Received: 6 September 2023 | Revised: 19 November 2023 | Accepted: 22 December 2023

DOI: 10.1002/ajim.23562

RESEARCH ARTICLE

AMERICAN JOURNAL OF INDUSTRIAL MEDICINE WILEY

Prevalent occupational exposures and risk of lung cancer among women: Results from the application of the Canadian Job-Exposure Matrix (CANJEM) to a combined set of ten case–control studies

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Funding information
Santé Publique France; Fondation pour la Recherche Médicale; French National Institute of Cancer (INCA); Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail; Institut de Recherche Robert-Sauvé en Santé et en Sécurité du Travail; Agence Nationale de la Recherche; Fonds de Recherche du Québec - Santé; Canadian Cancer Society; Intramural Research Program of NIH, National Cancer Institute, Division of Cancer Epidemiology and Genetics and the Center for Cancer Research; French Ministry of Labour (Direction Générale du Travail); French Ministry of work, solidarity and public function (Direction Générale de la Santé); Fondation de France; Association for Research on Cancer (ARC); Canadian Institutes for Health Research, Grant/Award Number: MOP-14704; German Federal Ministry of Education, Science, Research, and Technology, Grant/Award Number: 01 HK 173/0

Abstract

Background: Worldwide, lung cancer is the second leading cause of cancer death in women. The present study explored associations between occupational exposures that are prevalent among women, and lung cancer.

Methods: Data from 10 case–control studies of lung cancer from Europe, Canada, and New Zealand conducted between 1988 and 2008 were combined. Lifetime occupational history and information on nonoccupational factors including smoking were available for 3040 incident lung cancer cases and 4187 controls. We linked each reported job to the Canadian Job-Exposure Matrix (CANJEM), which provided estimates of probability, intensity, and frequency of exposure to each selected agent in each job. For this analysis, we selected 15 agents (cleaning agents, biocides, cotton dust, synthetic fibers, formaldehyde, cooking fumes, organic solvents, cellulose, polycyclic aromatic hydrocarbons from petroleum, ammonia, metallic dust, alkanes C18+, iron compounds, isopropanol, and calcium carbonate) that had lifetime exposure prevalence of at least 5% in the combined study population. For each agent, we estimated lung cancer risk in each study center for ever-exposure, by duration of exposure, and by cumulative exposure, using separate logistic regression models adjusted for smoking and other covariates. We then estimated the meta-odds ratios using random-effects meta-analysis.

Results and Conclusions: None of the agents assessed showed consistent and compelling associations with lung cancer among women. The following agents showed elevated odds ratio in some analyses: metallic dust, iron compounds, isopropanol, and organic solvents. Future research into occupational lung cancer risk factors among women should prioritize these agents.

KEYWORDS
job-exposure matrix, lung cancer, metals, occupational exposures, women

1 | INTRODUCTION

Worldwide, lung cancer is the third most diagnosed malignant cancer and the second leading cause of cancer death in women.[1] Tobacco smoking is the leading risk factor for lung cancer in women, as well as in men. However, in Western countries, around 20% of women diagnosed with lung cancer had never smoked.[2] Numerous occupational exposures have been identified as risk factors for lung cancer.[3] Among all cancers attributed to exposure to an occupational agent by the International Agency for Research on Cancer (IARC), lung cancer was the most commonly associated cancer site.[4] As early as the 1970s, Doll and Peto estimated that approximately 5% of lung cancer mortality in US women was attributable to occupational factors.[5] Similar results were reported for occupationally-attributable lung cancer risk among female workers in Germany in the 1990s.[6] A 2017 study concluded that a set of 10 recognized occupational carcinogens accounted for 2% of all incident lung cancer cases among French women.[7] These estimates likely underestimate the real burden of occupational risk factors for lung cancer in women, since risks were only estimated for a limited number of known carcinogens.

Despite the progress in identifying occupational lung carcinogens over the past decades, epidemiologic evidence of possible carcinogenicity is still sparse or entirely lacking for many occupational exposures. Moreover, much of past occupational cancer research focused on industrial workforces in male-dominated occupations; consequently, there has been little empirical evidence on occupational exposures incurred by women and the associated cancer risks, and published studies concerning women workers tended to be small and rather underpowered.[8] In addition, it is potentially misleading to assume that women and men exposed to the same occupational agent would have the same level of risk for cancer, given the biological sex-differences in absorption rate, metabolism, and cellular response.[9,10]

In this study, we aim to explore associations between occupational exposures prevalent in women and lung cancer risk using data of female workers from 10 case–control studies of lung cancer.

2 | METHODS

2.1 | Study population

The current analysis includes female participants from 10 case–control studies of lung cancer from Europe, Canada, and New Zealand, which collected lifetime working and smoking histories of study participants, including males and females.[11–20] Data collection periods for these studies ranged from 1988 to 2008. Seven of the included studies were from Europe (France,[15] Germany,[12,14] Italy,[13,19] Poland,[16] and the UK[20]), two were from Canada,[11,18] and one from New Zealand.[17] Lifetime occupational and smoking information was mainly collected using face-to-face interviews (approximately 80%), the rest was collected using telephone interviews. Cases in each study were incident lung cancer cases confirmed by histology or cytology, ascertained from local hospitals, clinics, or cancer registries. Controls were frequency-matched (approximately 96%) or individually-matched to cases by age and were recruited from the local general population. Two studies recruited additional hospital controls.[16,18] Participation proportions in the different study centers ranged from 53% to 89% among cases and 41%–87% among controls. The current analysis included 3040 female lung cancer cases and 4187 female controls. Supporting Information S1: Table S1 presents the number of cases and controls in each of the 10 study centers and the time period during which the fieldwork was conducted. In aggregate, the 7227 female workers in the combined study population had held 25,679 jobs that lasted at least 1 year. The principal investigator(s) of each of the 10 original studies obtained ethical approval from local institutional ethics review boards, and all participants gave informed consent.

2.2 | Occupational exposure assessment

Participants' jobs were coded according to the International Standard Classification of Occupations, Revised Edition 1968 (ISCO-68).[21] Occupational exposure to specific agents was assigned by linking participant's job titles to the Canadian Job-Exposure Matrix (CANJEM).

Detailed methodological descriptions of CANJEM (http://canjem.ca/) have been published.[22,23] Briefly, CANJEM is a general population job-exposure matrix (JEM) built from expert assessment of jobs held by participants in the time period 1950–2011 in five Montreal-based case-control studies (multi-site cancers,[24] lung cancer,[11] breast cancer,[25,26] and brain cancer[27]).

The same expert assessment method and the same team of experts was used in all of the studies on which CANJEM was built. When the team inferred that an agent was present in a worker's workplace, they noted the following dimensions of exposure: *confidence* that the worker really was exposed (possible, probable, or definite exposure); *intensity* (on a semi-quantitative scale by agent, where "low" represented a concentration above the background environmental level, and "high" represented the highest levels of concentration to that agent encountered in the Montreal work environment), and *frequency* of exposure (number of hours per week).

The exposure indices provided by CANJEM are formed by three axes: occupational code, time period, and agent. Each cell within CANJEM presents the proportion of all workers with a given occupation code who were considered exposed to a given agent. Further, mirroring the original expert decisions about each agent in each job, each cell describes the frequency distributions of confidence, intensity, and frequency of exposure among the workers who were considered to have been exposed.

CANJEM was built based on jobs held by all participants in the five case-control studies mentioned above, including 65% of male jobs and 35% of female jobs. Some occupations were predominantly held by males some by females, and some by both males and females. In an analysis of male-female differences in exposure assignment for job titles in which both sexes were present, it was found that for most of those job titles, there was considerable concordance in the exposure profiles between male and female workers.[28] For the present analysis, to benefit from the much larger sample, the CANJEM estimates were based on all workers, males and females.

For each of the 25,679 jobs held by women combined from the 10 study centers, we linked the ISCO-68 occupation code to CANJEM. We first attempted to link the jobs to the highest resolution (5-digit) of ISCO-68; if unlinkable at the highest resolution, we then linked them at the second highest resolution (3-digit) of ISCO-68. We were able to link CANJEM and provide estimates for 96.5% of all jobs using this strategy (83.6% of jobs were linked at the 5-digit resolution and 12.9% at the 3-digit resolution); the remaining jobs were excluded from the analysis. For each linked job, CANJEM provides the probability of exposure (ranging from 0% to 100%) to each of 258 occupational agents that were part of a checklist evaluated by the expert exposure assessors in the original case-control studies used to build CANJEM. This probability of exposure was calculated as the proportion of jobs with a given occupation code in the CANJEM source database that were considered by the experts to be exposed to the agent. When the probability of exposure to an agent is above 0%, CANJEM also provides estimates of confidence, intensity, and frequency of exposure based on the distributions of these parameters among workers who were considered exposed in the original Montreal studies. CANJEM allows the user to select any level of confidence as a threshold for considering the worker to have been "exposed", and we chose for the present analysis to include as "exposed" those exposure situations noted by the experts as Probable or Definite.

To categorize an agent's exposure status in a given job as exposed or unexposed, so as to be able to compute odds ratios, it was necessary to select a cutpoint on the probability of exposure scale. We chose a probability cutpoint of 50% (referred to as CANJEM-50%). For each combination of ISCO code and agent, when the probability of exposure was at least 50%, the job was considered as exposed to the agent, when the probability of exposure was less than 10%, the job was considered as unexposed to the agent, and when the probability of exposure was between 10% and 50%, the job was considered as "uncertainly exposed". We also conducted sensitivity

analyses changing the probability of exposure cutpoint to 25% (referred to as CANJEM-25%), where jobs with a probability of exposure of at least 25% were considered exposed, those with less than 10% were considered unexposed, and those between 10% and 25% were considered "uncertainly exposed".

2.3 | Selection of agents

It would have been untenable to present results in the present paper for all 258 agents present in CANJEM. It was necessary to significantly reduce the number of agents to be investigated. Three criteria were used: prevalence of the agent in the combined study sample, validity of CANJEM in assigning exposure to the agent, and redundancy among agents. To reduce statistical imprecision, we eliminated all agents that had very few exposed women in the combined data set for the present analysis; the operational decision was to only include agents with a lifetime ever exposed prevalence of 5% or higher in either cases or controls. When combining the 10 case–control studies and applying CANJEM-50%, this led to elimination of 232 agents. The validity of exposure assessment via CANJEM is difficult to ascertain, and it undoubtedly varies by agent. While we do not have data on the validity of the CANJEM-based assessments, we do have some data on the reliability of the assessments. Namely, using one of the Montreal case-control study datasets used to construct CANJEM as a testing ground, we applied CANJEM to the data set and we compared the resulting exposure estimates with those that had been produced originally in the case-by-case assessment of exposures by a team of experts.[29] Based on those results we further eliminated five agents with kappa values less than 0.30. Four agents were not assessed in our previous investigation[29] and were therefore excluded from the current analysis. Finally, we excluded two agents that hierarchically overlapped with other more specific agents (i.e., fabric dusts overlapped with cotton dust and synthetic fibers; aliphatic aldehydes overlapped with formaldehyde). Following these exclusions, we were left with the following 15 agents that form the focus of the present paper (listed in descending prevalence among cases): cleaning agents, biocides, cotton dust, synthetic fibers, formaldehyde, cooking fumes, organic solvents, cellulose, polycyclic aromatic hydrocarbons (PAHs) from petroleum, ammonia, metallic dust, alkanes C18+ (e.g., petroleum jelly), iron compounds, isopropanol, and calcium carbonate. As can be seen, this is an eclectic list that contains specific well-defined chemicals, families of chemicals, and general use categories. The agents were not selected based on previous evidence of lung carcinogenicity; thus, we adopted an attitude of pure exploration, allowing the data to drive the results. For the selected agents, Kappa values calculated from our above-mentioned investigation were above 0.70 for four agents, between 0.40 and 0.69 for six agents, and between 0.30 and 0.39 for five agents.[29]

2.4 | Exposure variables

For each of the 15 selected agents we conducted risk analyses in relation to the following metrics of exposure: ever exposure (never, uncertain, ever); duration of exposure (never, 1–10 years, >10 years); and cumulative exposure (CE). A participant would be considered "ever exposed" to an agent if any of her jobs exposed her to that agent. Duration of exposure was calculated as the sum of self-reported duration of each job in which the participant was exposed to an agent. CE was calculated as: $CE = \sum_{i=1}^{d} \frac{I_i}{25} \times \frac{F_i}{40}$, where i represents the ith year, d represents the total number of years exposed, Ii represents the intensity of exposure in year i, and Fi represents the number of hours exposed per week in year i. The values of Ii were transformed from low, medium, high to ratios of 1, 5, and 25 as these were the approximate ratios of intensity that the experts had in mind when coding intensity of exposure for most agents. The formula for cumulative exposure assigns equal weights to the intensity and frequency of exposure through dividing each measure by their highest value. We further categorized CE into three groups (never, ≤ median CE, > median CE) based on agent-specific median values among exposed controls. Participants with uncertain exposure were excluded from the duration or CE analyses.

2.5 | Statistical analysis

Unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of lung cancer associated with each agent's various exposure metrics in each of the 10 case–control studies, separately. The reference unexposed category for computation of the ORs for a given agent comprised participants who were never exposed to that agent. Models were adjusted for age (log-transformed), cigarette pack-years (log [pack-years +1]; pack-year was calculated as duration (years) × average cigarette smoking intensity per day/20),[30] years since quitting smoking cigarettes, ever employed in a blue-collar job (defined as jobs with an ISCO-68 first digit of 7, 8, or 9), and socioeconomic status (SES). In all study centers except New Zealand, education (no formal education, some primary, primary/some secondary, secondary/some college, and university) was used as the proxy for SES covariate adjustment, and in New Zealand, the Socio-Economic Index (NZSEI) was used as the proxy for SES.[31] The main analyses were conducted to assess ORs associated with exposure to each agent and lung cancer risk in all participating women, by smoking stratum, and by lung cancer histological subtypes. Smoking stratified analyses were conducted among never-, light-, and heavy smokers, separately. Light- and heavy smokers were categorized based on the median value of pack-years among controls who were ever-smokers. lung subtype analyses were conducted for the three most prevalent lung cancer histological subtypes: adenocarcinoma, squamous cell carcinoma, and small cell lung carcinoma. ORs and 95% CIs for each agent from each separate study center were then agglomerated using random-effects meta-analysis, and heterogeneity among studies was assessed using I^2 statistics.[32]

As sensitivity analyses, meta-analyzed lung cancer risks associated with exposure to each selected agent estimated using CANJEM-25%, instead of CANJEM-50%, were estimated for all women, and by

smoking stratum. In addition, we also performed pooled analyses on the association between exposure to each agent and lung cancer, including women from all ten participating study centers. Pooled analysis for each agent was adjusted for the same set of covariates included in the main meta-analysis. Study center was additionally included as a covariate. Because education data were unavailable in the New Zealand study, a category called "unavailable data" was assigned to all observations from this study center for the "education" covariate. Finally, we performed sensitivity analyses adjusting for a reduced set of covariates (only age and smoking) for the meta-analysis of associations between ever exposure to each agent and lung cancer risk among all women.

Note on "statistical significance". The concept of "statistical significance" is frequently misused and misinterpreted.[33] In the context of this study, the use of accurate wording that avoids the somewhat clichéd and objectionable "statistical significance" terminology would significantly burden the text. Our use of that terminology here is a convenient and widely understood shorthand for much longer and more accurate phrases to indicate that an observed OR estimate deviates from 1.0 in a way that is highly unlikely to be explained by natural statistical variability. We do not impute a causal interpretation on the use of this terminology.

Analyses were performed with R (V 4.3.0). Meta-analyses were performed with the "meta" package.[34]

3 | RESULTS

Selected socio-demographic, smoking, and occupational characteristics of 3040 female lung cancer cases and 4187 female controls in the 10 case–control studies are presented in Table 1. Both cases and controls had a median age of 61 years. Socioeconomic status represented by education was available in nine study centers and was lower in cases than in controls. In all study centers, lung cancer cases were more likely to be smokers and to smoke more than controls. The median number of jobs held was three for both cases and controls; however, the proportion of women who had ever held blue-collar jobs was higher in cases.

3.1 | Selected occupational agents

Supporting Information S1: Table S2 shows the definition of each included agent, up to five most prevalent occupations (ISCO-68 job titles) classified as ever exposed to that agent based on CANJEM-50% in our study sample of women, and the prevalence of lifetime exposure to each agent. Comparing the crude prevalence between cases and controls, we note that most of the prevalence estimates were higher among cases, and noticeably so for the following agents: alkanes C18+, iron compounds, metallic dust, organic solvents, cooking fumes, isopropanol, and PAHs from petroleum.

TABLE 1 Characteristics of women included in the 10 case–control studies of lung cancer; frequency distributions among cases and among controls.

Selected characteristics	Cases (n = 3040)	Controls (n = 4187)
Study centers		
Canada-Montreal[11]	14.1%	13.6%
Canada-Toronto[18]	6.4%	11.8%
France (10 departments)[15]	20.0%	18.0%
Germany-Munich plus selected regions[12]	16.8%	12.9%
Germany-Bremen[14]	5.4%	3.9%
Italy-Lombardy[13]	11.8%	10.9%
Italy-Turin and Veneto[19]	4.9%	6.0%
New Zealand[17]	7.5%	8.5%
Poland-Lodz and Warsaw[16]	7.8%	6.2%
United Kingdom-Liverpool[20]	5.2%	8.2%
Age (median in years [25%–75% percentile])	61 [53–68]	61 [53–69]
Education[a]		
University	11.6%	18.3%
Secondary/Some college (10–13 yrs)	20.5%	23.6%
Primary/Some secondary (6–9 yrs)	42.3%	33.2%
Some primary (< 6 yrs)	14.6%	13.7%
No formal education	0.8%	0.9%
Not available	10.1%	10.3%
Ever held blue-collar job(s)	48.6%	38.5%
Number of jobs held for at least a year (median)	3	3
Smoking status		
Never smoker	23.8%	58.9%
Former smoker	22.8%	22.0%
Current smoker	52.7%	18.4%
Missing	0.7%	0.7%
Pack-years (median among smokers)	31.5	14.7

[a]Information on education was available for all study centers except for New Zealand. For New Zealand, as a proxy socioeconomic status variable, we used a variable derived from the occupational class of the longest held occupation of the participant. Occupational class was determined using a classification of New Zealand occupations based on average levels of income and education in national census data. Values ranged from 10 (lowest class) to 90 (highest class). The median values of this variable among the New Zealand study participants were: 38.3 among cases and 34.0 among controls.

3.2 | Occupational agents and lung cancer risk among women in 10 case–control studies, overall and among never-smokers

Counting the main analyses and all the sensitivity and subgroup analyses, we derived 330 estimates of the OR between each agent and lung cancer. Most of these results are presented in Supporting Information S1: Tables S3–S8. Table 2 presents six of the results for each agent that we believe are most informative in inferring whether there is evidence of an association. The selected results in Table 2 include results for ever exposure to each agent estimated using CANJEM-50% and CANJEM-25%, and ORs estimated using meta- and pooled-analysis. Meta-ORs are presented separately for all participants and for non-smokers only. Additional meta-ORs for >10 years of exposure and high CE exposure are presented for all participants.

The analysis of each agent was conducted in models with all covariates mentioned above, but without any of the other occupational agents. Thus, mutual confounding among the agents cannot be excluded. Never exposure to an agent under investigation was used as the referent category in all analyses.

In our main meta-analyses where exposure to agents were estimated using CANJEM-50%, there were no clear associations between any of the 15 agents and lung cancer in all women combined. But on the other hand, many of the OR results were compatible with some indication of an increase in risk. To flag those agents that exhibited "suggestive" evidence of a possible association, we implemented the following threshold criteria: the point estimate should be at least 1.10 and the lower 95%CI at least 0.90; and for inverse associations, the point estimate should be at most 0.90 and the upper 95%CI at most 1.10. With these criteria, the following agents exhibited suggestive elevated meta-ORs: isopropanol and organic solvents. There were no clear suggestive inverse associations. Sensitivity analysis re-defining agent exposure using CANJEM-25% instead of CANJEM-50% resulted in overall similar meta-ORs; for some agents, the results were more towards the null. Sensitivity analysis replacing meta-analysis with pooled logistic regression (with study center as a covariate) also yielded overall similar results; with the exception that exposures to calcium carbonate and cellulose became statistically significantly below the null. Sensitivity analyses adjusted only for age and smoking produced overall similar but slightly further from the null results to the meta-analyses that also included some socioeconomic covariates (Supporting Information S1: Table S8).

Among never-smokers, there was an increased risk of lung cancer in women exposed to metallic dust (meta-OR, 95% CI = 1.78 (1.12–2.81)) vs. those that were never exposed, and a below-the-null OR in women who were exposed to calcium carbonate (meta-OR, 95% CI = 0.61 (0.39–0.98)). In addition, there was also a suggestive positive OR in never-smokers with exposure to iron compounds. In the sensitivity analysis using CANJEM-25% to categorize exposure status (Supporting Information S1: Table S7), there were statistically significant increased risks of lung cancer in never-smokers with exposure to metallic dust and iron compounds.

3.3 | Occupational agents and lung cancer risks by histological subtypes

Table 3 presents the meta-ORs between ever exposure to each agent and each of the following histological subtypes of lung cancer: adenocarcinoma, squamous cell carcinoma, and small cell carcinoma. For alkanes C18+, there were elevated ORs of both squamous cell and small cell carcinomas. For isopropanol, cleaning agents, biocides and cooking fumes, there were elevated ORs of squamous cell carcinoma; and for metallic dust and iron compounds, there were elevated OR of small cell carcinoma. A below-the-null association was observed between formaldehyde and small-cell carcinoma. None of the 15 examined agents exhibited suggestively increased risks with lung adenocarcinoma, the most prevalent lung cancer subtype in our study population.

4 | DISCUSSION

We estimated exposure to 15 relatively prevalent occupational agents, using CANJEM, in an analysis that combined data from 10 case–control studies of lung cancer in women. Despite the fact that this was one of the largest datasets ever assembled on a variety of occupational agents and cancer among women, the power to detect risks was modest and many of the OR estimates were quite imprecise.

None of the agents analyzed manifested a pattern of results that persuasively argued for a causal association with lung cancer in our study population. The following agents exhibited some suggestively increased ORs in some of the main or subgroup analyses: metallic dust, iron compounds, isopropanol, and organic solvents. None of the associations showed high heterogeneity in OR estimates among the ten participating centers.

The paucity of previous research on occupational exposures and cancer among women makes it hard to compare our results with prior knowledge; so, for some agents, we will compare our results with prior evidence of carcinogenicity among male or female workers.

Metallic dust and iron compounds: Past occupational studies have shown excess lung cancer risk among workers exposed to compounds of chromium, nickel, beryllium, cadmium, and arsenic.[35,36] However, previous evidence regarding associations between lung cancer and iron, lead, titanium, and many other metallic compounds were inconclusive or lacking.[35,36] These studies did not focus on metallic dust specifically but rather on metal compounds in general, and they mostly included male workers. Our research team had previously conducted expert assessment of occupational exposure to a large list of agents, including metallic dust in women and men from a Montreal-area population-based case-control study.[37] The experts assigned exposure to metallic dust to jobs with exposure to any metal dusts. The specified metallic dust considered includes dust from bronze, brass, stainless steel, mild steel, aluminum alloy, chrome, iron, nickel, copper, zinc, cadmium, tin, and lead. In this Montreal-based study, men who were assigned exposure to metallic dust tended to work in heavy industries with large machine tools, whereas

TABLE 2 Odds ratio between exposure to each of 15 selected agents, estimated using CANJEM-50% and CANJEM-25%, and lung cancer risk among all women and never-smoker women, combined analysis of 10 studies.

Agent	Population	Exposure metric	CANJEM version	Statistical approach[a]	*N* exposed cases[b]	*N* exposed controls[b]	*N* never-exposed cases[b]	*N* never-exposed controls[b]	OR	95% CI
Metallic dust	All	Ever exposed	CANJEM-50%	Meta-analysis	214	190	2421	3569	1.08	0.74–1.58
	All	Ever exposed	CANJEM-50%	Pooled analysis	214	190	2421	3569	1.13	0.89–1.45
	All	Ever exposed	CANJEM-25%	Meta-analysis	310	277	2421	3569	1.09	0.81–1.48
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	46	92	608	2161	**1.78**	**1.12–2.81**
	All	> 10 years	CANJEM-50%	Meta-analysis	68	60	2421	3569	1.17	0.63–2.18
	All	High CE	CANJEM-50%	Meta-analysis	116	96	2421	3569	1.26	0.87–1.81
Calcium carbonate	All	Ever exposed	CANJEM-50%	Meta-analysis	109	330	2757	3625	0.77	0.44–1.34
	All	Ever exposed	CANJEM-50%	Pooled analysis	109	330	2757	3625	**0.62**	**0.47–0.80**
	All	Ever exposed	CANJEM-25%	Meta-analysis	183	460	2757	3625	0.82	0.53–1.26
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	35	209	658	2113	**0.61**	**0.39–0.98**
	All	> 10 years	CANJEM-50%	Meta-analysis	75	214	2757	3625	0.89	0.48–1.65
	All	High CE	CANJEM-50%	Meta-analysis	55	168	2757	3625	0.81	0.42–1.56
Cotton dust	All	Ever exposed	CANJEM-50%	Meta-analysis	606	721	2062	3005	0.92	0.73–1.17
	All	Ever exposed	CANJEM-50%	Pooled analysis	606	721	2062	3005	0.87	0.73–1.03
	All	Ever exposed	CANJEM-25%	Meta-analysis	672	823	2062	3005	0.91	0.72–1.14
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	133	448	510	1775	0.87	0.58–1.30
	All	> 10 years	CANJEM-50%	Meta-analysis	234	327	2062	3005	0.87	0.68–1.12
	All	High CE	CANJEM-50%	Meta-analysis	288	365	2062	3005	0.93	0.71–1.22
Synthetic fibers	All	Ever exposed	CANJEM-50%	Meta-analysis	521	655	2149	3137	0.91	0.75–1.10
	All	Ever exposed	CANJEM-50%	Pooled analysis	521	655	2149	3137	0.88	0.74–1.06
	All	Ever exposed	CANJEM-25%	Meta-analysis	609	734	2149	3137	0.95	0.77–1.18
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	123	415	534	1845	0.84	0.58–1.23
	All	> 10 years	CANJEM-50%	Meta-analysis	208	305	2149	3137	0.87	0.68–1.10
	All	High CE	CANJEM-50%	Meta-analysis	231	328	2149	3137	0.89	0.71–1.12
Cellulose	All	Ever exposed	CANJEM-50%	Meta-analysis	296	399	2383	3390	0.82	0.61–1.11
	All	Ever exposed	CANJEM-50%	Pooled analysis	296	399	2383	3390	**0.73**	**0.60–0.89**
	All	Ever exposed	CANJEM-25%	Meta-analysis	446	584	2383	3390	0.84	0.66–1.07
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	47	198	612	2063	0.99	0.65–1.50
	All	> 10 years	CANJEM-50%	Meta-analysis	90	132	2383	3390	0.93	0.61–1.40
	All	High CE	CANJEM-50%	Meta-analysis	153	200	2383	3390	0.90	0.63–1.31
Ammonia	All	Ever exposed	CANJEM-50%	Meta-analysis	272	293	1930	2954	1.09	0.88–1.37
	All	Ever exposed	CANJEM-50%	Pooled analysis	272	293	1930	2954	1.11	0.90–1.37

TABLE 2 (Continued)

Agent	Population	Exposure metric	CANJEM version	Statistical approach[a]	*N* exposed cases[b]	*N* exposed controls[b]	*N* never-exposed cases[b]	*N* never-exposed controls[b]	OR	95% CI
	All	Ever exposed	CANJEM-25%	Meta-analysis	893	952	1930	2954	1.06	0.90–1.25
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	74	188	461	1721	1.09	0.78–1.52
	All	> 10 years	CANJEM-50%	Meta-analysis	92	119	1930	2954	0.99	0.71–1.39
	All	High CE	CANJEM-50%	Meta-analysis	129	147	1930	2954	1.08	0.80–1.45
Formaldehyde	All	Ever exposed	CANJEM-50%	Meta-analysis	514	645	1662	2515	0.92	0.77–1.09
	All	Ever exposed	CANJEM-50%	Pooled analysis	514	645	1662	2515	0.88	0.75–1.05
	All	Ever exposed	CANJEM-25%	Meta-analysis	915	1011	1662	2515	1.01	0.87–1.17
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	107	389	443	1548	0.91	0.68–1.21
	All	> 10 years	CANJEM-50%	Meta-analysis	199	280	1662	2515	0.95	0.72–1.24
	All	High CE	CANJEM-50%	Meta-analysis	239	328	1662	2515	0.93	0.74–1.18
Cooking fumes	All	Ever exposed	CANJEM-50%	Meta-analysis	485	498	2135	3164	1.03	0.86–1.24
	All	Ever exposed	CANJEM-50%	Pooled analysis	485	498	2135	3164	1.03	0.88–1.21
	All	Ever exposed	CANJEM-25%	Meta-analysis	784	869	2135	3164	1.00	0.85–1.16
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	77	270	540	1884	0.95	0.70–1.28
	All	> 10 years	CANJEM-50%	Meta-analysis	209	188	2135	3164	1.08	0.75–1.56
	All	High CE	CANJEM-50%	Meta-analysis	247	252	2135	3164	1.08	0.85–1.37
Isopropanol	All	Ever exposed	CANJEM-50%	Meta-analysis	159	163	2011	2970	1.19	0.90–1.57
	All	Ever exposed	CANJEM-50%	Pooled analysis	159	163	2011	2970	1.16	0.89–1.51
	All	Ever exposed	CANJEM-25%	Meta-analysis	666	796	2011	2970	1.00	0.87–1.15
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	30	79	503	1784	1.46	0.89–2.42
	All	> 10 years	CANJEM-50%	Meta-analysis	69	78	2011	2970	1.14	0.67–1.95
	All	High CE	CANJEM-50%	Meta-analysis	84	82	2011	2970	1.33	0.81–2.18
Organic solvents	All	Ever exposed	CANJEM-50%	Meta-analysis	449	435	1197	1881	1.07	0.88–1.31
	All	Ever exposed	CANJEM-50%	Pooled analysis	449	435	1197	1881	1.01	0.84–1.22
	All	Ever exposed	CANJEM-25%	Meta-analysis	1240	1334	1197	1881	0.98	0.84–1.15
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	74	213	335	1130	0.98	0.70–1.39
	All	> 10 years	CANJEM-50%	Meta-analysis	157	161	1197	1881	1.18	0.88–1.58
	All	High CE	CANJEM-50%	Meta-analysis	222	219	1197	1881	1.16	0.92–1.47
Iron compounds	All	Ever exposed	CANJEM-50%	Meta-analysis	160	140	2584	3733	1.10	0.75–1.61
	All	Ever exposed	CANJEM-50%	Pooled analysis	160	140	2584	3733	1.09	0.82–1.43
	All	Ever exposed	CANJEM-25%	Meta-analysis	239	215	2584	3733	1.09	0.79–1.51
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	34	64	638	2240	1.59	0.94–2.70

(Continues)

TABLE 2 (Continued)

Agent	Population	Exposure metric	CANJEM version	Statistical approach[a]	*N* exposed cases[b]	*N* exposed controls[b]	*N* never-exposed cases[b]	*N* never-exposed controls[b]	OR	95% CI
	All	> 10 years	CANJEM-50%	Meta-analysis	50	47	2584	3733	1.15	0.54–2.45
	All	High CE	CANJEM-50%	Meta-analysis	80	73	2584	3733	1.13	0.75–1.71
Alkanes C18 +	All	Ever exposed	CANJEM-50%	Meta-analysis	183	159	2288	3350	1.14	0.86–1.51
	All	Ever exposed	CANJEM-50%	Pooled analysis	183	159	2288	3350	1.10	0.84–1.43
	All	Ever exposed	CANJEM-25%	Meta-analysis	340	349	2288	3350	0.98	0.80–1.21
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	36	82	564	1980	1.30	0.81–2.07
	All	> 10 years	CANJEM-50%	Meta-analysis	63	50	2288	3350	1.37	0.85–2.19
	All	High CE	CANJEM-50%	Meta-analysis	98	85	2288	3350	1.19	0.82–1.72
PAHs from petroleum	All	Ever exposed	CANJEM-50%	Meta-analysis	279	295	1964	2868	0.92	0.72–1.17
	All	Ever exposed	CANJEM-50%	Pooled analysis	279	295	1964	2868	0.89	0.72–1.11
	All	Ever exposed	CANJEM-25%	Meta-analysis	558	644	1964	2868	0.87	0.73–1.02
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	54	156	491	1709	1.05	0.72–1.53
	All	> 10 years	CANJEM-50%	Meta-analysis	96	105	1964	2868	1.04	0.68–1.59
	All	High CE	CANJEM-50%	Meta-analysis	164	155	1964	2868	1.06	0.78–1.45
Cleaning agents	All	Ever exposed	CANJEM-50%	Meta-analysis	1288	1508	1146	1779	0.98	0.85–1.12
	All	Ever exposed	CANJEM-50%	Pooled analysis	1288	1508	1146	1779	0.96	0.84–1.09
	All	Ever exposed	CANJEM-25%	Meta-analysis	1428	1721	1146	1779	0.98	0.85–1.12
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	259	855	305	1056	0.83	0.67–1.04
	All	> 10 years	CANJEM-50%	Meta-analysis	747	828	1146	1779	1.06	0.91–1.22
	All	High CE	CANJEM-50%	Meta-analysis	755	783	1146	1779	1.09	0.92–1.29
Biocides	All	Ever exposed	CANJEM-50%	Meta-analysis	966	1096	1544	2383	1.03	0.89–1.18
	All	Ever exposed	CANJEM-50%	Pooled analysis	966	1096	1544	2383	1.01	0.89–1.16
	All	Ever exposed	CANJEM-25%	Meta-analysis	1126	1334	1544	2383	1.03	0.90–1.17
	Never-smokers	Ever exposed	CANJEM-50%	Meta-analysis	206	610	401	1413	0.96	0.77–1.20
	All	> 10 years	CANJEM-50%	Meta-analysis	518	589	1544	2383	1.06	0.90–1.25
	All	High CE	CANJEM-50%	Meta-analysis	489	550	1544	2383	1.07	0.91–1.26

Abbreviations: CANJEM, Canadian Job-Exposure Matrix; CE, cumulative exposure; CI, confidence interval; OR, odds ratio.

[a]The final model for each study center was adjusted for age (log-transformed), cigarette smoking (log [lifetime pack-years +1], and years since quitting), ever employed in a blue-collar job (yes/no), education or NZSEI (in OCANZ study center). The Meta-OR and 95%CI for each agent-lung cancer association was calculated using random-effects meta-analysis. The pooled OR was calculated including study center as an additional covariate. Results are not shown for 1–10 years of exposure, or low CE to each agent (available on request).

[b]The number of never-exposed and ever-exposed women to an agent does not add up to the total number of participants, as there were also women with uncertain exposure, which are excluded here.

commonly exposed jobs among women included punch press operators and sheet metal workers in light industries. The main sources of exposure for women determined by the experts for the Montreal study were dusts from mild steel, brass, and bronze; iron compounds; and occasionally arc or gas welding fumes. In the present study, we observed elevated ORs among women occupationally exposed to metallic dust and iron compounds. The elevated risk seen for metallic dust might be partially attributable to exposure to iron

TABLE 3 Odds ratio between ever exposure to each of 15 selected agents, estimated using CANJEM-50%, and lung cancer in women by histological subtypes, meta-analysis of 10 studies.

		Lung cancer histological subtypes								
		Adenocarcinoma			Squamous cell carcinoma			Small cell lung carcinoma		
Agent	Exposure metrics	No. cases	Meta-OR	Meta-OR 95% CI	No. cases	Meta-OR	Meta-OR 95% CI	No. cases	Meta-OR	Meta-OR 95% CI
Metallic dust	Never exposed (Ref)[a]	1076	Ref	-	465	Ref	-	363	Ref	-
	Ever exposed	69	1.08	0.74–1.56	55	1.45	0.80–2.65	45	1.65	0.88–3.13
Calcium carbonate	Never exposed (Ref)[a]	1192	Ref	-	545	Ref	-	442	Ref	-
	Ever exposed	55	0.70	0.42–1.17	19	0.82	0.33–2.02	15	0.81	0.37–1.75
Cotton dust	Never exposed (Ref)[a]	911	Ref	-	388	Ref	-	321	Ref	-
	Ever exposed	248	0.92	0.71–1.18	141	0.98	0.63–1.51	100	0.74	0.51–1.07
Synthetic fibers	Never exposed (Ref)[a]	943	Ref	-	406	Ref	-	336	Ref	-
	Ever exposed	222	0.99	0.78–1.26	114	0.93	0.61–1.42	82	0.78	0.52–1.16
Cellulose	Never exposed (Ref)[a]	1052	Ref	-	467	Ref	-	358	Ref	-
	Ever exposed	120	0.85	0.65–1.12	63	0.93	0.62–1.38	60	1.06	0.55–2.01
Ammonia	Never exposed (Ref)[a]	888	Ref	-	347	Ref	-	295	Ref	-
	Ever exposed	97	0.90	0.68–1.20	59	1.42	0.94–2.13	62	1.28	0.83–1.98
Formaldehyde	Never exposed (Ref)[a]	732	Ref	-	307	Ref	-	251	Ref	-
	Ever exposed	218	0.97	0.77–1.21	126	1.21	0.82–1.80	78	**0.68**	**0.47–0.99**
Cooking fumes	Never exposed (Ref)[a]	948	Ref	-	405	Ref	-	320	Ref	-
	Ever exposed	194	1.02	0.82–1.28	106	1.27	0.92–1.76	93	1.20	0.84–1.73
Isopropanol	Never exposed (Ref)[a]	893	Ref	-	374	Ref	-	314	Ref	-
	Ever exposed	64	1.16	0.82–1.65	36	**1.99**	**1.04–3.80**	30	1.40	0.80–2.45
Organic solvents	Never exposed (Ref)[a]	565	Ref	-	210	Ref	-	174	Ref	-
	Ever exposed	174	0.97	0.75–1.24	86	1.06	0.64–1.75	80	0.97	0.65–1.47
Iron compounds	Never exposed (Ref)[a]	1138	Ref	-	499	Ref	-	393	Ref	-
	Ever exposed	50	1.09	0.73–1.63	42	1.33	0.76–2.33	38	1.99	0.94–4.25
Alkanes C18 +	Never exposed (Ref)[a]	1037	Ref	-	424	Ref	-	344	Ref	-
	Ever exposed	53	0.95	0.64–1.41	48	1.49	0.93–2.40	42	**1.90**	**1.13–3.19**
PAHs from petroleum	Never exposed (Ref)[a]	911	Ref	-	368	Ref	-	280	Ref	-
	Ever exposed	92	0.75	0.52–1.08	70	1.14	0.77–1.69	58	1.28	0.82–2.00
Cleaning agents	Never exposed (Ref)[a]	541	Ref	-	190	Ref	-	166	Ref	-
	Ever exposed	513	0.85	0.72–1.01	283	**1.42**	**1.08–1.86**	225	0.88	0.63–1.22
Biocides	Never exposed (Ref)[a]	713	Ref	-	271	Ref	-	234	Ref	-
	Ever exposed	389	0.95	0.80–1.13	217	**1.38**	**1.01–1.88**	170	0.96	0.72–1.29

Abbreviations: CANJEM, Canadian Job-Exposure Matrix; CI, confidence interval; OR, odds ratio.

[a]The number of never-exposed and ever-exposed cases to an agent does not add up to the number of cases for each lung cancer subtype, as there were also cases with uncertain exposure, which are excluded here.

compounds. Occupational exposures during iron and steel founding, and welding fumes, have been classified as causes of lung cancer by IARC.[4]

Organic solvents: Occupational exposure to organic solvents was associated with a weakly suggestive elevated risk of lung cancer in our study. An occupational case-control study conducted in France has reported a positive association between lung cancer risk and women ever exposed to perchloroethylene, a common chlorinated solvent.[38]

Isopropanol: We observed a suggestive positive risk among women occupationally exposed to isopropanol, but no prior publications were identified for this agent among women.

Calcium carbonate: There were below-the null ORs associated with exposure to calcium carbonate among our study population of women. Teaching is the predominant occupation with this exposure, because of chalk use, and female teachers have been reported to have a lower lung cancer risk when compared to those in other occupations. In the large NOCCA study with 45-year follow-up data on cancer incidence by occupational category for 15 million people, the standardized incidence ratio of lung cancer among female teachers was 0.55 (95%CI, 0.53–0.58).[39] It is thought that non-occupational confounders (namely, smoking) may be responsible for low lung cancer risks among teachers,[40] and this may also explain a low risk among women exposed to calcium carbonate.

Cotton dust: It has been hypothesized that the presence of endotoxin in cotton textile manufacturing and agriculture industries could be protective for lung cancer.[41] In our analysis, the association between cotton dust and lung cancer was rather null. Most women exposed to cotton dust in our study population were sewers, tailors, and dressmakers, and hence had only worked with finished products of chemically treated cotton textiles; whereas endotoxin is mostly found at earlier stages of textile manufacturing where workers are exposed to raw cotton.

In our lung cancer histological subtype analyses, there were statistically significant positive associations between exposure to several agents (isopropanol, alkanes C18+, cleaning agents, and biocides) and risk for squamous cell carcinoma or small cell lung carcinoma, but not for adenocarcinoma. Since adenocarcinoma is less strongly associated with smoking compared to the other two examined subtypes,[42] it is possible that the increased risks observed for different agents and squamous cell carcinoma or small cell lung carcinoma could be partially attributed to residual confounding due to smoking or to the particular susceptibility of these cell types of tumors to chemical carcinogenesis. Most previous studies of occupational risk factors for lung cancer were underpowered to examine histological subtypes in women. Our study did not find clear associations between selected occupational risk factors and adenocarcinoma, the most prevalent subtype of lung cancer in women. Similar null findings for occupational exposures were also reported in a lung cancer study conducted among nonsmoking women in Germany.[43]

We chose to use random-effects meta-analysis instead of pooled logistic regression as the main analysis to examine lung cancer association with each agent. The choice between the two modeling approaches represents a trade-off between bias and precision. Compared to pooled analysis, meta-analysis provides a better control for confounding since it allows the effect of confounders to differ by study center and therefore reduces bias at the cost of increasing variance.[44] The meta-analysis approach also allowed the use of all available information for model adjustment, including different SES proxies in participating centers. Given that we have a relatively large sample of women in most of the study centers, we were able to carry out separate logistic regression analyses in each center and derive informative ORs for the meta-analyses. However, depending on the agent, for some subgroup meta-analyses, small numbers led to imprecise OR estimates. We also performed sensitivity analysis examining agent-lung cancer associations using the pooled logistic regression approach, which yielded similar results to those observed in the meta-analyses.

For the present study, separate models were conducted for our meta-analyses of lung cancer risk associated with each agent. Since models were not mutually adjusted for the presence of other occupational agents under investigation, there may be some mutual confounding if there are true risk factors among the selected agents.

We estimated women's occupational exposure to each agent using three exposure metrics: ever exposure, duration of exposure, and cumulative exposure. In the present analysis, we did not examine the effects associated with lagged exposure to each agent, nor did we examine peak exposure, which might also be a factor for lung carcinogenesis for some agents. We reasoned that there were already a huge number of analyses presented in this paper and that the further proliferation of models and results, at a cost of numbing the reader's attention, would do little to clarify possible causal associations.

Using CANJEM, we were able to assess women's lifetime occupational exposures to various agents for a large-scale analysis of ten case-control studies of lung cancer. Such an endeavor of assigning agent-specific exposure in a large study population with lifetime occupational histories would not have been feasible using case-by-case expert assessment due to cost and time constraints. CANJEM, like other JEMs, represents a reproducible and efficient tool that offers a transparent and systematic way to translate job titles into specific exposures, guaranteeing a standardized exposure assessment within and between different studies.[45–47] But there are certainly limitations to the validity of deriving exposure data from any JEM such as CANJEM.

The construction of a JEM can be accomplished in many ways with different degrees of expertise and data-based evidence. The validity of JEM entries depends on these factors, and they are difficult to discern, as JEM builders themselves are usually unable to objectively estimate the validity of the data in the JEM given a lack of available true gold standard measurement of past exposures. CANJEM was built from a large database of exposure assessments by “experts” in a series of case-control studies conducted in Montreal and involving job histories spanning about 50 years. The team of experts used a variety of information sources to derive their exposure estimates. Still, like any other JEM, CANJEM is premised on the notion that workers with the same job title, as encapsulated in a given occupational classification system, share similar occupational exposures. This may be true for some occupations and agents, but not all. There is exposure variability among workers who have the same occupation, and this is not normally captured in a JEM. To partially remediate the magnitude of exposure misclassification in our study, we classified exposures with a probability below but relatively close to the chosen cutpoint as “uncertain exposures” and removed them from the reference category in all regression analyses. In addition, we carried out sensitivity analyses replacing CANJEM-50% with a lower probability cutpoint (CANJEM-25%) to define exposure and obtained similar results.

The use of a JEM built in a particular population to estimate exposure in different populations is another potential source of error. CANJEM was built from information about the Montreal working population during the second half of the 20th century. In the present analysis, we applied CANJEM to 10 different populations in Europe, Canada, and New Zealand. We chose participating centers in countries that underwent industrialization in similar time periods, in hope that the workplace exposure profiles in given occupations would be roughly similar.

A final source of potential error in the exposure assessment is that since CANJEM was built using source exposure data from both male and female workers, the exposure estimate output of CANJEM would not be able to distinguish any potential exposure differences, if it exists, between a female or a male worker with the same job title.

All of these sources of error would create exposure misclassification, which is expected to be non-differential by disease status since both cases and controls would be assigned the same exposure for a given job title, and therefore it would likely lead to attenuated estimates of ORs.

5 | CONCLUSION

None of the agents assessed here manifested consistently increased lung cancer risks in women. However, the following agents showed elevated ORs in some of the main or subgroup analyses: metallic dust, iron compounds, organic solvents, and isopropanol. Future research into occupational lung cancer risk factors among women should prioritize these agents.

AUTHOR CONTRIBUTIONS

Mengting Xu designed the study's analytic strategy, conducted the analysis, and drafted the final manuscript, under supervision of Jack Siemiatycki, Vikki Ho, and Lesley Richardson. Jack Siemiatycki and Jérôme Lavoué are the PIs of the CANJEM database and provided the CANJEM database for use in this project. Ann Olsson, Joachim Schüz, Marie-Elise Parent, John R. McLaughlin, Paul A. Demers, Pascal Guénel, Loredana Radoi, Heinz-Erich Wichmann, Wolfgang Ahrens, Karl-Heinz Jöckel, Dario Consonni, Maria Teresa Landi, Loredana Radoi, Lorenzo Simonato, Andrea 't Mannetje, Beata Świątkowska, John K. Field, Neil Pearce, and Jack Siemiatycki are the PIs of the participating study centers and provided lung cancer databases for use in this project. All co-authors provided critical review of the manuscript and approved the submission of the manuscript.

ACKNOWLEDGMENTS

Mengting Xu was supported by the Fonds de la recherche en santé du Québec and Institut de recherche Robert-Sauvé en santé et en sécurité du travail. The participating case-control studies were funded by: the French National Research Agency (ANR); the French National Institute of Cancer (INCA); the French Agency for Food, Environmental and Occupational Health and Safety (ANSES); the National Agency of Public Health (Santé Publique France); the Foundation for Medical Research (FRM); the Foundation of France; the Association for Research on Cancer (ARC); the French Ministry of Labour (Direction Générale du Travail); the French Ministry of work, solidarity and public function (Direction Générale de la Santé); the German Federal Ministry of Education, Science, Research, and Technology (grant no. 01 HK 173/0); the Intramural Research Program of NIH, National Cancer Institute, Division of Cancer Epidemiology and Genetics and the Center for Cancer Research; the Canadian Cancer Society; the Fonds de recherche en santé du Québec; and the Canadian Institutes for Health Research (MOP-14704).

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

John Meyer declares that he has no conflict of interest in the review and publication decision regarding this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study can be requested from the corresponding author who will in turn make the request to each of the participating center Principal Investigators, who are located in several different countries and operate under their respective national data protection regulations.

ETHICS APPROVAL AND INFORMED CONSENT

The principal investigators of each of the 10 original studies that contributed data to this analysis obtained ethical approval from local institutional ethics review boards, and all participants gave written informed consent.

DISCLAIMER

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Xu M, Ho V, Lavoué J, et al. Prevalent occupational exposures and risk of lung cancer among women: results from the application of the Canadian Job-Exposure Matrix (CANJEM) to a combined set of ten case–control studies. *Am J Ind Med*. 2024;67:200-213. doi:10.1002/ajim.23562