})	Not evaluated	Repair of footwear and other leather goods, manufacture of footwear, repair of motor vehicles and motorcycle, petroleum refineries, crude petroleum and natural gas production
	Aliphatic alcohols	Not evaluated	Barber and beauty shops, distilling, rectifying and blending spirits, sanity and similar services, fur dressing and dyeing industries
	PAHs from any source	Not evaluated	Repair of motor vehicles and motorcycles, coal mining, manufacture of miscellaneous products of petroleum and coal, non-ferrous ore mining, stone quarrying and sand pits
	PAHs from petroleum	Not evaluated	Repair of motor vehicles and motorcycles, coal mining, non-ferrous ore mining, stone quarrying, clay and sand pits, other passenger land transport
	Mononuclear aromatic hydrocarbons	Not evaluated	Manufacture of footwear, tire and tube industries, manufacture of miscellaneous products of petroleum and coal, repair of motor vehicles and motorcycles
Metallic compounds	Lead compounds	2A	Public administration, building equipment contractors, automotive repair and maintenance, commercial and industrial machinery repair and maintenance
General categories	Other paints, varnishes	Not evaluated	Manufacture of paints, varnishes and lacquers, manufacture of textiles, manufacture of wood and cork products, construction, manufacture of furniture and fixtures
	Cleaning agents	Not evaluated	Barber and beauty shops, domestic services, sanity and similar services, personal services, restaurants, cafés and other eating and drinking places
	Biocides	Not evaluated	Barber and beauty shops, photographic studios, medical, dental and other health services, tanneries and leather finishing

[a] IARC classifications: (1) carcinogenic to humans; (2A) probably carcinogenic to humans; (2B) possibly carcinogenic to humans; (3) unclassifiable as to its carcinogenicity in humans (115)

[b] The Canadian Job Exposure Matrix (116)

2.3.2.1 Summary of reviewed agents

Few studies have examined the association between occupational exposure to prevalent agents and lung cancer risk, with the exception of formaldehyde and engine emissions. There has been no study for four agents including cosmetic talc, carbon monoxide, anaesthetic gases, and "other paints, varnishes" in relation to lung cancer. Moreover, analysis of occupational lung cancer risk was mostly restricted to men, usually due to the small number of exposed women. Indeed, in the review, occupational exposure to eight agents (namely, abrasives dust, concrete dust, ashes, calcium sulfate, calcium carbonate hydrogen chloride, soldering fumes, and PAHs from any source) and lung cancer risk have been examined among male workers only. Furthermore, the associations between occupational exposure to five agents (namely, aliphatic aldehydes, cooking fumes, synthetic adhesives, aliphatic alcohols, and biocides) and lung cancer risk have been investigated by one study and only among female workers.

2.3.3 Sex differences in studies of occupational lung cancer

Historically occupational health studies largely focused on the effects of exposures in male workers. In a review, Niedhammer et al. found that female workers were less often investigated and sex differences were not considered in many studies with a mixed population of female and male workers (117). In a systematic review of occupational lung cancer studies published between 2003-2014, men-only studies were the most frequent (55.6%) and even among studies consisting of both sexes, half had a male-predominant study population with a men-to-women ratio larger than 3.5 (118). Given the differences in exposure profiles (119) and biological responses to exposures between men and women (120), findings from male workers are not necessarily generalizable to females (117). The lower representation of women in occupational lung cancer studies is not justifiably explained by fewer women working in the target population since in many

developed countries like Canada, women account for nearly half of the labor force (121) and they spend equivalent hours in the workplace as men (7.8 hours per day in women and 7.6 hours per day in men) (122).

2.4 Relevance of the study

Worldwide, lung cancer is the most prevalent cancer with the highest mortality rate among all cancers (22). Although cigarette smoking is the primary risk factor (3), it is estimated that around 10-20% of diagnosed lung cancer cases occur among never smokers (29). In addition to smoking, there is evidence in never smokers to support a causal relationship between lung cancer and sex, age, ETS, family history of lung cancer, outdoor/indoor air pollution, and history of tuberculosis and pneumonia infections.

Occupational lung cancer is an important public health issue. Though 2% to 8% of all cancer deaths are attributable to exposure to workplace substances (11,13,15,16), occupational cancers have received little public health attention. Occupational carcinogens are almost entirely preventable, although, there has been hardly any evidence for many workplace exposures. In addition, for most of the investigated exposures due to a small number of studies, the findings are too inconsistent to draw any definitive conclusions about their lung carcinogenicity. Moreover, much of our understanding of lung carcinogens is derived from studies on male workers (117,118) and thus, not necessarily generalizable for female occupational health.

Since most Canadian adults spend a large portion of their days in the working environment, exposure to workplace chemicals could make a huge impact on their health. Exploring the role of these occupational exposures is important for the understanding of the etiology and pathogenesis of lung cancer and refining public health efforts. This thesis aimed to provide evidence for lung

carcinogenicity of several workplace substances, for which we have limited knowledge, especially among female workers.

Chapter 3. Methodology

3.1 Objective

The objective of this thesis was to determine the associations between exposure to prevalent occupational agents and lung cancer risk, among male and female workers.

3.2 The CARTaGENE study

A case-cohort study was nested within the CARTaGENE study, the largest prospective cohort study of men and women in Quebec, Canada started in 2009. The CARTaGENE study recruited participants between the age of 40 to 69 years residing in the metropolitan areas of Montreal, Quebec, Sherbrooke, Saguenay, Trois-Rivières, and Gatineau. Participants were recruited based on a stratified sampling of individuals from the provincial health insurance registries-FIPA files (*fichier administratif des inscriptions des personnes assurées de la Régie de l'assurance maladie du Québec* (RAMQ)) (123). Sampling was stratified by age, sex, and postal code groups and was proportional to the density of the population from the 2006 Census (124). Participants were excluded if they resided outside of the selected regions, in First Nations Reserves or long-term health care facilities, or were in prison.

For recruitment, information packages were mailed to potential participants, and following that, they were contacted by telephone (through a call centre at the RAMQ) to schedule a baseline interview in one of the clinical assessment sites. The recruitment was carried out in two phases (Phase A between 2009-2010 and Phase B between 2012-2015) and follow-ups have been conducted annually.

3.3 Study participants

In the case-cohort study, cases included all participants with an incident diagnosis of lung cancer occurring during the follow-up period from baseline to 2016 and were identified through a linkage of CARTaGENE participants to RAMQ (n=246). Ten of these participants had a history of cancer (other than non-melanoma skin cancer) prior to their lung cancer diagnosis and thus, were excluded.

For comparison, a sub-cohort was established based on a stratified sample of the CARTaGENE cohort at baseline at a ratio of at least four sub-cohort members for one case (4:1 ratio). Prior to sampling, we excluded participants with missing information on cancer history and those with a history of cancer (other than non-melanoma skin cancer) at baseline. Further, participants with missing data on their longest-held job (e.g., job title and industry) were excluded; 9,915 eligible participants remained and a sub-cohort of 1,107 individuals were randomly sampled based on the sex- and age- (in 5-year intervals) distributions of the CARTaGENE cohort.

3.4 Exposure ascertainment and derivation

All participants provided information on their longest-held occupation, including job title, industry, and age at which the job started/ended at baseline. The longest-held job questionnaire is provided in Appendix I. Furthermore, participants in Phase A were recontacted between 2011-2012 to complete a follow-up survey including information on lifetime occupational history that was collected using open-ended questions (see Appendix II). All jobs (longest-held job and all jobs from the lifetime occupational history) were coded according to the International Standard Classification of Occupations 1968 (ISCO-68) by an occupational hygienist.

Among participants who had information on both their longest-held job and lifetime occupational history, priority was given to the job code with the longest duration derived from the lifetime occupational history since more details were provided by participants which facilitates job coding. Eighty-eight of 236 lung cancer cases were excluded from analyses since they self-reported to "being unemployed/unable to work" or their reported job could not be coded (e.g., due to the provided information being too broad). Among the sub-cohort, 71 of 1,107 participants were also excluded as their reported job could not be coded.

CANJEM is one of the currently available generic JEMs that was designed to provide Canadian-relevant information on the probability, frequency, and intensity of exposure for a list of 258 agents (including mostly chemicals but also some biological and physical hazards) for a given job code in a specific time period (91). CANJEM was developed from the expert-based assessments of more than 30,000 jobs from four Canadian case-control studies conducted between 1979 and 2004 (91,125). Thus, the validity of the expert assessments performed within these case-control studies informs upon the validity of CANJEM. In a validation study comparing expert assessment versus previously recorded measurements of substances using air sampling for the particular jobs (e.g., welders), high levels of validity were found (average sensitivity of 90% and no specificity estimation due to unknown true negatives) (126). Similarly, as multiple experts participated in the assessment of exposure in the previous case-control studies, the inter-rater reliability of occupational exposures was evaluated and a high degree of reliability was reported (83).

CANJEM was used to estimate occupational exposures in the case-cohort study. The core of CANJEM consists of three dimensions: time period, occupational/industrial classification (i.e., job codes), and agent; these options lead to different configurations of CANJEM. For this thesis,

all available agents in CANJEM were included using the time period of 1950-2005 since this period covers those years that our participants were working. As the assigned ISCO-68 job codes varied in terms of resolution from the 2-digit (most broad) to the 5-digit (most precise), CANJEM was configured according to the two, three, five-digit ISCO-68 resolution. Additional criteria applied to this configuration included frequency of exposure of at least 30 minutes per week and a reliability level (or the occupational hygienists' confidence that the exposure occurred) of "possible" or greater. After these CANJEM specifications, each "cell" in CANJEM thus provided, for every job code, an estimate of the probability of exposure to an agent as well as the associated intensity, frequency, and frequency-weighted intensity (FWI) of exposure.

Job codes pertaining to the longest-held job of study participants were linked to CANJEM according to the most specific ISCO resolution; for job codes that could not be linked according to the 5-digit ISCO resolution, linkage at the 3 or 2-digit ISCO resolution was next attempted. After linkage of the longest-held job of each participant with CANJEM, the probability of exposure to 258 agents was available, as well as the associated intensity, frequency, and FWI for those exposed. The probability of exposure is the proportion of jobs in a given cell that were considered exposed to the agent and range from 0% to 100%. In our main analysis, occupational exposure to each agent was parametrized into three categories: "Unexposed" when the probability of exposure to that agent was 0, "Uncertainly exposed" when the probability of exposure was between 0 to 25%, and "Exposed" when the probability of exposure was 25% or greater. Agents were retained only if there were five or more exposed cases, resulting in a total of 28 agents included in our main analysis. Table 3.1 presents the 28 agents retained for analysis and their categories in CANJEM.

Table 3.1 Retained chemical agents and their categories in CANJEM

Category	Occupational agent
Dusts	Abrasive dust, concrete dust, ashes, cosmetic talc, calcium sulfate, calcium carbonate, wood dust
Gases	Carbon monoxide, ammonia, hydrogen chloride, formaldehyde, anaesthetic gases, aliphatic aldehydes
Inorganic fumes	Soldering fumes
Combustion fumes	Cooking fumes, gasoline engine emissions
Organic liquids and vapours	Isopropanol, synthetic adhesives, organic solvents, alkanes (C_5-C_{17}), aliphatic alcohols, PAHs from any source, PAHs from petroleum, mononuclear aromatic hydrocarbons
Metallic compounds	Lead compounds
General categories	Cleaning agents, biocides, other paints, varnishes

3.5 Statistical analysis

Unconditional multivariable logistic regression was used to estimate odds ratios (OR) between lung cancer and the selected occupational agents, while controlling for potential confounders. OR for each agent was calculated contrasting Unexposed versus the Uncertainly exposed and Exposed categories. To account for the case-cohort design, which involves comparing a random sample of the cohort (i.e., the sub-cohort) to all incident cases that occur (i.e., regardless of whether they are in the selected sub-cohort), we used the robust sandwich covariance matrix estimator (see equation in Appendix III) to estimate 95% confidence intervals (95% CI) (127,128). Analysis was conducted in the total population and separately in sex-stratified models; for some agents, the analysis was restricted to only one sex due to insufficient numbers of exposed cases for a given agent.

Potential confounding factors were identified a *priori* through a comprehensive literature review on PubMed, Cochrane library (Systematic Reviews and Trials), EMBASE, and MEDLINE databases. Using directed acyclic graphs (DAG), minimal sufficient adjustment sets for estimating

the total effect of an occupational agent on lung cancer included age, sex, smoking, ETS (at home and the workplace), family history of lung cancer, and established occupational lung carcinogens (including crystalline silica, chrysotile asbestos, amphibole asbestos, nickel fumes, nickel, diesel engine emissions, cadmium, chromium (VI), soot, coal combustion products, coal tar and pitch, and benzo[a]pyrene) (Figure 4.1). Briefly, occupational exposure to lung carcinogens was parametrized dichotomously as a summary variable as unexposed to any versus exposure to at least one of the listed carcinogens; a suggestive increased lung cancer risk was observed (OR=1.59; 95% CI: 0.82-3.08 adjusting for sex and age). Information on these covariates was collected at baseline.

Smoking is the most important risk factor for lung cancer. Since models with more than one smoking-related factor are susceptible to multicollinearity and instability (129), a comprehensive smoking index (CSI) was calculated by integrating smoking intensity, duration, and time since quitting (130).

There was minimal missing data that were observed for three covariates including ETS (eight missing), family history of lung cancer (two missing), and CSI (two missing). There was no overlap in missing data for these three covariates across all participants, and all three covariates were missing less than 5% of the data points. For ETS and family history of lung cancer, missing data were replaced by the mode in the entire population and for smoking, the two participants with missing data were excluded.

Finally, we investigated the familywise error rate due to the multiple hypothesis testing in our main analysis using the Benjamini-Hochberg procedure (131). Other approaches to control for the familywise error rate is the Bonferroni method; however, this method has an inherent weakness in increasing the likelihood of type II errors (132). Thus, the Benjamini-Hochberg procedure was

applied. All statistical analyses were run on R version 4.0.3 using packages including car, tidyvers, sandwich, lmtest, ISLR, mice, and dplyr.

3.6 Sensitivity analysis

In sensitivity analyses, various categorization strategies of the probability of exposure were considered and included in Chapter 4 as Supplementary Tables. These categorizations strategies included: 1) redefining "Unexposed" as those with a probability of exposure between 0-5%, "Uncertainly exposed" as those with a probability of exposure between 5-25%, and "Exposed" as those with a probability of exposure greater than 25% and; 2) redefining "Unexposed" as those with a probability of exposure 0, "Uncertainly exposed" as those with a probability of exposure between 0-50%, and "Exposed" as those with a probability of exposure equal or greater than 50%.

In addition to the sensitivity analyses included in Chapter 4, the following analyses were conducted to ensure the robustness of study finding. First, in addition to using the probability of exposure to define exposure status, the FWI was used. In CANJEM, the FWI is calculated using this formula:

$$\text{FWI} = \text{Intensity} * (\text{frequency}/40 \text{ hours})$$

In this sensitivity analysis, we excluded participants who were "Uncertainly exposed." Then, the FWI of the selected agents in our main analysis was assigned to job codes. "Exposed" was then redefined as those with FWI above or equal to the median in the sub-cohort; "Unexposed" included those less than the median FWI in the sub-cohort. In essence, this sensitivity analysis was performed to contrast whether defining occupational exposure based on the probability of exposure versus the FWI has an impact on the observed associations. Second, recall that in the main analysis CANJEM was configured to include all exposures recorded at a reliability level of possible or greater. In a sensitivity analysis, CANJEM was re-extracted with cells defined as exposed if the

exposure occurred at a reliability level of “probable” and “definite” to evaluate whether the reliability of exposure assignment had an influence on the observed associations. Occupational exposure to each agent was similarly parametrized into three categories “Unexposed” when the probability of exposure to that agent was 0, “Uncertainly exposed” when the probability of exposure was between 0 to 25%, and “Exposed” when the probability of exposure was 25% or greater.

Ethical Considerations

Ethics approval has been obtained from Comité d’éthique de la recherche (CER) of Centre hospitalier de l'Université de Montréal (CHUM) for the ongoing CIHR-funded project co-led by Drs. Ho and Koushik (see Appendix IV). The current dissertation is part of this approved study and access to CARTaGENE cohort has been granted.

Chapter 4. Manuscript

This manuscript was written in accordance with the instructions for authors provided by the Journal of Occupational and Environmental Medicine (OEM), a peer-reviewed journal.

Title:

Occupational exposures and lung cancer risk – an analysis of the CARTaGENE study

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4.1 Abstract

Objective: To determine associations between prevalent occupational agents and lung cancer risk.

Methods: A case-cohort design was nested within the CARTaGENE prospective cohort study. Cases included all participants with an incident diagnosis of lung cancer occurring from 2009 to 2016 (n=147). A sub-cohort of 1,032 individuals was sampled at baseline. Information on participants' longest-held job was collected and coded by an occupational hygienist; job codes were then linked to the Canadian Job Exposure Matrix to determine the probability of exposure. Twenty-eight agents with five or more exposed cases were retained. Separate multivariable logistic regression models with robust variance estimators were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations between each agent and lung cancer risk while controlling for established lung cancer risk factors, notably smoking.

Results: Increased overall lung cancer risk was found among those exposed versus unexposed to ashes (OR= 4.42; 95% CI: 1.75-11.15), calcium sulfate (OR=4.13; 95% CI: 1.20-14.20), hydrogen chloride (OR= 3.79; 95% CI: 1.07-13.41), formaldehyde (OR=3.73; 95% CI: 1.51-9.19), cooking fumes (OR= 2.92; 95% CI:1.33-6.42), alkanes (OR=4.33; 95% CI:1.41-13.29), aliphatic aldehydes (OR=3.94 ; 95% CI: 1.41-10.98), and cleaning agents (OR=2.60; 95% CI: 1.50-4.52). A decrease in lung cancer risk was found among participants exposed to carbon monoxide (OR=0.29; 95% CI: 0.12-0.74) and polycyclic aromatic hydrocarbons from petroleum (OR=0.18; 95% CI: 0.05-0.60).

Conclusion Our findings provide support for the role of several occupational agents, for which we have limited knowledge, in contributing to lung cancer risk.

Keywords Lung cancer; occupational exposure; risk factor

4.2 Introduction

Lung cancer remains the most commonly diagnosed cancer with the lowest net survival rates as a result of diagnosis at an advanced stage (1). Although cigarette smoking is the strongest risk factor for lung cancer (2), it also occurs among individuals who have never smoked (3), suggesting that other factors such as the combinations of genetic predisposition, environmental exposures, and other lifestyle factors may contribute to risk.

Almost half of the established human carcinogens are found mainly in the occupational environment (4). It has been estimated that in developed countries, 2% to 8% of all cancer deaths and between 2% to 6% of cancer incidence is attributable to workplace exposures, with lung cancer as the leading malignancy (5–13). Over half of the occupational lung cancer burden is attributable to exposure to asbestos (14). Although the role of occupational exposures like asbestos, silica, and diesel engine emissions has been studied in relation to lung cancer etiology, the carcinogenic effects of many agents remain unclear due to the sparse epidemiologic evidence examining the effects of these agents in humans. Moreover, much of our understanding of occupational risk factors for lung cancer is derived from studies on male workers (15,16) and thus, not necessarily generalizable to female occupational health due to differences in exposure profiles and possible biological responses between men and women (15,17,18).

Occupational exposures could have a significant impact on public health since workers spend a large portion of their time at work where they may be exposed to higher levels of potentially harmful substances than those found in the general population. Therefore, exploring the role of these agents is important for the understanding of the etiology of lung cancer. We examined lung cancer risk in relation to prevalent chemical agents in the workplace among male and female workers in a case-cohort study nested within the CARTaGENE study.

4.3 Methods

4.3.1 The CARTaGENE study

This study started in 2009, and enrolled men and women between the ages of 40 and 69 years residing in the metropolitan areas of Montreal, Quebec, Sherbrooke, Saguenay, Trois-Rivières, and Gatineau in Quebec, Canada. A detailed description of the CARTaGENE study has been presented elsewhere (19). For the present analysis, a case-cohort design was used. During follow-up from 2009 to 2016, 147 participants, diagnosed with incident lung cancer, were identified through linkage of CARTaGENE participants to the public health insurance program of Quebec (Régie de l'Assurance Maladie du Québec). For comparison, a sub-cohort of 1,032 individuals was established using stratified sampling of the CARTaGENE cohort at baseline based on sex- and 5-year age-distribution. Participants with a reported history of cancer (other than non-melanoma skin cancer) at baseline were excluded.

Participants provided information on their longest-held occupation, including job title, industry, and age at which the job started/ended at baseline and were recontacted between 2011-2012 to complete a follow-up survey including information on lifetime occupational history that was collected using open-ended questions. All jobs were coded according to the International Standard Classification of Occupations 1968 (ISCO-68) by an occupational hygienist. Among participants with information on both their longest-held job and lifetime occupational history, priority was given to the job with the longest duration derived from the lifetime occupational history since more details were available to facilitate job coding.

4.3.2 Assessment of occupational exposures in the longest-held job

The Canadian Job Exposure Matrix (CANJEM) was used to estimate occupational exposures. CANJEM provides Canadian-relevant information on the probability, intensity, and frequency, and frequency-weighted intensity (FWI) of exposure to a list of 258 agents (including mostly chemicals but

also some biological and physical hazards) for a given occupational code during a specific time period (20). CANJEM consists of three dimensions: time period, occupational/industrial classification, and agent. For this study, all available agents in CANJEM were included using the time period of 1950-2005, covering those years that our participants were working.

Job codes pertaining to the longest-held job of participants were linked to CANJEM according to the most specific ISCO-68 resolution (i.e., 5-digit). For those that could not be linked at the highest resolution, linkage was attempted at the 3 or 2-digit resolution. Among all job codes, 99.7% were successfully linked to CANJEM; of these, 46.3% were linked using 5-digit resolution, 41.8% using 3-digit resolution, 11.9% using 2-digit resolution. Jobs that could not be linked were excluded from the analysis.

The linkage resulted in an estimate of the probability of exposure to each of 258 agents, as well as the associated intensity, frequency, and FWI for those exposed. Probability of exposure is the proportion of jobs in a given CANJEM cell (defined by a combination of a specific occupational code, time period, and occupational agent) that were considered exposed to the agent and ranges from 0% to 100%. In our main analysis, occupational exposure to each agent was parametrized into three categories: "Unexposed" when the probability of exposure to that agent was 0, "Uncertainly exposed" when the probability of exposure was between 0 to 25%, and "Exposed" when the probability of exposure was 25% or greater. Agents were retained only if there were five or more exposed cases, resulting in a total of 28 agents included in our main analysis.

4.3.3 Statistical analysis

Unconditional multivariable logistic regression was used to estimate odds ratios (OR) for lung cancer risk associated with the selected 28 occupational agents, in separate models. To account for the case-cohort design, we used the robust variance estimator to calculate 95% confidence intervals (95% CI) (21,22). The analysis was conducted in the total population and in sex-stratified models; for some

agents, the analysis was restricted to only one sex due to insufficient numbers of exposed cases. Specifically, in sex-specific analyses, 20 and 13 agents were examined in relation to lung cancer risk in men and women, respectively.

Potential confounding factors were identified *a priori* through a comprehensive literature review on lung cancer risk factors. Using directed acyclic graphs (DAG), minimal sufficient adjustment sets for estimating the total effect of an occupational agent on lung cancer included age, sex, smoking, environmental tobacco smoke (ETS) at home and workplace, established occupational lung carcinogens (i.e. crystalline silica, chrysotile asbestos, amphibole asbestos, nickel fumes, nickel, diesel engine emissions, cadmium, chromium (VI), soot, coal combustion products, coal tar and pitch, and benzo[a]pyrene) (23), and family history of lung cancer (Figure 1). Information on the non-occupational covariates was collected at baseline, while occupational exposure to lung carcinogens experienced in the longest-held job were estimated via CANJEM using the same procedure as the main exposures of interest. Smoking, the most important risk factor for lung cancer, was represented by a comprehensive smoking index (CSI), calculated by integrating smoking intensity, duration, and time since quitting (24). There was minimal missing data for ETS (eight missing), family history of lung cancer (two missing), and CSI (two missing). For ETS and family history, missing data were replaced by the mode in the entire population and for smoking, the two participants with missing data were excluded.

To account for the family-wise error rate due to the multiple hypothesis testing in our main analysis, we applied the Benjamini-Hochberg procedure to control for the false discovery rate (25). Finally, sensitivity analyses were conducted considering alternative categorization strategies of the probability of exposure including: 1) defining “Unexposed” as those with a probability of exposure between 0-5%, “Uncertainly exposed” as those with a probability of exposure between 5-25%, and “Exposed” as those with a probability of exposure 25% or greater and; 2) defining “Unexposed” when the probability of exposure to that agent was 0, “Uncertainly exposed” when the probability of exposure was between 0 to 50%, and “Exposed” when the probability of exposure was 50% or greater.

4.4 Results

In the CARTaGENE cohort, 147 incident lung cancer cases were diagnosed during follow-up and 1,032 sub-cohort members were sampled for comparison. Table 4.1 summarizes the selected characteristics of our study population at baseline. Overall, the mean age of cases was higher than sub-cohort members; cases also had a lower level of education, and lower annual income than sub-cohort members. Compared to the sub-cohort, cases were more likely to smoke, and be exposed to ETS at home and/or the workplace.

Twenty-eight agents with at least five exposed cases were retained for analysis of lung cancer risk. Table 2 presents the estimated ORs for lung cancer risk associated with the selected 28 agents in the total population and separately by sex. In the total population, increased lung cancer risk was observed when participants were exposed to ashes (OR= 4.42 ; 95% CI: 1.75-11.15), calcium sulfate (OR=4.13 ; 95% CI: 1.20-14.20), hydrogen chloride (OR= 3.79; 95% CI: 1.07-13.41), formaldehyde (OR=3.73 ; 95% CI: 1.51-9.19), cooking fumes (OR= 2.92; 95% CI:1.33-6.42), alkanes (C5-C17) (OR=4.33 ; 95% CI:1.41-13.29), aliphatic aldehydes (OR=3.94 ; 95% CI: 1.41-10.98), and cleaning agents (OR=2.60 ; 95% CI: 1.50-4.52). Moreover, there was a decrease in lung cancer risk among participants exposed to carbon monoxide (OR=0.29; 95% CI:0.12-0.74) and polycyclic aromatic hydrocarbons (PAHs) from petroleum (OR= 0.18; 95% CI: 0.05-0.60) (Table 4.2).

In sex-stratified analysis, only seven agents had a sufficient number of cases in both men and women to facilitate comparisons. The associations between lung cancer risk and formaldehyde, isopropanol, aliphatic aldehydes, cleaning agents, and biocides appeared restricted to women only. In addition, female workers exposed to calcium carbonate and cooking fumes experienced an elevated risk of lung cancer. Male workers experienced an elevated risk when exposed to calcium sulfate and a moderate decrease in risk exposure to carbon monoxide and PAHs from petroleum that were previously observed in the total population (Table 4.2).

After adjustment for multiple testing applying the Benjamini-Hochberg procedure, associations between lung cancer risk and exposure to ashes, cleaning agents, PAHs from petroleum, formaldehyde, cooking fumes, aliphatic aldehydes, carbon monoxide, alkanes, and calcium sulfate remained statistically significant (Table 4.2).

Sensitivity analysis redefining the categories of Unexposed (probability of exposure between 0-5%) and Uncertainly exposed (probability of exposure between 5-25%), revealed consistent associations for nine of the ten agents with associations observed in the main analysis (namely, for ashes, calcium sulfate, formaldehyde, hydrogen chloride, alkanes, aliphatic aldehydes, cleaning agents, carbon monoxide, and PAHs from petroleum). Cooking fumes were not considered as less than five cases were exposed after redefinition. In this sensitivity analysis, synthetic adhesives, organic solvents, and other paints and varnishes were found to increase lung cancer risk, although the results for these agents were not statistically significant in the main analysis, though consistent in their directionality of effect (Supplementary Table 4.1).

When further redefining our exposure categories as Unexposed (probability of exposure 0), Uncertainly exposed (probability of exposure between 0-50%), and Exposed (probability of exposure 50% or greater), a smaller number of agents were retained for analysis (13 agents). Among those, occupational exposure to aliphatic aldehydes and cleaning agents were the only associations from the main analysis that indicated risks which were also considerably greater. The OR of developing lung cancer for exposure to cleaning agents was 2.60 in our main analysis but changing the threshold of exposure increased the risk to 3.45 (Supplementary Table 4.2).

4.5 Discussion

In this case-cohort study nested within the CARTaGENE cohort, elevated risks were consistently observed for workers exposed to ashes (in the total population), calcium sulfate (in the total population and men), formaldehyde (in the total population and women), aliphatic aldehydes (in the total population

and women), and cleaning agents (in the total population and women). Occupational exposure to carbon monoxide (in the total population and men) and PAHs from petroleum (in the total population and men) were consistently associated with a reduction in lung cancer risk. Additional agents with ORs greater than 1.5 were observed but we restrict our discussion here to those agents with the most consistently demonstrated associations throughout the sensitivity analyses.

In our study, workers who were ever exposed to ashes during their longest-held job were four times more likely to develop lung cancer than those unexposed. Our finding is supported by evidence from an *in vitro* study that showed ash as the by-product of coal combustion induced a genotoxic and mutagenic effect through oxidative stress mechanism (26). Moreover, other studies on volcanic ash also suggested that inhaling this dust could generate respiratory symptoms and abnormalities (27); however, it is likely to be more harmful to individuals with pre-existing lung diseases (28). A review also highlighted positive associations between lung cancer risk and residing near municipal solid waste incinerators which generate ashes. The authors noted a large degree of heterogeneity between studies (29). In a case-control study of multiple types of cancers, Siemiatycki et al. reported associations between lung cancer risk and exposure to ashes (OR= 1.9; 90% CI: 1.0-3.7) (30). By contrast, analysis of lung cancer risk among certain occupations such as firefighters who are potentially exposed to ashes revealed no increased risk of lung cancer (31–33).

In our study, we found a four-fold increase in lung cancer risk for those who were exposed to calcium sulfate (also known as gypsum), an inorganic compound with various applications from the construction industry to dental and orthopedic plasters, in the entire population and also among male workers. A case-control study of lung cancer conducted by Siemiatycki et al. reported an elevated risk in workers who were exposed to calcium sulfate (OR= 1.7; 90% CI: 1.2-2.4) (30). In another case-control study among male workers, no statistically significant elevated risk has been found for non-adenocarcinoma lung cancer (34). Moreover, analysis of lung cancer risk among certain occupations

such as construction workers who are substantially exposed to calcium sulfate showed a suggestive increased risk among male workers in this industry (35).

Formaldehyde is the most studied exposure in the aliphatic aldehydes group that is widely used in the production of industrial resins used in manufacturing products such as plastics, adhesives and binders (for wood products), synthetic fibres, and disinfectant (36). This organic compound is classified as carcinogenic to humans (Group 1) based on sufficient evidence for nasopharyngeal cancer (37). However, evidence regarding lung cancer risk was inconclusive. In our study, we observed an almost 4-fold increase in risk for exposed workers that is in contrast with a recent systematic review and meta-analysis which supported a null association (risk estimate =1.04; 95% CI: 0.97-1.12) (38). However, it is important to note that though this meta-analysis pooled results from 31 studies, there was considerable heterogeneity between the studies and many of the studies had inadequate adjustment for smoking (38). Specifically, in sub-analyses, pooled results including only studies which were considered high quality (risk estimate =1.13; 95% CI: 1.08-1.19), conducted after 1996 (risk estimate =1.13; 95% CI: 1.07-1.19), and among studies that used a job exposure matrix (risk estimate =1.24; 95% CI: 1.08-1.43) revealed elevated risks for lung cancer (38). Moreover, Xu et al. explored occupational risk factors for lung cancer among women in Montreal and reported a suggestive association for formaldehyde (OR=1.4; 95% CI: 0.8-2.4) (39). In the present study, an association between aliphatic aldehydes and lung cancer risk was observed in the entire population and also among females. The same Xu et al. case–control study reported a suggestive positive association between aliphatic aldehydes and lung cancer among women (39).

A threefold increase in lung cancer risk was found in the entire population and female workers who were exposed to cleaning agents. These agents could be simple sulfonated fatty acids or complex synthetic materials that have cleansing actions with the help of water. Female professional cleaners have been reported to use on average 2.4 cleaning products per day with at least one strong irritant such as bleach or hydrochloric acid that could affect lung function rapidly following its use (40). Other studies also confirmed the negative effects on respiratory conditions of cleaning agents, even for periods as short

as one hour (41,42). Menvielle et al. found a statistically significant increased lung cancer risk in male workers who were exposed to household cleaning products (43). Similarly, lung cancer analysis among professions who are extensively exposed to cleaning agents such as cleaners, housemaids, hairdressers/barbers, and launderers/dry cleaners revealed an elevated risk for lung cancer (44–51).

Carbon monoxide is produced largely as a result of incomplete combustion due to poor mixing of air and fuel. This odorless gas is considered a waste product and air pollutant in cities (52), as well as a toxic gas which could lead to respiratory failure when it accumulates to a dangerous level in a tightly sealed or enclosed space. Interestingly, our data revealed an inverse association between carbon monoxide and occupational lung cancer risk which is similar to the findings of an investigation of long-term exposure to this agent as an air pollutant and lung cancer mortality in the American Cancer Society cohort, 1982-1998 (53). This association disappeared when they used carbon monoxide data prior to 1980 (53,54). It is unclear why a protective effect was observed but recent findings in cell culture and animal models suggested that carbon monoxide may affect cancer cell proliferation in non-small cell lung cancer and lung tumor treatment (55,56). Findings also support that carbon monoxide helps to fight against the Warburg effect (cancer cell metabolism alteration with the purpose of fast growth) by increasing cancer cell respiration and consequently creating metabolic exhaustion (mitochondrial collapse) (57,58).

Polycyclic aromatic hydrocarbons are a group of more than 100 organic compounds that are naturally present in coal and tar deposits or can be formed by incomplete combustion of any organic material (e.g., oil, wood) (59,60). They are found in several industries in which workers are exposed to complex mixtures (e.g., coal tars and pitch) that are classified as lung carcinogens. Reports showed that in three Canadian provinces of Ontario, Nova Scotia, and Alberta, between 0.5% to 0.7% of the estimated total lung cancers diagnosed each year are due to occupational exposure to PAHs (59). However, benzo(a)pyrene is the only agent in this group that is classified as carcinogenic for humans (61). Benzo(a)pyrene has been considered as a general marker of PAHs due to the difficulty in isolating and

measuring the effect of each PAH in the carcinogenic mixtures (4,62). Since using one agent as an indicator of all other PAHs may be misleading, (62) PAH exposure was defined according to source material such as petroleum, wood, and coal (30). In our study, we found an inverse association between PAH from petroleum and lung cancer risk in the entire population and male workers. Similarly, lower risk of lung cancer associated with occupational PAH exposure among men was reported in another large prospective cohort in the Netherlands in which the authors speculated that it was due to a chance finding (63). In addition, a population-based case-control study conducted among male workers reported no association between exposure to PAH from petroleum and lung cancer risk (62). However, a case-control study revealed an elevated risk in workers who were exposed to PAH from petroleum. (OR=1.2; 90% CI:1.0-1.6) (30).

We had limited power to explore most associations in our sex-stratified analysis due to the small number of exposed cases. However, among those limited agents with a sufficient number of cases in both females and males, generally, female workers were found to have a higher excess risk of developing lung cancer. For example, observed association for exposure to cleaning agents was almost two times greater in exposed women than exposed men. Unfortunately, we could not explore the reasons behind this finding; further research is required. However, previous studies have posited that sex-based differences in biological responses to exposures and hormonal factors may account for observed excess lung cancer risk in women (64–68).

The strengths of this study include the large study population and prospective design that afforded an opportunity to avoid recall bias in the reporting of important confounders such as smoking as well as to address current knowledge gaps for occupational agents. We used a composite measure of smoking to integrate the different dimensions of smoking history and parsimoniously adjust for smoking in our analyses. However, an important limitation of the study was that around 50% of job codes were linked to CANJEM at a low resolution (i.e., 2 and 3-digits ISCO-68 resolution) in our main analysis. Consequently, this led us to aggregate different occupations with broadly similar exposure profiles into

one group, irrespective of exposure variability between professions. Additional limitations include the possibility of uncontrolled confounding due to factors, such as outdoor and indoor air pollution that we were not able to consider.

4.6 Conclusion

In summary, an elevated risk of lung cancer was found in relation to occupational exposure to several agents including ashes, calcium sulfate, formaldehyde, aliphatic aldehydes, and cleaning agents. Future studies should explore dose-response patterns and mechanistic studies are needed to explore the human carcinogenicity of these agents.

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Contributors

SM, VH, and RP designed the study's analytical strategy. SM conducted the analysis. SM and VH interpreted the results of the analysis for this paper. SM drafted the manuscript under supervision of VH and AK. RP, AK, and JS critically revised and commented on the manuscript.

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Figure 4.1 Directed acyclic graph representing causal relationships and potential biasing pathways affecting the association between exposure to a chemical agent in the workplace and lung cancer

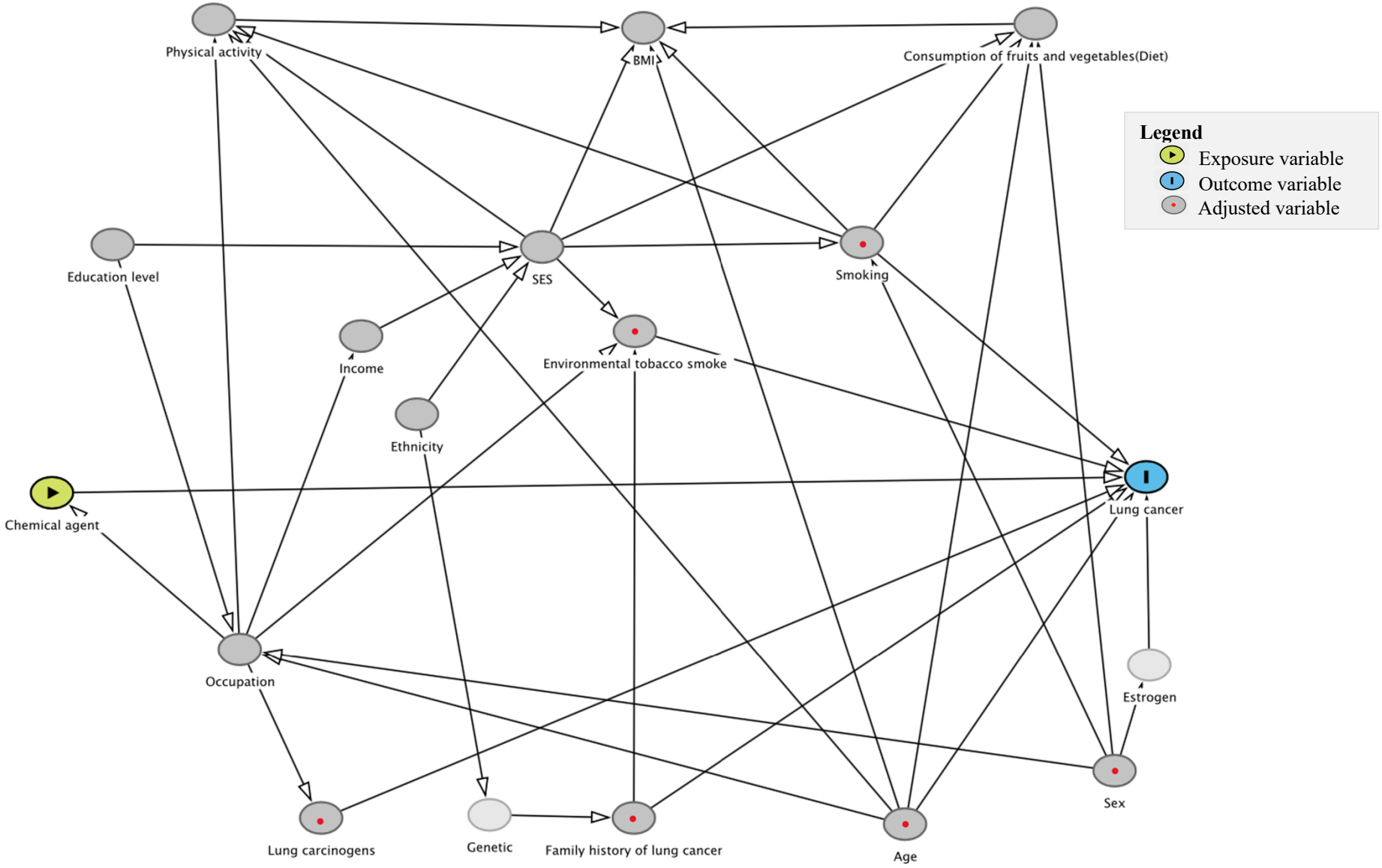

Table 4.1 Baseline characteristics of study participants, n (%)

	All (N=1179)		Females (N=646)		Males (N=533)	
	Cases (N=147)	**Sub-cohort (N=1032)**	**Cases (N=80)**	**Sub-cohort (N=566)**	**Cases (N=67)**	**Sub-cohort (N=466)**
Age at baseline						
40 to 54 years old	49(33.3)	614(59.5)	30(37.5)	345(61.0)	19(28.4)	269(57.7)
55 to 70 years old	98(66.7)	418(40.5)	50(62.5)	221(39.0)	48(71.6)	197(42.3)
Ethnicity						
French Canadian	93(63.3)	669(64.8)	47(58.8)	381(67.3)	46(68.7)	288(61.8)
Other	54(36.7)	363(35.2)	33(41.2)	185(32.7)	21(31.3)	178(38.2)
Highest level of education						
High school or lower	55(37.4)	204(19.8)	36(45.0)	113(20.0)	19(28.4)	91(19.5)
Technical school and college	47(32.0)	320(31.0)	23(28.8)	186(32.9)	24(35.8)	134(28.8)
University	45(30.6)	507(49.1)	21(26.3)	267(47.2)	24(35.8)	240(51.5)
Missing	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Income (Average total annual income before tax received by entire household)						
<49 999	59(40.1)	266(25.8)	38(47.5)	161(28.4)	21(31.3)	105(22.5)
50 000 to 99 999	60(40.8)	362(35.1)	28(35.0)	208(36.7)	32(47.8)	154(33.0)
≥ 100 000	22(15.0)	378(36.6)	11(13.8)	178(31.4)	11(16.4)	200(42.9)
Missing	6(4.1)	26(2.5)	3(3.8)	19(3.4)	3(4.5)	7(1.5)
Family history of lung cancer (Mother, father, sibling, child)	126(85.7)	905(87.7)	69(86.3)	498(88.0)	57(85.1)	407(87.3)
No	19(12.9)	127(12.3)	9(11.2)	68(12.0)	10(14.9)	59(12.7)
Yes	2(1.4)	0(0.0)	2(2.5)	0(0.0)	0(0.0)	0(0.0)
Missing						
Smoking status						
Never smoker	44(29.9)	524(50.8)	27(33.8)	304(53.7)	17(25.4)	220(47.2)
Ex-smoker	61(41.5)	333(32.3)	29(36.2)	176(31.1)	32(47.7)	157(33.7)
Current smoker	42(28.6)	175(16.9)	24(30.0)	86(15.2)	18(26.9)	89(19.1)
Environmental tobacco smoke exposure (home and workplace)	94(63.9)	743(72.0)	55(68.8)	438(77.4)	39(58.2)	305(65.5)
Never	50(34.0)	284(27.5)	22(27.5)	126(22.3)	28(41.8)	158(33.9)
Ever	3(2.0)	5(0.5)	3(3.7)	2(0.3)	0(0.0)	3(0.6)
Missing						

Exposures to lung carcinogens in the longest held job [a]						
Unexposed to any	133(90.5)	966(93.6)	79(98.8)	559(98.8)	54(80.6)	407(87.3)
Exposed to at least one	14(9.5)	66(6.4)	1(1.3)	7(1.2)	13(19.4)	59(12.7)

[a] Including crystalline silica, chrysotile asbestos, amphibole asbestos, nickel fumes, nickel, diesel engine emissions, cadmium, chromium (VI), soot, coal combustion products, coal tar and pitch, and benzo[a]pyrene

Table 4.2 Adjusted OR and 95% CI of lung cancer risk associated with exposure to the selected occupational agents – defining "Unexposed" as those with a probability of exposure 0, "Uncertainly exposed" as those with a probability of exposure between 0-25%, and "Exposed" as those with a probability of exposure equal to or greater than 25%

Selected Agents	All (N=1179)			Females (N=646)			Males (N=533)		
	Cases	Sub-cohort	OR adjusted (95% CI) [a]	Cases	Sub-cohort	OR adjusted (95% CI) [b, c]	Cases	Sub-cohort	OR adjusted (95% CI) [b, c]
Abrasives dust									
Unexposed	47	337	1.00 (Ref)	23	197	1.00 (Ref)	24	140	1.00 (Ref)
Uncertainly exposed	94	665	0.96 (0.65-1.41)	56	366	-	38	299	0.65 (0.36 -1.16)
Exposed	6	30	0.89 (0.26-2.98)	1	3	-	5	27	0.51 (0.13- 2.06)
Concrete dust									
Unexposed	90	587	1.00 (Ref)	49	355	1.00 (Ref)	41	232	1.00 (Ref)
Uncertainly exposed	52	430	0.79 (0.53-1.16)	31	211	-	21	219	0.52 (0.29-0.93)
Exposed	5	15	1.57 (0.39-6.27)	0	0	-	5	15	1.24 (0.28-5.45)
Ashes									
Unexposed	94	724	1.00 (Ref)	55	413	1.00 (Ref)	39	311	1.00 (Ref)
Uncertainly exposed	44	294	1.19 (0.79-1.77)	20	146	1.09 (0.60-1.95)	24	148	-
Exposed	9	14	4.42 (1.75-11.15) [d]	5	7	3.98 (0.96-16.54)	4	7	-
Cosmetic talc									
Unexposed	100	683	1.00 (Ref)	47	374	1.00 (Ref)	53	309	1.00 (Ref)
Uncertainly exposed	32	259	1.01 (0.64-1.60)	20	126	1.67 (0.92-3.04)	12	133	-
Exposed	15	90	1.31 (0.70- 2.44)	13	66	1.70 (0.83-3.48)	2	24	-
Calcium sulfate									
Unexposed	58	455	1.00 (Ref)	33	267	1.00 (Ref)	25	188	1.00 (Ref)
Uncertainly exposed	81	560	1.14 (0.78-1.65)	47	298	-	34	262	0.98 (0.56-1.74)
Exposed	8	17	4.13 (1.20-14.20) [d]	0	1	-	8	16	4.69 (1.10-19.99)
Calcium carbonate									
Unexposed	42	395	1.00 (Ref)	17	217	1.00 (Ref)	25	178	1.00 (Ref)
Uncertainly exposed	91	544	1.54 (1.02-2.33)	53	295	2.34 (1.27-4.31)	38	249	-
Exposed	14	93	1.66 (0.86-3.22)	10	54	3.01 (1.27-7.18)	4	39	-

Wood dust						-			
Unexposed	33	256	1.00 (Ref)	22	162	1.00 (Ref)	11	94	1.00 (Ref)
Uncertainly exposed	106	755	0.95 (0.61-1.47)	57	403	-	49	352	1.08 (0.52-2.26)
Exposed	8	21	2.60 (0.80-8.48)	1	1	-	7	20	2.43 (0.61-9.66)
Carbon monoxide									
Unexposed	24	106	1.00 (Ref)	16	76	1.00 (Ref)	8	30	1.00 (Ref)
Uncertainly exposed	114	836	0.57 (0.34-0.97)	62	470	-	52	366	0.50 (0.20-1.26)
Exposed	9	90	0.29 (0.12-0.74) [d]	2	20	-	7	70	0.25 (0.07-0.90)
Ammonia									
Unexposed	42	322	1.00 (Ref)	21	185	1.00 (Ref)	21	137	1.00 (Ref)
Uncertainly exposed	96	680	1.07 (0.71-1.61)	54	368	1.31 (0.76-2.28)	42	312	-
Exposed	9	30	2.11 (0.90-4.94)	5	13	3.44 (0.97-12.17)	4	17	-
Hydrogen chloride									
Unexposed	61	374	1.00 (Ref)	35	239	1.00 (Ref)	26	135	1.00 (Ref)
Uncertainly exposed	81	649	0.75 (0.51-1.09)	43	326	-	38	323	-
Exposed	5	9	3.79 (1.07-13.41)	2	1	-	3	8	-
Formaldehyde									
Unexposed	9	111	1.00 (Ref)	2	53	1.00 (Ref)	7	58	1.00 (Ref)
Uncertainly exposed	121	873	1.40 (0.67-2.93)	69	496	3.36 (0.74-15.12)	52	377	0.85 (0.35-2.10)
Exposed	17	48	3.73(1.51-9.19) [d]	9	17	12.13 (2.22-66.40)	8	31	1.92 (0.61-6.06)
Anaesthetic gases									
Unexposed	106	730	1.00 (Ref)	48	383	1.00 (Ref)	58	347	1.00 (Ref)
Uncertainly exposed	28	239	0.98 (0.62-1.57)	21	133	1.56 (0.86-2.82)	7	106	-
Exposed	13	63	1.72 (0.87-3.40)	11	50	1.87 (0.87-4.02)	2	13	-
Soldering fumes									
Unexposed	83	637	1.00 (Ref)	50	387	1.00 (Ref)	33	250	1.00 (Ref)
Uncertainly exposed	59	378	1.17 (0.80-1.71)	30	178	-	29	200	0.94 (0.53-1.65)
Exposed	5	17	2.44 (0.73-8.14)	0	1	-	5	16	2.37 (0.66-8.51)
Cooking fumes									
Unexposed	69	491	1.00 (Ref)	38	267	1.00 (Ref)	31	224	1.00 (Ref)
Uncertainly exposed	66	510	0.98 (0.67-1.44)	33	282	0.91 (0.54-1.52)	33	228	-
Exposed	12	31	2.92 (1.33- 6.42) [d]	9	17	3.65 (1.33-10.07)	3	14	-

Gasoline engine emissions									
Unexposed	8	58	1.00 (Ref)	6	39	1.00 (Ref)	2	19	1.00 (Ref)
Uncertainly exposed	130	859	0.92 (0.41-2.09)	71	487	-	59	372	0.96 (0.18-5.14)
Exposed	9	115	0.40 (0.14-1.15)	3	40	-	6	75	0.39 (0.06-2.59)
Isopropanol									
Unexposed	45	328	1.00 (Ref)	12	152	1.00 (Ref)	33	176	1.00 (Ref)
Uncertainly exposed	79	591	0.95 (0.63-1.41)	51	333	1.93 (1.00-3.74)	28	258	0.54 (0.30-0.95)
Exposed	23	113	1.54 (0.86-2.75)	17	81	2.67 (1.17-6.06)	6	32	1.16 (0.42-3.21)
Synthetic adhesives									
Unexposed	34	226	1.00 (Ref)	17	133	1.00 (Ref)	17	93	1.00 (Ref)
Uncertainly exposed	107	792	0.88 (0.58-1.36)	61	428	-	46	364	-
Exposed	6	14	2.78 (0.87- 8.92)	2	5	-	4	9	-
Organic solvents									
Unexposed	4	33	1.00 (Ref)	3	17	1.00 (Ref)	1	16	1.00 (Ref)
Uncertainly exposed	110	866	1.12 (0.35-3.59)	64	508	0.63 (0.16-2.54)	46	358	2.77 (0.26-29.33)
Exposed	33	133	2.16 (0.62-7.49)	13	41	1.69 (0.36-7.95)	20	92	4.09 (0.36-46.68)
Other paints, varnishes									
Unexposed	46	279	1.00 (Ref)	28	189	1.00 (Ref)	18	108	1.00 (Ref)
Uncertainly exposed	94	722	0.77 (0.51-1.16)	52	376	-	42	346	0.53 (0.28-1.01)
Exposed	7	13	3.47 (0.92-13.12)	0	1	-	7	12	2.98 (0.62-14.27)
Lead compounds									
Unexposed	23	140	1.00 (Ref)	15	94	1.00 (Ref)	8	46	1.00 (Ref)
Uncertainly exposed	112	806	0.83 (0.50-1.38)	63	457	-	49	349	0.72 (0.30-1.71)
Exposed	12	86	0.60 (0.24-1.53)	2	15	-	10	71	0.53 (0.15-1.87)
Alkanes (C5-C17)									
Unexposed	7	98	1.00 (Ref)	3	58	1.00 (Ref)	4	40	1.00 (Ref)
Uncertainly exposed	123	877	1.79 (0.78-4.11)	73	501	-	50	376	1.26 (0.40-3.96)
Exposed	17	57	4.33 (1.41-13.29) [d]	4	7	-	13	50	2.41 (0.60-9.69)
Aliphatic alcohols									
Unexposed	15	119	1.00 (Ref)	5	44	1.00 (Ref)	10	75	1.00 (Ref)
Uncertainly exposed	107	782	0.95 (0.52-1.76)	57	439	1.00 (0.36-2.77)	50	343	0.94 (0.42-2.07)
Exposed	25	131	1.35 (0.65-2.81)	18	83	1.75 (0.57-5.36)	7	48	0.91 (0.29-2.86)

Aliphatic aldehydes									
Unexposed	6	79	1.00 (Ref)	2	36	1.00 (Ref)	4	43	1.00 (Ref)
Uncertainly exposed	123	903	1.43 (0.59-3.50)	69	511	2.03 (0.44-9.35)	54	392	1.12 (0.36-3.54)
Exposed	18	50	3.94 (1.41-10.98) [d]	9	19	6.56 (1.19-36.10)	9	31	2.92 (0.76-11.31)
PAHs from any source									
Unexposed	7	57	1.00 (Ref)	4	38	1.00 (Ref)	3	19	1.00 (Ref)
Uncertainly exposed	120	846	1.14 (0.48-2.70)	73	504	-	47	342	0.94 (0.25-3.60)
Exposed	20	129	0.88 (0.30-2.65)	3	24	-	17	105	0.78 (0.15-3.92)
PAHs from petroleum									
Unexposed	15	72	1.00 (Ref)	10	50	1.00 (Ref)	5	22	1.00 (Ref)
Uncertainly exposed	124	870	0.66 (0.35-1.25)	68	501	-	56	369	0.63 (0.20-1.99)
Exposed	8	90	0.18 (0.05-0.60) [d]	2	15	-	6	75	0.13 (0.02-0.68)
Mononuclear aromatic hydrocarbons									
Unexposed	20	150	1.00 (Ref)	14	90	1.00 (Ref)	6	60	1.00 (Ref)
Uncertainly exposed	113	826	0.91 (0.54-1.55)	63	469	-	50	357	1.24 (0.49-3.15)
Exposed	14	56	1.53 (0.57-4.09)	3	7	-	11	49	1.60 (0.43-5.93)
Cleaning agents									
Unexposed	29	328	1.00 (Ref)	13	187	1.00 (Ref)	16	141	1.00 (Ref)
Uncertainly exposed	83	545	1.70 (1.06-2.72)	41	271	2.63 (1.34-5.16)	42	274	1.04 (0.53-2.03)
Exposed	35	159	2.60 (1.50-4.52) [d]	26	108	3.77 (1.79-7.95)	9	51	1.69 (0.68-4.19)
Biocides									
Unexposed	26	237	1.00 (Ref)	9	102	1.00 (Ref)	17	135	1.00 (Ref)
Uncertainly exposed	93	647	1.26 (0.78-2.03)	50	362	1.62 (0.77-3.40)	43	285	1.07 (0.56-2.04)
Exposed	28	148	1.79 (0.98-3.28)	21	102	2.54 (1.09-5.91)	7	46	1.20 (0.44-3.28)

[a] Adjusted for sex, age, CSI, environmental tobacco smoke exposure, family history of lung cancer, and lung carcinogens exposures

[b] Adjusted for age, CSI, environmental tobacco smoke exposure, family history of lung cancer, and lung carcinogens exposures

[c] Empty cells were not analyzed if there were less than five "Exposed" cases

[d] Significant based on Benjamini-Hochberg procedure corrected p-values

Supplementary Table 4.1 Adjusted OR and 95% CI of lung cancer risk associated with exposure to the selected occupational agents - defining "Unexposed" as those with a probability of exposure between 0-5%, "Uncertainly exposed" as those with a probability of exposure between 5-25%, and "Exposed" as those with a probability of exposure equal or greater than 25%

Selected Agents	All(N=1179)			Females(N=646)			Males(N=533)		
	Cases	Sub-cohort	OR adjusted (95% CI) [a]	Cases	Sub-cohort	OR adjusted (95% CI) [b, c]	Cases	Sub-cohort	OR adjusted (95% CI) [b, c]
Abrasives dust									
Unexposed	121	896	1.00 (Ref)	70	531	1.00 (Ref)	51	365	1.00 (Ref)
Uncertainly exposed	20	106	1.25 (0.69-2.29)	9	32	-	11	74	0.82 (0.37-1.83)
Exposed	6	30	1.00 (0.30-3.30)	1	3	-	5	27	0.67 (0.18-2.54)
Concrete dust									
Unexposed	137	974	1.00 (Ref)	79	561	1.00 (Ref)	58	413	1.00 (Ref)
Uncertainly exposed	5	43	0.89 (0.32-2.44)	1	5	-	4	38	-
Exposed	5	15	1.81 (0.46-7.07)	0	0	-	5	15	-
Ashes									
Unexposed	128	1003	1.00 (Ref)	68	552	1.00 (Ref)	60	451	1.00 (Ref)
Uncertainly exposed	10	15	5.36 (2.09-13.75)	7	7	10.66 (3.03-37.48)	3	8	-
Exposed	9	14	4.39 (1.76-10.97)	5	7	4.13 (1.00-17.11)	4	7	-
Cosmetic talc									
Unexposed	126	930	1.00 (Ref)	62	489	1.00 (Ref)	64	441	1.00 (Ref)
Uncertainly exposed	6	12	6.64 (2.01-21.98)	5	11	5.74 (1.56-21.13)	1	1	-
Exposed	15	90	1.39 (0.75-2.60)	13	66	1.60 (0.80-3.21)	2	24	-
Calcium sulfate									
Unexposed	134	982	1.00 (Ref)	79	558	1.00 (Ref)	55	424	1.00 (Ref)
Uncertainly exposed	5	33	1.08 (0.38-3.05)	1	7	-	4	26	-
Exposed	8	17	3.79 (1.12-12.77)	0	1	-	8	16	-
Calcium carbonate									
Unexposed	123	887	1.00 (Ref)	69	502	1.00 (Ref)	54	385	1.00 (Ref)
Uncertainly exposed	10	52	1.27 (0.53-3.03)	1	10	-	9	42	-
Exposed	14	93	1.28 (0.70-2.35)	10	54	-	4	39	-
Wood dust									
Unexposed	127	928	1.00 (Ref)	76	537	1.00 (Ref)	51	391	1.00 (Ref)
Uncertainly exposed	12	83	1.19 (0.62-2.30)	3	28	-	9	55	1.38 (0.62-3.08)
Exposed	8	21	2.79 (0.91-8.58)	1	1	-	7	20	2.41 (0.71-8.16)
Carbon monoxide									
Unexposed	106	628	1.00 (Ref)	70	438	1.00 (Ref)	36	190	1.00 (Ref)
Uncertainly exposed	32	314	0.50 (0.30-0.81)	8	108	-	24	206	0.48 (0.26-0.91)
Exposed	9	90	0.33 (0.13-0.80)	2	20	-	7	70	0.29 (0.10-0.89)

Ammonia									
Unexposed	116	891	1.00 (Ref)	62	507	1.00 (Ref)	54	384	1.00 (Ref)
Uncertainly exposed	22	111	1.49 (0.87-2.56)	13	46	2.58 (1.24-5.36)	9	65	-
Exposed	9	30	2.13 (0.95-4.77)	5	13	3.27 (0.97-11.05)	4	17	-
Hydrogen chloride									
Unexposed	129	937	1.00 (Ref)	74	531	1.00 (Ref)	55	406	1.00 (Ref)
Uncertainly exposed	13	86	1.08 (0.56-2.05)	4	34	-	9	52	-
Exposed	5	9	4.67 (1.34-16.20)	2	1	-	3	8	-
Formaldehyde									
Unexposed	92	713	1.00 (Ref)	52	411	1.00 (Ref)	40	302	1.00 (Ref)
Uncertainly exposed	38	271	1.03 (0.68-1.58)	19	138	1.13 (0.63-2.05)	19	133	0.93 (0.50-1.74)
Exposed	17	48	2.77 (1.52-5.06)	9	17	3.97 (1.58-9.97)	8	31	2.16 (0.91-5.15)
Gasoline engine emissions									
Unexposed	87	524	1.00 (Ref)	59	350	1.00 (Ref)	28	174	1.00 (Ref)
Uncertainly exposed	51	393	0.72 (0.49-1.07)	18	176	-	33	217	0.82 (0.46-1.46)
Exposed	9	115	0.37 (0.17-0.80)	3	40	-	6	75	0.36 (0.13-1.03)
Isopropanol									
Unexposed	107	824	1.00 (Ref)	53	441	1.00 (Ref)	54	383	1.00 (Ref)
Uncertainly exposed	17	95	1.16 (0.65-2.09)	10	44	1.95 (0.91-4.21)	7	51	0.68 (0.27-1.72)
Exposed	23	113	1.63 (0.96-2.77)	17	81	1.78 (0.93-3.39)	6	32	1.52 (0.57-4.09)
Synthetic adhesives									
Unexposed	122	897	1.00 (Ref)	75	534	1.00 (Ref)	47	363	1.00 (Ref)
Uncertainly exposed	19	121	1.15 (0.64-2.06)	3	27	-	16	94	-
Exposed	6	14	3.17 (1.04-9.70)	2	5	-	4	9	-
Organic solvents									
Unexposed	50	455	1.00 (Ref)	31	271	1.00 (Ref)	19	184	1.00 (Ref)
Uncertainly exposed	64	444	1.38 (0.92-2.07)	36	254	1.38 (0.80-2.40)	28	190	1.40 (0.74-2.65)
Exposed	33	133	2.29 (1.28-4.10)	13	41	3.10 (1.34-7.13)	20	92	1.81 (0.81-4.03)
Other paints, varnishes									
Unexposed	122	909	1.00 (Ref)	71	538	1.00 (Ref)	51	371	1.00 (Ref)
Uncertainly exposed	18	110	1.22 (0.66-2.27)	9	27	-	9	83	0.70 (0.30-1.66)
Exposed	7	13	4.69 (1.22-18.02)	0	1	-	7	12	4.30 (0.93-19.96)
Lead compounds									
Unexposed	112	674	1.00 (Ref)	71	454	1.00 (Ref)	41	220	1.00 (Ref)
Uncertainly exposed	23	272	0.42 (0.25-0.71)	7	97	-	16	175	0.37 (0.19- 0.72)
Exposed	12	86	0.47 (0.18-1.18)	2	15	-	10	71	0.40 (0.13-1.30)

Alkanes (C5-C17)									
Unexposed	101	777	1.00 (Ref)	66	497	1.00 (Ref)	35	280	1.00 (Ref)
Uncertainly exposed	29	198	1.13 (0.69-1.85)	10	62	-	19	136	0.94 (0.48-1.85)
Exposed	17	57	2.65 (1.18-5.96)	4	7	-	13	50	1.86 (0.71-4.87)
Aliphatic alcohols									
Unexposed	89	701	1.00 (Ref)	45	382	1.00 (Ref)	44	319	1.00 (Ref)
Uncertainly exposed	33	200	1.32 (0.85-2.05)	17	101	1.66 (0.89-3.10)	16	99	1.11 (0.57-2.15)
Exposed	25	131	1.50 (0.89-2.55)	18	83	1.98 (1.03-3.82)	7	48	0.98 (0.37-2.60)
Aliphatic aldehydes									
Unexposed	82	665	1.00 (Ref)	48	393	1.00 (Ref)	34	272	1.00 (Ref)
Uncertainly exposed	47	317	1.15 (0.76-1.72)	23	154	1.22 (0.69-2.14)	24	163	1.11 (0.61-2.02)
Exposed	18	50	2.95 (1.62-5.38)	9	19	3.55 (1.44-8.76)	9	31	2.74 (1.15-6.55)
PAHs from any source									
Unexposed	82	546	1.00 (Ref)	53	392	1.00 (Ref)	29	154	1.00 (Ref)
Uncertainly exposed	45	357	0.81 (0.52-1.26)	24	150	-	21	207	0.46 (0.24-0.88)
Exposed	20	129	0.72 (0.31-1.63)	3	24	-	17	105	0.57 (0.19-1.70)
PAHs from petroleum									
Unexposed	99	618	1.00 (Ref)	64	425	1.00 (Ref)	35	193	1.00 (Ref)
Uncertainly exposed	40	324	0.69 (0.45-1.07)	14	126	-	26	198	0.58 (0.32-1.05)
Exposed	8	90	0.21 (0.07-0.66)	2	15	-	6	75	0.13 (0.03-0.56)
Mononuclear aromatic hydrocarbons									
Unexposed	104	766	1.00 (Ref)	67	484	1.00 (Ref)	37	282	1.00 (Ref)
Uncertainly exposed	29	210	0.95 (0.59-1.54)	10	75	-	19	135	0.87 (0.45-1.70)
Exposed	14	56	1.61 (0.65-4.02)	3	7	-	11	49	1.19 (0.40-3.51)
Cleaning agents									
Unexposed	93	740	1.00 (Ref)	48	403	1.00 (Ref)	45	337	1.00 (Ref)
Uncertainly exposed	19	133	0.87 (0.47-1.62)	6	55	1.03 (0.39-2.69)	13	78	0.76 (0.33-1.74)
Exposed	35	159	1.80 (1.15-2.83)	26	108	1.99 (1.14-3.49)	9	51	1.57 (0.71-3.47)
Biocides									
Unexposed	48	832	1.00 (Ref)	52	437	1.00 (Ref)	57	395	1.00 (Ref)
Uncertainly exposed	10	52	1.38 (0.66-2.88)	7	27	1.81 (0.65-5.06)	3	25	-
Exposed	28	148	1.53 (0.95-2.48)	21	102	1.80 (1.01-3.24)	7	46	-

[a] Adjusted for sex, age, CSI, environmental tobacco smoke exposure, family history of lung cancer, and lung carcinogens exposures

[b] Adjusted for age, CSI, environmental tobacco smoke exposure, family history of lung cancer, and lung carcinogens exposures

[c] Empty cells were not analyzed if there were less than five “Exposed” cases

Supplementary Table 4.2 Adjusted OR and 95% CI of lung cancer risk associated with exposure to the selected occupational agents - defining "Unexposed" as those with a probability of exposure 0, "Uncertainly exposed" as those with a probability of exposure between 0-50%, and "Exposed" as those with a probability of exposure equal or greater than 50%

	All(N=1179)			Females(N=646)			Males(N=533)		
Selected Agents	**Cases**	**Sub-cohort**	**OR adjusted (95% CI) [a]**	**Cases**	**Sub-cohort**	**OR adjusted (95% CI) [b, c]**	**Cases**	**Sub-cohort**	**OR adjusted (95% CI) [b, c]**
Calcium carbonate									
Unexposed	42	395	1.00 (Ref)	17	217	1.00 (Ref)	25	178	1.00 (Ref)
Uncertainly exposed	94	555	1.57 (1.05-2.37)	56	304	2.41 (1.31-4.42)	38	251	-
Exposed	11	82	1.47 (0.71-3.03)	7	45	2.61 (0.99-6.87)	4	37	-
Carbon monoxide									
Unexposed	24	106	1.00 (Ref)	16	76	1.00 (Ref)	8	30	1.00 (Ref)
Uncertainly exposed	118	895	0.56 (0.33-0.94)	62	485	-	56	410	-
Exposed	5	31	0.38 (0.09-1.61)	2	5	-	3	26	-
Cooking fumes									
Unexposed	69	491	1.00 (Ref)	38	267	1.00 (Ref)	31	224	1.00 (Ref)
Uncertainly exposed	70	515	1.04 (0.71-1.51)	37	287	1.01 (0.61-1.68)	33	228	-
Exposed	8	26	2.04 (0.85-4.89)	5	12	2.24 (0.65-7.72)	3	14	-
Gasoline engine emissions									
Unexposed	8	58	1.00 (Ref)	6	39	1.00 (Ref)	2	19	1.00 (Ref)
Uncertainly exposed	134	914	0.89 (0.39-2.03)	72	510	-	62	404	-
Exposed	5	60	0.37 (0.10-1.29)	2	17	-	3	43	-
Isopropanol									
Unexposed	45	328	1.00 (Ref)	12	152	1.00 (Ref)	33	176	1.00 (Ref)
Uncertainly exposed	92	687	0.95 (0.65-1.41)	60	401	1.89 (0.98-3.62)	32	286	-
Exposed	10	17	3.61 (1.42-9.18)	8	13	7.69 (2.49-23.80)	2	4	-
Organic solvents									
Unexposed	4	33	1.00 (Ref)	3	17	1.00 (Ref)	1	16	1.00 (Ref)
Uncertainly exposed	135	937	1.24 (0.39-3.99)	74	525	-	61	412	3.01 (0.28-32.16)
Exposed	8	62	0.79 (0.18-3.44)	3	24	-	5	38	1.63 (0.12-23.04)
Lead compounds									
Unexposed	23	140	1.00 (Ref)	15	94	1.00 (Ref)	8	46	1.00 (Ref)
Uncertainly exposed	117	869	0.81 (0.49-1.34)	63	468	-	54	401	0.69 (0.29-1.65)
Exposed	7	23	1.41 (0.40- 4.93)	2	4	-	5	19	0.80 (0.16-3.98)
Aliphatic alcohols									
Unexposed	15	119	1.00 (Ref)	5	44	1.00 (Ref)	10	75	1.00 (Ref)
Uncertainly exposed	122	876	0.98 (0.54-1.80)	67	493	1.07 (0.39-2.94)	55	383	-
Exposed	10	37	1.75 (0.67-4.58)	8	29	2.00 (0.55-7.35)	2	8	-

Aliphatic aldehydes									
Unexposed	6	79	1.00 (Ref)	2	36	1.00 (Ref)	4	43	1.00 (Ref)
Uncertainly exposed	128	919	1.47 (0.60-3.58)	70	513	2.05 (0.44-9.45)	58	406	1.17 (0.37-3.66)
Exposed	13	34	4.07 (1.39-11.91)	8	17	6.61 (1.17- 37.41)	5	17	2.96 (0.66-13.27)
PAHs from any source									
Unexposed	7	57	1.00 (Ref)	4	38	1.00 (Ref)	3	19	1.00 (Ref)
Uncertainly exposed	132	921	1.14 (0.48-2.68)	73	521	-	59	400	0.96 (0.25-3.67)
Exposed	8	54	0.64 (0.16-2.67)	3	7	-	5	47	0.30 (0.04-1.96)
PAHs from petroleum									
Unexposed	15	72	1.00 (Ref)	10	50	1.00 (Ref)	5	22	1.00 (Ref)
Uncertainly exposed	125	912	0.62 (0.33-1.17)	68	509	-	57	403	0.57 (0.18-1.76)
Exposed	7	48	0.35 (0.09-1.28)	2	7	-	5	41	0.22 (0.04-1.21)
Cleaning agents									
Unexposed	29	328	1.00 (Ref)	13	187	1.00 (Ref)	16	141	1.00 (Ref)
Uncertainly exposed	89	607	1.65 (1.03-2.62)	46	316	2.49 (1.28-4.84)	43	291	1.02 (0.53-2.00)
Exposed	29	97	3.45 (1.91-6.24)	21	63	5.24 (2.36-11.67)	8	34	2.09 (0.79-5.51)
Biocides									
Unexposed	26	237	1.00 (Ref)	9	102	1.00 (Ref)	17	135	1.00 (Ref)
Uncertainly exposed	96	677	1.24 (0.77-2.00)	51	380	1.58 (0.75-3.33)	45	297	1.05 (0.56-1.99)
Exposed	25	118	2.10 (1.11-3.97)	20	84	2.84 (1.20-6.71)	5	34	1.50 (0.47-4.75)

[a] Adjusted for sex, age, CSI, environmental tobacco smoke exposure, family history of lung cancer, and lung carcinogens exposures

[b] Adjusted for age, CSI, environmental tobacco smoke exposure, family history of lung cancer, and lung carcinogens exposure

[c] Empty cells were not analyzed if there were less than five “Exposed” cases

Chapter 5. Supplementary results

The primary objective of this thesis was to examine the associations between exposure to prevalent occupational agents and lung cancer risk, among male and female workers. Throughout this thesis, a number of sensitivity analyses were conducted to ensure the robustness of study findings. This chapter will present additional findings corresponding to the impacts of frequency and intensity of exposure, and the effects of the reliability of exposure assignment on the observed associations presented in the main analysis (Chapter 4).

5.1 Assessing the impact of changing our exposure parametrization by the incorporation of frequency and intensity of exposure

A sensitivity analysis was conducted to assess the impact of using CANJEM's FWI on the observed associations in the main analysis. Briefly, participants that are "Uncertainly exposed" to an agent are excluded from this analysis. Using CANJEM, the FWI of prevalent agents were assigned to the remaining job codes and then "Exposed" was redefined as those with FWI above or equal to the median in the sub-cohort and "Unexposed" included those below the FWI median. Table 5.1 summarizes the associations between prevalent occupational exposures defined according to the FWI and lung cancer risk. As compared to the main analysis, a smaller number of agents were retained for this sensitivity analysis (25 of 28 agents) which includes eight of ten agents that revealed associations in the main analysis. Among those eight observed associations from main analysis, occupational exposure to ashes, cleaning agents, and carbon monoxide were the only agents that were associated with lung cancer risk which were also stronger in this sensitivity analysis. Moreover, calcium carbonate, soldering fumes, and biocides were found to

increase lung cancer risk, although the results for these agents were not statistically significant in the main analysis, though consistent in their directionality of effect.

5.2 Assessing the influence of the reliability of the exposure assignment

To evaluate the impact of the reliability of the exposure assignment on the observed associations, CANJEM was reconfigured with cells defined as exposed if the exposure occurred at a reliability level of "probable" and "definite". Occupational exposure to each agent was parametrized into three categories "Unexposed" when the probability of exposure to that agent was 0, "Uncertainly exposed" when the probability of exposure was between 0 to 25%, and "Exposed" when the probability of exposure was 25% or greater. Using this new CANJEM, 77.9% were linked at a 5-digit resolution and 22.1% at the 2 or 3-digit resolution. Table 5.2 summarizes the associations between prevalent occupational exposures and lung cancer using the reconfigured CANJEM. In this sensitivity analysis, nine of ten agents that indicated association in the main analysis were retained (including ashes, calcium sulfate, formaldehyde, cooking fumes, alkanes, aliphatic aldehydes, cleaning agents, carbon monoxide, and PAHs from petroleum). Compared to the main analysis, in general, similar but relatively stronger associations were found for those who were exposed to ashes, calcium sulfate, formaldehyde, and aliphatic aldehydes. In contrast, associations with cooking fumes and cleaning agents were attenuated in this sensitivity analysis. Moreover, agents such as cosmetic talc, wood dust, ammonia, and anaesthetic gases with suggestive elevated risks in the main analysis appeared to increase occupational lung cancer risk in this sensitivity analysis. Occupational exposure to carbon monoxide and PAHs from petroleum as well as gasoline engine emissions and PAHs from any source revealed decreased risks of lung cancer; the two latter agents were not statistically significant in the main analysis.

Table 5.1 Adjusted OR and 95% CI of lung cancer risk associated with exposure to the selected occupational agents - defining "Unexposed" as those with FWI below the median in the sub-cohort of the specific agent and "Exposed" as those with FWI above or equal to the median in the sub-cohort of that specific agent

	Assessing the impact of frequency and intensity of exposure								
	All			Females			Males		
Selected Agents	**Cases**	**Sub-cohort**	**OR adjusted (95% CI) [a]**	**Cases**	**Sub-cohort**	**OR adjusted (95% CI) [b, c]**	**Cases**	**Sub-cohort**	**OR adjusted (95% CI) [b, c]**
Abrasives dust									
Unexposed	47	394	1.00 (Ref)	23	198	1.00 (Ref)	24	151	1.00 (Ref)
Exposed	6	18	3.26 (0.93- 11.49)	1	2	-	5	16	2.26 (0.54-9.40)
Concrete dust									
Unexposed	90	591	1.00 (Ref)	49	355	1.00 (Ref)	41	236	1.00 (Ref)
Exposed	5	11	3.47 (0.55- 21.75)	0	0	-	5	11	3.15 (0.48- 20.81)
Ashes									
Unexposed	94	724	1.00 (Ref)	55	413	1.00 (Ref)	39	311	1.00 (Ref)
Exposed	9	14	4.67(1.78-12.25)	5	7	4.40 (1.05-18.34)	4	7	-
Cosmetic talc									
Unexposed	107	694	1.00 (Ref)	53	384	1.00 (Ref)	54	310	1.00 (Ref)
Exposed	8	79	0.77 (0.34-1.75)	7	56	0.99 (0.39- 2.49)	1	23	-
Calcium sulfate									
Unexposed	61	462	1.00 (Ref)	33	268	1.00 (Ref)	28	194	1.00 (Ref)
Exposed	5	10	2.49 (0.43-14.37)	0	0	-	5	10	2.44 (0.36-16.72)
Calcium carbonate									
Unexposed	46	434	1.00 (Ref)	19	236	1.00 (Ref)	27	198	1.00 (Ref)
Exposed	10	54	2.50 (1.13- 5.52)	8	35	4.20 (1.53- 11.55) [d]	2	19	-
Wood dust									
Unexposed	33	262	1.00 (Ref)	22	162	1.00 (Ref)	11	100	1.00 (Ref)
Exposed	8	15	4.00 (0.82-19.59)	1	1	-	7	14	2.69 (0.36- 20.02)
Carbon monoxide									
Unexposed	27	132	1.00 (Ref)	17	81	1.00 (Ref)	10	51	1.00 (Ref)
Exposed	6	64	0.25 (0.07- 0.90)	1	15	-	5	49	0.30 (0.06-1.44)
Ammonia									
Unexposed	45	337	1.00 (Ref)	21	192	1.00 (Ref)	24	145	1.00 (Ref)
Exposed	6	15	3.00 (0.97-9.31)	5	6	7.45 (1.76-31.59)	1	9	-

Formaldehyde									
Unexposed	21	130	1.00 (Ref)	9	62	1.00 (Ref)	12	68	1.00 (Ref)
Exposed	5	29	0.92 (0.27-3.18)	2	8	-	3	21	-
Anaesthetic gases									
Unexposed	106	732	1.00 (Ref)	48	384	1.00 (Ref)	58	348	1.00 (Ref)
Exposed	13	61	1.95 (0.97- 3.91)	11	49	2.07 (0.92-4.66)	2	12	-
Soldering fumes									
Unexposed	83	643	1.00 (Ref)	50	387	1.00 (Ref)	33	256	1.00 (Ref)
Exposed	5	11	3.82 (1.07-13.62)	0	1	-	5	10	5.16 (1.08- 24.57)
Gasoline engine emissions									
Unexposed	10	103	1.00 (Ref)	7	60	1.00 (Ref)	3	43	1.00 (Ref)
Exposed	7	70	0.90 (0.26-3.16)	2	19	-	5	51	1.25 (0.18-8.72)
Isopropanol									
Unexposed	54	355	1.00 (Ref)	18	172	1.00 (Ref)	36	183	1.00 (Ref)
Exposed	14	86	1.21 (0.60-2.43)	11	61	1.74 (0.70-4.32)	3	25	-
Organic solvents									
Unexposed	19	78	1.00 (Ref)	12	44	1.00 (Ref)	7	34	1.00 (Ref)
Exposed	18	88	0.88 (0.33-2.34)	4	14	-	14	74	0.60 (0.15-2.35)
Other paints, varnishes									
Unexposed	47	299	1.00 (Ref)	28	189	1.00 (Ref)	19	110	1.00 (Ref)
Exposed	6	11	2.94 (0.53-16.44)	0	1	-	6	10	4.09 (0.40-41.48)
Lead compounds									
Unexposed	30	171	1.00 (Ref)	16	96	1.00 (Ref)	14	75	1.00 (Ref)
Exposed	5	55	0.32 (0.10-1.06)	1	13	-	4	42	-
Alkanes (C5-C17)									
Unexposed	17	124	1.00 (Ref)	4	61	1.00 (Ref)	13	63	1.00 (Ref)
Exposed	7	31	0.85 (0.22-3.26)	3	4	-	4	27	-
Aliphatic alcohols									
Unexposed	24	146	1.00 (Ref)	11	64	1.00 (Ref)	13	82	1.00 (Ref)
Exposed	16	104	0.88 (0.40-1.95)	12	63	1.25 (0.46-3.34)	4	41	-
Aliphatic aldehydes									
Unexposed	19	99	1.00 (Ref)	9	47	1.00 (Ref)	10	52	1.00 (Ref)
Exposed	5	30	0.62 (0.15-2.50)	2	8	-	3	22	-
PAHs from any source						-			
Unexposed	16	86	1.00 (Ref)	5	40	1.00 (Ref)	11	46	1.00 (Ref)
Exposed	11	100	0.43 (0.16-1.16)	2	22		9	78	0.39 (0.12-1.33)

PAHs from petroleum									
Unexposed	17	86	1.00 (Ref)	11	52	1.00 (Ref)	6	34	1.00 (Ref)
Exposed	6	76	0.32 (0.08-1.18)	1	13	-	5	63	0.26 (0.04-1.66)
Mononuclear aromatic hydrocarbons									
Unexposed	29	177	1.00 (Ref)	15	95	1.00 (Ref)	14	82	1.00 (Ref)
Exposed	5	29	0.66 (0.12-3.51)	2	2	-	3	27	-
Cleaning agents									
Unexposed	29	349	1.00 (Ref)	13	203	1.00 (Ref)	16	146	1.00 (Ref)
Exposed	35	138	3.19 (1.81-5.64)	26	92	4.98 (2.31-10.71)	9	46	1.45 (0.56-3.74)
Biocides									
Unexposed	27	258	1.00 (Ref)	10	118	1.00 (Ref)	17	140	1.00 (Ref)
Exposed	27	127	2.07 (1.09-3.94)	20	86	2.90 (1.19-7.09) [d]	7	41	1.48 (0.50-4.38)

[a] Adjusted for sex, age, CSI, environmental tobacco smoke exposure, family history of lung cancer, and lung carcinogens exposures

[b] Adjusted for age, CSI, environmental tobacco smoke exposure, family history of lung cancer, and lung carcinogens exposures

[c] Empty cells were not analyzed if there were less than five “Exposed” cases

[d] Not adjusted for lung carcinogen exposures since there was no case exposed to any lung carcinogen.

Table 5.2 Adjusted OR and 95% CI of lung cancer risk associated with exposure to the selected occupational agents (CANJEM with cells defined as exposed if the exposure occurred at a reliability level of "probable" and "definite") - defining "Unexposed" as those with a probability of exposure 0, "Uncertainly exposed" as those with a probability of exposure between 0-25%, and "Exposed" as those with a probability of exposure equal or greater than 25%

	Assessing the influence of the reliability of the exposure assignment								
	All(N=1179)			Females(N=646)			Males(N=533)		
Selected Agents	**Cases**	**Sub-cohort**	**OR adjusted (95% CI) [a]**	**Cases**	**Sub-cohort**	**OR adjusted (95% CI) [b, c]**	**Cases**	**Sub-cohort**	**OR adjusted (95% CI) [b, c]**
Abrasives dust									
Unexposed	66	446	1.00 (Ref)	33	258	1.00 (Ref)	33	188	1.00 (Ref)
Uncertainly exposed	71	556	0.86 (0.59-1.24)	46	305	-	25	251	0.56 (0.32- 0.99)
Exposed	10	30	2.14 (0.73- 6.34)	1	3	-	9	27	1.56 (0.48-5.09)
Inorganic insulation dust									
Unexposed	105	757	1.00 (Ref)	65	463	1.00 (Ref)	40	294	1.00 (Ref)
Uncertainly exposed	35	268	1.05 (0.67-1.63)	15	102	-	20	166	0.86 (0.47-1.58)
Exposed	7	7	8.28 (1.94-35.45)	0	1	-	7	6	10.48 (2.15-51.04)
Concrete dust									
Unexposed	112	739	1.00 (Ref)	64	453	1.00 (Ref)	48	286	1.00 (Ref)
Uncertainly exposed	30	275	0.77 (0.49-1.22)	16	112	-	14	163	0.48 (0.26-0.91)
Exposed	5	18	1.26 (0.31-5.04)	0	1	-	5	17	1.03 (0.23-4.49)
Inorganic pigments									
Unexposed	75	498	1.00 (Ref)	40	288	1.00 (Ref)	35	210	1.00 (Ref)
Uncertainly exposed	66	523	0.80 (0.55-1.17)	39	276	-	27	247	0.57 (0.32-1.02)
Exposed	6	11	2.75 (0.90- 8.36)	1	2	-	5	9	2.56 (0.66-9.92)
Ashes									
Unexposed	118	877	1.00 (Ref)	63	489	1.00 (Ref)	55	388	1.00 (Ref)
Uncertainly exposed	23	148	1.08 (0.65-1.80)	14	72	-	9	76	-
Exposed	6	7	5.58 (1.65-18.84)	3	5	-	3	2	-
Cosmetic talc									
Unexposed	113	872	1.00 (Ref)	52	450	1.00 (Ref)	61	422	1.00 (Ref)
Uncertainly exposed	26	140	1.83 (1.10-3.04)	21	99	2.31 (1.26-4.21)	5	41	-
Exposed	8	20	3.18 (1.22-8.30)	7	17	3.99 (1.42-11.23)	1	3	-

Calcium sulfate									
Unexposed	87	655	1.00 (Ref)	47	379	1.00 (Ref)	40	276	1.00 (Ref)
Uncertainly exposed	53	362	1.20 (0.82-1.77)	33	186	-	20	176	0.85 (0.46-1.54)
Exposed	7	15	4.55 (1.18-17.55)	0	1	-	7	14	4.22 (0.98-18.19)
Calcium carbonate									
Unexposed	80	597	1.00 (Ref)	39	337	1.00 (Ref)	41	260	1.00 (Ref)
Uncertainly exposed	50	350	1.07 (0.72-1.60)	32	184	1.60 (0.93-2.75)	18	166	0.64 (0.34-1.20)
Exposed	17	85	1.77 (0.98-3.21)	9	45	2.25 (1.00-5.03)	8	40	1.41 (0.57-3.51)
Wood dust									
Unexposed	64	424	1.00 (Ref)	39	262	1.00 (Ref)	25	162	1.00 (Ref)
Uncertainly exposed	73	584	0.81 (0.55-1.18)	40	302	-	33	282	0.73 (0.40-1.30)
Exposed	10	24	3.37 (1.16-9.73)	1	2	-	9	22	3.01 (0.92-9.85)
Carbon monoxide									
Unexposed	40	186	1.00 (Ref)	22	125	1.00 (Ref)	18	61	1.00 (Ref)
Uncertainly exposed	99	765	0.63 (0.41-0.96)	56	423	-	43	342	0.46 (0.23-0.92)
Exposed	8	81	0.34 (0.14-0.79)	2	18	-	6	63	0.25 (0.08-0.72)
Ammonia									
Unexposed	68	436	1.00 (Ref)	30	240	1.00 (Ref)	38	196	1.00 (Ref)
Uncertainly exposed	70	573	0.79 (0.54-1.14)	45	316	1.12 (0.67-1.87)	25	257	-
Exposed	9	23	2.41(1.03-5.64)	5	10	4.01(1.07-14.97)	4	13	-
Formaldehyde									
Unexposed	35	286	1.00 (Ref)	17	147	1.00 (Ref)	18	139	1.00 (Ref)
Uncertainly exposed	95	710	1.15 (0.74-1.77)	56	402	1.28 (0.70-2.34)	39	308	1.01 (0.53-1.91)
Exposed	17	36	3.85 (1.92-7.74)	7	17	3.33 (1.11- 9.98)	10	19	4.65 (1.76-12.28)
Anaesthetic gases									
Unexposed	119	823	1.00 (Ref)	59	414	1.00 (Ref)	60	409	1.00 (Ref)
Uncertainly exposed	22	197	0.89 (0.54-1.47)	16	142	0.88 (0.48-1.61)	6	55	-
Exposed	6	12	3.68 (1.18-11.49)	5	10	3.47(0.97-12.41)	1	2	-
Soldering fumes									
Unexposed	99	709	1.00 (Ref)	60	420	1.00 (Ref)	39	289	1.00 (Ref)
Uncertainly exposed	43	307	1.02 (0.68-1.53)	20	145	-	23	162	0.91 (0.49-1.68)
Exposed	5	16	2.54 (0.76-8.43)	0	1	-	5	15	2.69 (0.76-9.50)
Cooking fumes									
Unexposed	93	657	1.00 (Ref)	48	345	1.00 (Ref)	45	312	1.00 (Ref)
Uncertainly exposed	42	345	0.92 (0.61-1.38)	23	205	0.89 (0.51-1.54)	19	140	-
Exposed	12	30	2.91 (1.34-6.34)	9	16	3.79(1.37-10.47)	3	14	-

Gasoline engine emissions									
Unexposed	24	134	1.00 (Ref)	16	82	1.00 (Ref)	8	52	1.00 (Ref)
Uncertainly exposed	113	768	0.79 (0.47-1.33)	60	441	-	53	327	1.07 (0.43-2.69)
Exposed	10	130	0.36 (0.16-0.83)	4	43	-	6	87	0.35 (0.11-1.19)
Isopropanol									
Unexposed	62	442	1.00 (Ref)	20	210	1.00 (Ref)	42	232	1.00 (Ref)
Uncertainly exposed	70	495	0.97 (0.67-1.41)	47	282	1.67 (0.94-2.98)	23	213	-
Exposed	15	95	1.16 (0.61- 2.22)	13	74	1.75 (0.80-3.84)	2	21	-
Synthetic adhesives									
Unexposed	52	325	1.00 (Ref)	28	186	1.00 (Ref)	24	139	1.00 (Ref)
Uncertainly exposed	86	686	0.80 (0.54-1.17)	50	375	-	36	311	0.70 (0.40-1.25)
Exposed	9	21	2.09 (0.76-5.78)	2	5	-	7	16	1.64 (0.50-5.42)
Organic solvents									
Unexposed	25	147	1.00 (Ref)	13	90	1.00 (Ref)	12	57	1.00 (Ref)
Uncertainly exposed	90	760	0.73 (0.44-1.20)	54	435	0.90 (0.46-1.80)	36	325	0.52 (0.24-1.11)
Exposed	32	125	1.52 (0.78-2.95)	13	41	2.42 (0.93-6.32)	19	84	0.93 (0.37-2.33)
Mineral spirits post 1970									
Unexposed	71	505	1.00 (Ref)	39	299	1.00 (Ref)	32	206	1.00 (Ref)
Uncertainly exposed	71	515	0.96 (0.66-1.38)	41	265	-	30	250	0.68 (0.39-1.19)
Exposed	5	12	1.67 (0.39-7.10)	0	2	-	5	10	1.68 (0.36-7.93)
Lead compounds									
Unexposed	46	254	1.00 (Ref)	30	162	1.00 (Ref)	16	92	1.00 (Ref)
Uncertainly exposed	91	695	0.73 (0.49-1.10)	48	389	-	43	306	0.78 (0.39-1.53)
Exposed	10	83	0.58 (0.26-1.30)	2	15	-	8	68	0.56 (0.20-1.60)
Alkanes (C5-C17)									
Unexposed	48	328	1.00 (Ref)	29	212	1.00 (Ref)	19	116	1.00 (Ref)
Uncertainly exposed	83	635	0.87 (0.58-1.31)	46	341	1.01 (0.60-1.71)	37	294	0.66 (0.35-1.24)
Exposed	16	69	1.44 (0.64-3.22)	5	13	4.00 (0.95-16.93)	11	56	0.75 (0.29-1.98)
Aliphatic alcohols									
Unexposed	42	298	1.00 (Ref)	14	150	1.00 (Ref)	28	148	1.00 (Ref)
Uncertainly exposed	84	607	0.98 (0.65-1.49)	52	334	1.70 (0.89-3.28)	32	273	0.59 (0.32-1.08)
Exposed	21	127	1.13 (0.62-2.05)	14	82	1.87 (0.81-4.30)	7	45	0.74 (0.27-2.01)
Aliphatic aldehydes									
Unexposed	25	201	1.00 (Ref)	11	97	1.00 (Ref)	14	104	1.00 (Ref)
Uncertainly exposed	101	789	1.01 (0.62-1.65)	60	450	1.22 (0.60- 2.49)	41	339	0.81 (0.40-1.64)
Exposed	21	42	3.99 (1.99-7.99)	9	19	3.97 (1.37-11.45)	12	23	4.28 (1.61-11.37)

PAHs from any source									
Unexposed	24	121	1.00 (Ref)	13	76	1.00 (Ref)	11	45	1.00 (Ref)
Uncertainly exposed	113	795	0.72 (0.43-1.21)	64	462	-	49	333	0.64 (0.29-1.43)
Exposed	10	116	0.26 (0.10-0.68)	3	28	-	7	88	0.17 (0.05-0.62)
PAHs from petroleum									
Unexposed	33	176	1.00 (Ref)	19	113	1.00 (Ref)	14	63	1.00 (Ref)
Uncertainly exposed	106	761	0.75 (0.47-1.18)	59	436	-	47	325	0.66 (0.32-1.35)
Exposed	8	95	0.21 (0.08-0.59)	2	17	-	6	78	0.15 (0.04-0.51)
Mononuclear aromatic hydrocarbons									
Unexposed	43	256	1.00 (Ref)	27	150	1.00 (Ref)	16	106	1.00 (Ref)
Uncertainly exposed	90	711	0.70 (0.46-1.05)	49	405	-	41	306	0.83 (0.42-1.65)
Exposed	14	65	0.99 (0.42-2.34)	4	11	-	10	54	0.78 (0.28-2.23)
Cleaning agents									
Unexposed	43	407	1.00 (Ref)	17	225	1.00 (Ref)	26	182	1.00 (Ref)
Uncertainly exposed	69	479	1.31 (0.84-2.04)	37	237	2.36 (1.25-4.46)	32	242	0.71 (0.37-1.37)
Exposed	35	146	2.38 (1.43-3.96)	26	104	3.57 (1.79-7.13)	9	42	1.65 (0.70-3.93)
Biocides									
Unexposed	50	395	1.00 (Ref)	17	179	1.00 (Ref)	33	216	1.00 (Ref)
Uncertainly exposed	69	497	1.12 (0.74-1.67)	42	285	1.54 (0.83-2.88)	27	212	0.85 (0.47-1.51)
Exposed	28	140	1.71 (1.00-2.92)	21	102	2.26 (1.11- 4.62)	7	38	1.32 (0.51-3.43)

[a] Adjusted for sex, age, CSI, environmental tobacco smoke exposure, family history of lung cancer, and lung carcinogens exposures

[b] Adjusted for age, CSI, environmental tobacco smoke exposure, family history of lung cancer, and lung carcinogens exposure

[c] Empty cells were not analyzed if there were less than five “Exposed” cases

Chapter 6. Discussion

The primary objective of this thesis was to examine the associations between exposure to prevalent occupational agents and lung cancer risk, among male and female workers. Nesting a case-cohort study within the CARTaGENE prospective cohort study provided a unique opportunity to increase the knowledge base, particularly among female workers, regarding the role of occupational exposures in lung cancer etiology. This chapter will address and interpret the findings presented in the manuscript in more detail, as well as those results presented in the additional results chapter. This chapter will also discuss what our results add to the current literature on occupational lung cancer and consider the strengths and limitations of the study.

6.1 Summary of key findings

6.1.1 Summary of key findings in Chapter 4

The results of our main analysis revealed increased risks of lung cancer in workers exposed to ashes (in the total population), calcium sulfate (in the total population and men), calcium carbonate (in women), hydrogen chloride (in the total population), formaldehyde (in the total population and women), cooking fumes (in the total population and women), isopropanol (in women), alkanes (in the total population), aliphatic aldehydes (in the total population and women), cleaning agents (in the total population and women), and biocides (in women). Moreover, occupational exposure to carbon monoxide (in the total population and men) and PAHs from petroleum (in the total population and men) were associated with a reduction in lung cancer risk. Among seven (of 28) agents with a sufficient number of cases in both sexes, female workers were found to have a higher excess risk of developing lung cancer in five agents including

formaldehyde, isopropanol, aliphatic aldehydes, cleaning agents, and biocides. Two remaining agents including organic solvents and aliphatic alcohols indicated no association in both male and female workers.

Sensitivity analyses assessing the impact of varying the thresholds of the probability of exposure used to define exposure categories were conducted. First in redefining the categories of Unexposed (probability of exposure between 0-5%) and Uncertainly exposed (probability of exposure between 5-25%), 25 (of 28) agents were retained for this sensitivity analysis which included nine of the ten agents that revealed associations in the main analysis (namely, for ashes, calcium sulfate, hydrogen chloride, formaldehyde, alkanes, aliphatic aldehydes, cleaning agents, carbon monoxide, and PAHs from petroleum). Similar to the main analysis, occupational exposure to these nine agents were associated with lung cancer risk. Second, in redefining the categories of Unexposed (probability of exposure 0) and Uncertainly exposed (probability of exposure between 0-50%), a smaller number of agents were retained for analysis (13 of 28) which included five of the ten agents that revealed associations in the main analysis (including carbon monoxide, cooking fumes, aliphatic aldehydes, PAHs from petroleum, and cleaning agents). Among those five associations, only aliphatic aldehydes and cleaning agents were indicated risks after redefinition which were also considerably greater.

6.1.2 Summary of key findings of Chapter 5

In a sensitivity analysis that redefined occupational exposure based on the FWI, 25 agents (of 28) were retained for analysis which included eight of the ten agents that revealed associations in the main analysis. Occupational exposure to ashes, cleaning agents, and carbon monoxide were the only associations from the main analysis that indicated associations with lung cancer. Further, when using CANJEM with cells defined as exposed if the exposure occurred at a

reliability level of “probable” and “definite”, 29 agents were retained for this sensitivity analysis which included 26 agents (of 28) from the main analysis. Among those, nine of the ten agents with indicated associations in the main analysis also remained for this sensitivity analysis. Eight agents were similarly found to be associated with lung cancer risk (namely for ashes, calcium sulfate, formaldehyde, cooking fumes, aliphatic aldehydes, cleaning agents, carbon monoxide, and PAHs from petroleum).

6.2 Comparison with relevant literature

The results of this case-cohort study consistently showed elevated lung cancer risks for occupational exposure to ashes, calcium sulfate, formaldehyde, aliphatic aldehydes, and cleaning agents. Our results are not unexpected since these occupational agents are mostly dusts and gases and thus mechanistically, they could enter the lung via inhalation and affect lung function. Further, these findings are supported by evidence in the existing literature, though limited studies have examined these exposures in relation to the risk of developing lung cancer. Occupational exposure to ashes and lung cancer risk has been investigated by only one epidemiological study that revealed a two-fold elevated risk in exposed male workers (97). Similarly, the results from this thesis showed that workers who were ever exposed to ashes were four times more likely to develop lung cancer than those unexposed in the entire population, however, due to limited number of exposed cases among men only, we did not conduct sex-specific analysis.

Moreover, a four-fold increase in lung cancer risk was found in this thesis for workers who were exposed to calcium sulfate in the entire population and among male workers. In contrast, case-control studies revealed either small or suggestive elevated risks in male workers (96,97). Occupational exposure to formaldehyde in relation to lung cancer risk has been reviewed. The pooled results from 31 studies revealed elevated risks of lung cancer in sub-analyses of high-

quality studies (risk estimate =1.13; 95% CI: 1.08-1.19), conducted after 1996 (risk estimate =1.13; 95% CI: 1.07-1.19), that used a JEM (risk estimate =1.24; 95% CI: 1.08-1.43) (105). These reported risk estimates are more modest than the 4-fold increased risk associated with formaldehyde that was observed in this thesis. The observed positive association between aliphatic aldehydes and lung cancer risk in female workers was also found in a population-based case-control study (OR=1.2; 95% CI: 0.7-1.9) (103), though the association observed in this thesis was much stronger (OR=6.56). Cleaning agents have been shown to have negative effects on respiratory conditions (133). In this thesis, workers who were exposed to cleaning agents were three times more likely to develop lung cancer than those unexposed in the entire population; in female workers, an almost four-fold increase in lung cancer risk was observed. In two case-control studies, no excess risk was observed in women who were exposed to cleaning agents in the workplace (103) while exposed male workers were found to have elevated risk of developing lung cancer (111).

The consistent protective associations observed between lung cancer risk and occupational exposure to carbon monoxide and PAHs from petroleum were unexpected. To our knowledge, no epidemiological study has investigated occupational exposure to carbon monoxide and lung cancer risk. It is unclear why a protective effect was observed but recent findings suggested that carbon monoxide may affect cancer cell proliferation as well as fighting against the Warburg effect (cancer cell metabolism alteration with the purpose of fast growth) via creating metabolic exhaustion for cancer cells (134–137). Moreover, the protective association observed for occupational exposure to PAHs from petroleum in the entire population and male workers is not in line with findings from other studies that reported no association or small elevated risk of lung cancer in men (97,110).

6.3 Study validity: methodological strengths and limitations

6.3.1 Selection bias

Selection bias could be introduced when the study participation or likelihood of being retained in a cohort study systematically differs by the outcome and exposure status. This could lead to a study population that is not representative of the true distribution of exposure and outcome in the general population. In phase A of the CARTaGENE study, a total of 20,007 participants enrolled with an overall participation rate of 25.6% (124). However, given the prospective cohort design of this study, factors affecting the enrollment of participants are unlikely to introduce selection bias. Moreover, lung cancer status (outcome) was identified through a linkage of CARTaGENE participants to RAMQ, therefore, a differential loss to follow up which increases the possibility of introducing selection bias is unlikely.

Nevertheless, selection bias could also occur in a study when the exclusion criteria cause unrepresentative distributions of exposure and/or covariates in the study population compared to the target population. In this study, participants were excluded if they self-reported to "being unemployed/unable to work" (30 lung cancer cases), their reported job could not be coded (58 lung cancer cases and 71 sub-cohorts), their job codes could not be linked to CANJEM (three sub-cohorts), or if they lacked smoking information (one case and one participant in sub-cohort). The exclusion of 30 lung cancer cases who were unemployed or unable to work is unlikely to have consequential effects on any effect estimates derived from the study population since their lung cancer could not be categorized as an occupational in nature. However, the exclusion of the 58 lung cancer cases due to an unlikable job code could have skewed the distribution of exposures in the case population and thus, act as a potential source of selection bias. Finally, the exclusion of a

small number of participants due to missing data on smoking is unlikely to have introduced selection bias.

6.3.2 Information bias, measurement error, and exposure misclassification

Information bias could occur in a study when study variables (exposure, health outcome, or covariates) are inaccurately measured or classified. Given our case-cohort study design, any differential misclassification of occupational exposures based on lung cancer status is unlikely. However, all studies generally deal with some degree of exposure misclassification. For example, using exposure information estimated for the longest-held job rather than the entire work history may introduce exposure misclassification in this thesis. However, since more than 61% of individuals in CARTaGENE population have held only one job and even among those with more than one job, the longest-held job still represented the majority of their working life, it is anticipated that the exposure misclassification is minimal and non-differential and would attenuate the ORs towards the null.

CANJEM was used to estimate exposure to occupational agents in this study. The high validity and reliability of the expert assessments that CANJEM was built on informs on its utility (83,126). However, there are some methodological considerations associated with the use of CANJEM. First, similar to other JEMs, CANJEM provides an average estimate of exposure for a given job code, resulting in the allocation of the same levels of exposure to all workers with a shared job code which could result in non-differential exposure misclassification and thus, could lead to biased estimates. Since our parametrization of exposure was a 3-level categorical variable, the direction of bias is less obvious and may be either towards or away from the null value. Further, when using CANJEM, a probability of exposure to certain agents associated with a job code is provided. Currently, there is no consensus on the optimal way to use this metric to define exposure

status. Some have created a binary variable (exposed/unexposed) or a 3-category exposure variable (unexposed/uncertain/exposed) from the continuous probability according to a cut-point (138,139) while others have used this index by integrating it with concentration and duration of exposure to create a cumulative exposure variable (140). In a study that examined the validity of CANJEM in comparison to the expert assessment approach, the impact of different approaches for exposure categorization using the probability of exposure was examined; thresholds between 25% to 50% were reported to be the most valid (89). Therefore, in this thesis to ensure the robustness of study findings, additional sensitivity analyses were conducted modifying the definition of "Exposed" based on the probability of exposure threshold of 50% rather than 25% (in our main analysis). As expected, raising the threshold of probability of exposure used to define exposed jobs led to a smaller number of agents that were retained for analysis. Among those, occupational exposure to aliphatic aldehydes and cleaning agents were the only associations from the main analysis that remained and with considerably wider 95% CIs. Overall, prioritizing the specificity of our exposure assessment approach, i.e., by setting the threshold of 50% versus 25%, at this hypothesis generating stage may be preferable to use especially for more prevalent agents.

6.3.2.1 Outcome misclassification

Lung cancer cases in this thesis were identified through a linkage of CARTaGENE participants to the RAMQ administrative database. Given, the validity of RAMQ for identifying patients and its universal coverage in the province of Québec, it is highly unlikely that cases and sub-cohorts were misclassified.

6.3.3 Confounding

Confounding is a potential threat to the internal validity of any epidemiological study. Broadly, there are two main approaches for adjustment-variable selection: knowledge-based and empirically-based approaches. DAG is a knowledge-based approach that is suitable when there is a considerable literature regarding a given disease (141). In this thesis, potential confounding factors were identified *a priori* through a comprehensive literature review and DAGs were used as a confounder selection strategy. The minimal sufficient adjustment sets for estimating the total effect of an occupational agent on lung cancer included age, sex, smoking, ETS, known occupational lung carcinogens, and family history of lung cancer. Occupational lung carcinogens were identified as a potential confounder if they were classified as human lung carcinogen by IARC. A single confounder variable was created considering these exposures together in order to reduce the number of adjusted variables in our multivariate models. However, using this approach may have introduced some misclassification since a subject with exposure to one lung carcinogen is classified as "ever" exposed similar to a participant with exposure to more than one lung carcinogen.

Moreover, to reduce the effects of collinearity between agents particularly those in the same category, separate models were used to estimate OR and 95% CI for the associations between each agent and lung cancer risk. However, given the high correlations among agents such as dusts (95), the elevated risks that were found in this category could be partially due to residual confounding by another carcinogenic dust which was not controlled for as part of our occupational lung carcinogens covariate. This may limit our ability to interpret the association observed for this category of agents. Although we attempted to control for all well-established lung cancer risk factors which were associated with occupations, there still remains uncertainty with regards to

uncontrolled confounding by outdoor air pollution. This variable was not considered as a confounder to our models since air pollution data was not available in our dataset. Finally, residual confounding may also have been an issue in our analyses due to the use of a summary variable to represent participants' exposure to established occupational lung carcinogens. Adjusting for this covariate as a dichotomized ever/never exposed variable may not have adequately captured the effects of these established lung carcinogens on lung cancer risk.

6.3.4 Other methodological considerations in this thesis

In comparison to previous studies, the main strength of this study was the ability to study a wide range of occupational agents using a prospective study design. However, given the relatively low prevalence of many occupational agents within our study population, our study had limited power to explore most associations, particularly in sex-specific analyses and among female workers.

In this cohort study, multivariable logistic regression was used to estimate OR for lung cancer risk associated with ever versus never exposure to selected prevalent agents during the longest-held job. The Cox proportional hazards regression model could have been used in our main analysis since the case-cohort design provided an opportunity to prospectively follow participants and document survival time (e.g., diagnosis of lung cancer for cases). This model has features that make it more popular than other models especially the logistic model. For example, the Cox model in contrast to logistic regression benefits from more information (i.e., the survival times and censoring) which the logistic model ignores (142). However, important assumptions such as the proportionality of the hazard ratio over time and time-independent explanatory variables must be met. In addition to checking these assumptions, the key decision is how to define the time 0 that could be an indicator of true survival time. Generally, if participants were already at risk for the

outcome prior to study entry (e.g., like in our study where occupational exposures during their longest-held job was of interest), and time and age when participants first became at risk is unknown, then true survival time is underestimated since the true survival time is left-truncated.

In occupational cancer cohort studies, left truncation occurs when a cohort consists of prevalent hires defined as workers hired prior to follow-up started (baseline). It has been shown that including prevalent hires (left-truncated data) could induce a downward bias on estimates since the proportion of workers susceptible to the effects of exposure decrease as the time between study baseline and the date of hire increased (e.g., due to for instance developing understudied cancer) (143). Consequently, in occupational cancer cohort studies, using time-on-study follow-up as survival time is questionable and using incident hires defined as workers hired during the follow-up period is advocated.

Our study consists of a mix of prevalent hires and those, who have terminated their longest-held job and so time zero was not evident. There were three possible definitions for time 0 considered including:

- Time 0 could have been defined as the time of entering to study (baseline). As discussed, participants in our cohort that comprised of prevalent hires have variable lengths of time since hire at baseline that causes left truncation and that could cause underestimation of the measures of association. Moreover, the relatively short follow-up (the median in cases = 3.35 years) demonstrates time-on-study would have unlikely affected the observed associations.
- Time 0 could have been defined as the start year/age of the longest-held job (time since hire). An issue in using time since hire is the timing of data collection on covariates. In using the Cox model, we would have to assume that information on covariates have

not changed since the starting of the longest-held job to the time that they are actually measured in our study (baseline) in order to fulfil the Cox assumption of time-independent explanatory variables. Moreover, there were 37 (8 cases and 29 sub cohorts) participants with missing data since they reported job duration rather than start age/date.

- Time 0 could have been defined as the stop year/age of the longest-held job. Of 1179 participants, 783 of the participants' longest-held jobs were their current job at the time of entering this study (mostly sub cohorts). However, for the rest, the median stop year of the longest-held job was 2001 (n=363) or the stop year was missing (n= 33; 6 cases and 27 sub cohorts). Since there is some evidence to support lung cancer risk reduction following cessation of exposure (e.g., cease of exposure to occupational agents at the longest-held job) (144), the Cox assumption of constant HR over time will not be met.

6.4 External validity

The external validity of a study is the extent to which the results of a study could be generalized to our original target population and also, to that of other target populations. CARTaGENE is the largest ongoing prospective health study of men and women, residing in metropolitan areas of Quebec, representing a total of 55.7% of the Quebec population (124). The CARTaGENE study recruited participants based on a stratified sampling of individuals from the provincial health insurance registries to ensure that the study population is representative of the Quebec population. Thus, in light of the consideration of internal validity discussed above, the findings of this case-cohort study that was nested within the CARTaGENE cohort could be generalizable to the Quebec worker population. With respects to the larger Canadian population, comparing the socio-demographic characteristics of the CARTaGENE participants with the

general population using the 2006 Canadian Census showed a general similarity in the distribution of these characteristics with the exception of education level and slightly over-representation of ethnic minorities (124). Thus, similarly, the characteristics of our study population should allow our results to be generalizable to Canadian workers. As for other target populations beyond Canada, there is no reason to believe the any of the associations observed in this study would not be generalizable to other populations.

6.5 Conclusion and future directions

This thesis used the unique opportunity offered by the CARTaGENE prospective cohort study and the availability of CANJEM to investigate the role of a variety of occupational agents in the development of lung cancer. Our results show an excess risk of lung cancer in relation to occupational exposure to several agents including ashes, calcium sulfate, hydrogen chloride, formaldehyde, cooking fumes, alkanes, aliphatic aldehydes, and cleaning agents. Interestingly, occupational exposure to carbon monoxide and PAHs from petroleum were associated with a reduction in lung cancer risk. Moreover, among those limited agents with a sufficient number of cases in both female and male workers, generally, female workers were found to have a higher risk of developing lung cancer.

Future dose-response investigations and mechanistic studies are needed to explore the human carcinogenicity of these agents. Moreover, an important aspect of lung cancer that this thesis was unable to examine was whether associations differed by the main histological types of lung cancer risk that should be explored in the future studies.

Occupational lung cancer is an important public health issue since workers spend a large portion of their days in the working environment where they may be exposed to higher levels of potentially harmful lung carcinogens than those found in the general population. Through the

continued evaluation of the occupational exposures in different study populations, the etiology and pathogenesis of lung cancer can be better understood which are essential in refining public health efforts to reduce lung cancer incidence.

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Appendix I. The longest held job questionnaire

10.1) Considering the occupation you held for the longest time, what kind of business, industry or service was it?

1	☐	Agriculture, hunting and forestry
2	☐	Fishing
3	☐	Mining and quarrying
4	☐	Manufacturing
5	☐	Electricity, gas and water supply
6	☐	Construction
7	☐	Wholesale and retail trade; repair of motor vehicles, motorcycles and personal and household goods
8	☐	Hotels and restaurants
9	☐	Transport, storage and communications
10	☐	Financial intermediation
11	☐	Real estate, renting and business activities
12	☐	Public administration and defence; compulsory social security
13	☐	Education
14	☐	Health and social work
15	☐	Other community, social and personal service activities
16	☐	Activities of private households as employers and undifferentiated production activities of private households
17	☐	Extraterritorial organizations and bodies
77	☐	Other
88	☐	Prefer not to answer
99	☐	Don't know

Specifications: The list describes the economic activities of the industry: e.g., agriculture, hunting and related service activities.

Skip pattern: If PREFER NOT TO ANSWER or DON'T KNOW, go to 11, page 26.

10.2) Can you be more precise about the kind of business, industry or service it was?

OPEN_____

88	☐	Prefer not to answer
99	☐	Don't know

11) What was the job title of the occupation that you have held for the longest time?

1 ☐ Legislators, senior-officials and managers
2 ☐ Professionals
3 ☐ Technicians and associate professionals
4 ☐ Clerks
5 ☐ Service workers and shop and market sales workers
6 ☐ Skilled agricultural and fishery workers
7 ☐ Craft and related workers
8 ☐ Plant and machine operators and assemblers
9 ☐ Elementary occupations
10 ☐ Armed forces
77 ☐ Other
88 ☐ Prefer not to answer
99 ☐ Don't know

12) What was your age when you started working there? Or, in what year did you start working there?

____Age when started working there

OR

____Date when started working there (year)

8888 ☐ Prefer not to answer
9999 ☐ Don't know

13) Considering the occupation you held for the longest time, which of the following best describes your working schedule for this occupation?

1	☐	Regular - daytime schedule or shift
2	☐	Regular - evening shift
3	☐	Regular - night shift
4	☐	Rotating shift, changing periodically from days to evenings or to nights
5	☐	Split shift, consisting of two or more distinct periods each day
6	☐	Irregular schedule, or on call
7	☐	Other
88	☐	Prefer not to answer
99	☐	Don't know

Specifications: A night shift is work during the early hours of the morning, after midnight. An evening shift is work during the evening ending at or before midnight.

14) What was your age when you stopped working there? Or, in what year did you stop working there?

____Age when stopped working there

OR

____Date when stopped working there (year)

8888	☐	Prefer not to answer
9999	☐	Don't know

Appendix II. Job history questionnaire

SECTION - 5 OCCUPATIONAL HISTORY (read instructions on page 2)

Have you ever have a job for more than 3 months? ☐ Yes [**If Yes**, complete the following questions] ☐ No [**If No**, go to section 8]

1- Job title: _____ eg. Automobile machinist

2 - Job description: _____

e.g. Repaired transmissions and brakes; cleaned and degreased parts;

3 - Please indicate the start and end dates of your most recent job: For ongoing job please indicate the current month and year as end date.

- Start date :_____/_____ (mm/yyyy)
- End date :_____/_____ (mm/yyyy)

3.1 - If you cannot remember the exact dates, estimate the duration of this job: _____ months, _____ years

4 – Company's name: _____ eg. DEF Automotive Inc.

5 - What does (or did) your company do at this site?

_____

eg. Full service vehicule maintenance and car repairs

6 - Do you agree to provide the FULL address of this company? ☐ Yes ☐ No, **If Yes**, go to question 7]

6.1 - If No, do you agree to provide ONLY the first 3 characters of the postal code? ☐ Yes ☐ No

[**If Yes**, complete only the **postal code** field in the ADDRESS box at the bottom of the page] **[If No**, go to question 8]

7 - What is (or was) the address of the company? Please complete the information in the ADDRESS box at the bottom of the page. If you cannot recall the exact street address, tell us the name of the nearest cross-street or the nearest town if you worked in a rural location. Specify the region if it is (or was) not a fixed workplace.

For jobs with changing work schedules, AVERAGE your work load over the whole year.

8 - On average, how many HOURS PER WEEK do (or did) you work? _____ hours ☐ Can't recall

9 - On average, how many WEEKS PER YEAR do (or did) you work? _____ weeks ☐ Can't recall

10 - On average, how many DAYS PER MONTH do (or did) you work 3 or more hours between midnight and 5am? _____ days ☐ Can't recal

11 - For this job, which of the following BEST describes your work pattern?

☐ Regular daytime schedule or shift
☐ Regular evening shift (shift ends before midnight)
☐ Regular night shift (between midnight and 5am)
☐ Other, specify_____
☐ Rotating shift, changing periodically from days to evenings or to nights
☐ Split shift, consisting of two or more distinct periods each day
☐ Irregular schedule, or on call
☐ Don't know

12 - What percentage of time do (or did you) spend working outdoors? _____% [If 0%, go to question 14**]**

13 - Do (or did you) your work require you to work outdoors in the summer months? ☐ Yes ☐ No

13.1 - If Yes, on average, how much time each day are (or were) you in the sun between 11am and 4pm?

☐ Less than 1 hour ☐ 1-2 hours ☐ 2-4 hours ☐ More than 4 ☐ Can't recall

14 - On average, how many MINUTES PER DAY do (or did) you spend commuting TO AND FROM work via the following means of transportation?

14.1 - During the summer months (June-Aug)	☐ Car _____ min/day	☐ Train _____ min/day	☐ Walk_____ min/day	
	☐ Bus _____ min/day	☐ Subway_____ min/day	☐ Other, specify_____, ____min/day	
14.2 - During the coole months (Sept-May)	☐ Car _____ min/day	☐ Train _____ min/day	☐ Walk_____ min/day	
	☐ Bus _____ min/day	☐ Subway_____ min/day	☐ Other, specify_____, ____min/day	

ADDRESS

Number Street Direction Cross street (if address unknown)

City Province Rural address: nearest town or village

Postal code Region

Appendix III. Sandwich covariance matrix estimator equation

Data in a regression setup, i.e., (y_i, x_i) for $i = 1, \ldots, n$

Distribution that is controlled by a k-dimensional parameter vector θ

An estimating function $\psi(\cdot)$ is available for this type of models such that $E[\psi(y, x, \theta)] = 0$

For the covariance matrix $S(\theta)$, a sandwich formula can be given:

$$S(\theta) = B(\theta)M(\theta)B(\theta)$$

The "bread" is the inverse of the expectation of its first derivative ψ' (again with respect to θ).

$$B(\theta) = (E[-\psi'(y, x, \theta)])^{-1}$$

The "meat" of the sandwich $M(\theta)$ is the variance of the estimating function

$$M(\theta) = VAR[\psi(y, x, \theta)]$$

Appendix IV. Research ethics board certificate

Comité d'éthique de la recherche du CHUM
Pavillon R, 900 rue St-Denis, 3e étage
Montréal (Québec) H2X 0A9

Formulaire de demande de renouvellement annuel de l'approbation d'un projet de recherche

Date de dépôt du formulaire: **2018-02-28 09:25**
Date d'approbation du projet par le CER: **2017-03-29**
Numéro(s) de projet: **2017-7178, CE 16.418 - MJB**
Statut du formulaire: **Approuvé**

Déposé par: **Lacaille, Julie**
Identifiant nagano: **Physical activity and lung cancer**
Formulaire: **F9 - 37240**

Suivi du BCER

1. **Statut de la demande:**
   Demande approuvée

2. **La demande a été traitée par :**
   Lynda Ferlatte
   date de traitement:
   2018-03-04

3. **Renouvellement accordé**
   du 28 mars 2018 au 28 mars 2019

Section 1 - Renseignements généraux

1. **Indiquez, en français, le titre complet du projet de recherche**

   Activité physique au travail et risque du cancer du poumon

2. **Indiquez le nom du chercheur responsable local (CHUM)**

Ho, Vikki

Est-ce que le chercheur principal satisfait aux exigences d'attestation de recherche du CRCHUM?

Oui

3. **Est-ce que le formulaire et/ou documents soumis au CER doivent être vus en réunion plénière (Full Board) selon les exigences des organismes subventionnaires (NIH, RTOG, NCIC, etc.)**

Non

4. **Indiquez le statut actuel du projet de recherche**

Projet en cours pour lequel aucun participant n'a encore été recruté dans notre établissement

Donnez-en la raison:

Il n'y aura aucun participants recrutés pour ce projet. (étude sur banque de données dénominalisées)

Section 2 - Projet de recherche

1. **Date à laquelle le projet de recherche a commencé:**

2017-04-01

2. **Date à laquelle le projet de recherche devrait se terminer:**

2019-03-31

3. **Quel est le profil des participants de recherche?**

Quel est le sexe des participants à la recherche?

- ☐ Hommes
- ☐ Femmes
- ☐ Autres

Quel est le niveau d'aptitude des participants à la recherche?

- ☐ Majeurs aptes
- ☐ Majeurs inaptes
- ☐ Mineurs
- ☐ Majeurs, mais dont l'inaptitude est subite

Informations complémentaires des participants à la recherche?

- ☐ Membres du personnel de l'établissement
- ☐ Personnes recrutées dans un groupe témoin
- ☐ Personnes hospitalisées
- ☐ Personnes vues en consultation (consultation externe, clinique privée, hôpital de jour, etc.)
- ☐ Personnes qui se présentent à l'urgence de l'établissement
- ☐ Personnes proches des sujets
- ☐ Personnes touchées par un programme ciblé (précisez)
- ☑ Autre, spécifiez

Précisions complémentaires

Le Canadian Partnership for Tomorrow Project est une plateforme de recherche sur la santé de la population qui contient une multitude de données de plus de 300 000 Canadiens et canadiennes âgés de 35-69 au moment de leur enrôlement dans une étude régionale de cohorte mené dans différentes provinces canadiennes.

4. **Veuillez cocher "oui" si votre projet est une banque ou une étude sur dossiers. Si vous cochez "OUI" à cette question, vous pouvez répondre "0" aux questions obligatoires du point 5 (question suivante).**

Oui

5. **Informations relatives aux participants CHUM/CRCHUM:**

Nombre de participants à recruter initialement:

0

Nombre de participants qui ont effectivement été recrutés:

0

Nombre de participants dont la participation n'est pas terminée (suivi en cours):

0

Nombre de participants dont la participation est terminée:

0

Nombre de participants ayant abandonné (retrait volontaire):

0

Nombre de participants exclus ou retirés du projet:

0

Section 3 - Informations autres centres

1.

S'agit-il d'un projet multicentrique ?

Non

Section 4 - Dernière année

1. **Au cours de la dernière année et par rapport à la situation au moment de la dernière approbation du CÉR :**

Avez-vous rapporté tous les effets indésirables graves au Comité d'éthique depuis la dernière approbation du CÉR ?

- ☐ OUI
- ☑ NON
- ☐ N/A

Si non, veuillez en informer le CÉR via un formulaire F3 ou F4 selon le cas et joindre les documents pertinents.

Avez-vous rapporté tous les changements ou amendements (protocole, formulaire de consentement, etc.) depuis la dernière approbation du CÉR ?

- ☑ OUI
- ☐ NON
- ☐ N/A

Signature

1. **J'atteste que les renseignements fournis dans le présent formulaire sont exacts.**

Nom et prénom de la personne qui a complété ce formulaire

Lacaille Julie