Original research

Occupational environment and ovarian cancer risk

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ABSTRACT

Objectives To investigate employment in an occupation or industry and specific occupational exposures in relation to ovarian cancer risk.

Methods In a population-based case–control study conducted in Montreal, Canada (2011–2016), lifetime occupational histories were collected for 491 cases of ovarian cancer and 897 controls. An industrial hygienist coded the occupation and industry of each participant's job. Associations with ovarian cancer risk were estimated for each of several occupations and industries. Job codes were linked to the Canadian job-exposure matrix, thereby generating exposure histories to many agents. The relationship between exposure to each of the 29 most prevalent agents and ovarian cancer risk was assessed. Odds ratios and 95% confidence intervals (OR (95% CI)) for associations with ovarian cancer risk were estimated using logistic regression and controlling for multiple covariates.

Results Elevated ORs (95% CI) were observed for employment ≥10 years as Accountants (2.05 (1.10 to 3.79)); Hairdressers, Barbers, Beauticians and Related Workers (3.22 (1.25 to 8.27)); Sewers and Embroiderers (1.85 (0.77 to 4.45)); and Salespeople, Shop Assistants and Demonstrators (1.45 (0.71 to 2.96)); and in the industries of Retail Trade (1.59 (1.05 to 2.39)) and Construction (2.79 (0.52 to 4.83)). Positive associations with ORs above 1.42 were seen for high cumulative exposure versus never exposure to 18 agents: cosmetic talc, ammonia, hydrogen peroxide, hair dust, synthetic fibres, polyester fibres, organic dyes and pigments, cellulose, formaldehyde, propellant gases, aliphatic alcohols, ethanol, isopropanol, fluorocarbons, alkanes (C5–C17), mononuclear aromatic hydrocarbons, polycyclic aromatic hydrocarbons from petroleum and bleaches.

Conclusions Certain occupations, industries and specific occupational exposures may be associated with ovarian cancer risk. Further research is needed to provide a more solid grounding for any inferences in this regard.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The aetiology of ovarian cancer remains poorly understood and few modifiable risk factors have been identified.
⇒ Certain occupations and workplace exposures may be associated with ovarian cancer; overall, the epidemiological evidence is limited as only a few occupations and workplace exposures have been assessed and previous studies suffer from some methodological limitations.

WHAT THIS STUDY ADDS

⇒ This population-based study aimed at generating new hypotheses explored occupations, industries and 29 specific occupational exposures in relation to ovarian cancer, adjusting for important confounders.
⇒ We observed associations suggesting that accountancy, hairdressing, sales, sewing and related occupations may be linked to excess risks.
⇒ Many of the specific occupational exposures that were suggestively associated with increased risks were related to hairdressing-related occupations. Due to imprecision of our estimates and the presence of multiple correlated exposures, inferences of these results are limited.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further population-based research is needed to evaluate possible hazards for female workers and occupations commonly held by women.

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INTRODUCTION

Established risk factors for ovarian cancer, including family history of ovarian cancer, genetic mutations, low parity, no breastfeeding and never or short duration of oral contraceptive use,[1] are not easily modifiable, thus, primary prevention is limited. Studies of migrants have shown that ovarian cancer incidence and mortality rates in immigrants drift in time to those prevalent in the host country,[2 3] suggesting that environmental factors may play a role in ovarian carcinogenesis. The occupational environment may be a source of exposures. The role of women in society has drastically changed over the past century, exemplified by the increased participation rates of women in the labour force,[4] which may have led to greater exposures to potential carcinogens in the workplace. In general, relatively few studies have evaluated occupational hazards faced by female workers compared with male workers.[5]

Past research on the occupational environment and ovarian cancer risk has examined occupations, industries and specific occupational exposures. Most research aimed at identifying occupations or industries with excess ovarian cancer risks were studies of single occupational cohorts or proportionate mortality studies[6] and often had a small number of cases, did not consider past occupations and/or lacked data on important confounders. Only a few recent studies have overcome some of these limitations.[7–10] Over all this research, occupations in which elevated risks of ovarian cancer have been reported include teachers, nurses, hairdressers, beauticians and printing industry, white-collar, and professional occupations.[6 7 10]

For specific occupational exposures, the agent which has been most studied is asbestos. It has been classified as 'carcinogenic to humans' (Group 1) by the International Agency for Research on Cancer (IARC) because of its relation with mesothelioma and cancers of the ovary, lung and larynx.[11] Ionising radiation has also been classified as a Group 1 carcinogen by IARC mainly based on evidence from animal studies while occupational studies on ionising radiation have reported inconsistent results.[12 13] Talc has received considerable attention due to controversies regarding asbestos-contaminated talc, but most research has been focused on the perineal use of talcum powder.[14] Three studies that have examined workplace exposure to talc yielded conflicting results.[15–17] Other specific exposures have been examined in relation to ovarian cancer, but with only a small number of studies of any given one.[6] Suggestive associations have been reported for occupational exposure to solvents, pesticides, textile dust, polycyclic aromatic hydrocarbons (PAHs) and diesel/gasoline.[6 12 18]

Overall, very few population-based studies have examined ovarian cancer incidence in relation to occupations, let alone for occupational exposures. Using lifetime occupational history information from a population-based case–control study, we conducted an exploratory analysis examining two dimensions of the occupational environment, employment in an occupation or industry and specific occupational exposures, with regards to ovarian cancer risk.

MATERIALS AND METHODS

Study population

The PRevention of OVArian Cancer in Quebec (PROVAQ) study has been described elsewhere.[19] Briefly, study participants were women aged 18–79 who were Canadian citizens, residents of the Greater Montreal area and able to communicate in French or English. Cases were recruited from seven Montreal hospitals between 2010 and 2016, where eligible women were newly diagnosed with epithelial ovarian cancer, including primary peritoneal and fallopian tube cancers. A total of 652 cases were eligible for inclusion into the study, of whom 78% (n=507) gave consent to participate. Interviews with cases were conducted on average 4.8 months after diagnosis. Nine participating cases were later excluded as their cancers were found to be non-epithelial or metastatic, leaving 498 cases. Population controls were identified from the Quebec Electoral List and were frequency matched to cases on 5-year age categories and electoral district. Of 1634 eligible controls, 56% (n=908) agreed to an interview. All study participants provided written informed consent.

This analysis was restricted to participants who were ever employed in a job for more than 6 months outside the home, leading to the exclusion of 5 cases and 9 controls who were exclusively homemakers or students. Four participants (2 cases, 2 controls) were further excluded due to incomplete job history, leaving 491 cases and 897 controls for the analysis.

Data collection and job coding

During an in-person interview, trained interviewers collected participants' information on sociodemographic characteristics, medical history, medication use, reproductive history, anthropometric measurements, lifestyle factors and lifetime job history. For each job held for at least 6 months, participants reported the job title, start date, end date, working hours, shift work pattern and main tasks performed. Using the job title and description of tasks, each job was assigned an occupational and industrial classification code by an industrial hygienist, blinded to participants' case–control status. Occupation was coded using the International Standard Classification of Occupations 1968 (ISCO), containing a maximum of five-digit codes. Industry was coded according to the North American Industry Classification System 2012 (NAICS), containing a maximum of seven-digit codes.

Duration of employment

We examined occupations in our study according to three-digit ISCO codes, while industries were defined according to two-digit NAICS codes. The duration of employment in a job was calculated from the job start and end dates, attributing half the duration of full-time jobs for part-time jobs. The cumulative duration of employment in an occupation or industry was calculated by summing the duration of jobs with the same ISCO or NAICS code across a participant's job history. Cumulative duration of employment in an occupation or industry was then categorised as never, <10 years and ≥10 years.

Assessment of occupational exposure

To determine participants' exposure to specific agents in the workplace, we used the Canadian job-exposure matrix (CANJEM). CANJEM was built from information on the individual expert assessment of 258 agents in over 30 000 jobs held by more than 8000 participants in four population-based case–control studies conducted in Montreal, Canada, between 1979 and 2004.[20 21] For a given occupation and time period in which the job took place, CANJEM provides estimates on the probability, concentration, frequency and reliability of exposure to an agent. Probability was evaluated as the proportion of jobs considered exposed to the agent by experts, ranging from 0% to 100%. Experts then assessed the concentration, frequency and reliability of exposure for each job and agent combination. Concentration estimates, specific to each agent, were rated as low, medium or high. Frequency of exposure was rated as the number of hours exposed to the agent per week (maximum 40 hours). Reliability signified the experts' confidence in their assessment, indicated as possible, probable or definite.

For concentration and frequency, we used the median value for an agent across all exposed jobs in CANJEM. Estimates extracted from CANJEM were restricted to those having a reliability of exposure of probable or definite. The linkage of participants' jobs to CANJEM was performed in a stepwise manner using combinations of five-digit or three-digit ISCO codes and four, two and one time periods (online supplemental table 1). Jobs that failed to link with CANJEM were excluded. As the entire job histories of 1 case and 2 controls failed to link with CANJEM, these participants were excluded. The analysis of specific occupational exposures was based on 490 cases and 895 controls.

Exposure to agents was parameterised in three ways: ever exposure, duration of exposure and cumulative exposure. Ever exposure to an agent was defined as having worked a job with a probability of exposure of ≥50% for at least two cumulative years. Participants never exposed to an agent were defined as having never been exposed to the agent at any probability of exposure. Participants who were not classified as having ever or never exposure to an agent were classified as having uncertain exposure, defined as having exclusively worked a job with either a probability of exposure >0–<50% to the agent at any

Table 1 Selected characteristics of the PROVAQ study population, n (%)

	Cases (n=491)	Controls (n=897)
Age		
<45	62 (12.6)	108 (12.0)
45–54	128 (26.1)	212 (23.6)
55–64	160 (32.6)	293 (32.7)
≥65	141 (28.7)	284 (31.7)
Ancestry*		
French Canadian	334 (68.1)	599 (66.9)
Other European	115 (23.5)	216 (24.1)
Other/Mixed	41 (8.4)	81 (9.0)
Education level		
≤High school	189 (38.5)	280 (31.2)
College, technical	143 (29.1)	270 (30.1)
≥University, undergraduate	159 (32.4)	347 (38.7)
Neighbourhood household total income (median)*†		
<$50 000	137 (28.0)	239 (26.6)
$50 000–$99 999	274 (56.0)	486 (54.2)
≥$100 000	78 (16.0)	172 (19.2)
Ever been married or lived as married		
Yes	444 (90.4)	843 (94.0)
No	47 (9.6)	54 (6.0)
Parity*		
Nulliparous	164 (33.4)	189 (21.1)
1	102 (20.8)	160 (17.9)
2	154 (31.4)	353 (39.4)
≥3	71 (14.5)	194 (21.6)
Age at first birth among parous women*		
<25	152 (48.7)	284 (41.8)
25–29	109 (34.9)	248 (36.5)
≥30	51 (16.4)	147 (21.7)
Oral contraceptive use*		
Never	104 (21.3)	169 (18.8)
<1 year	94 (19.2)	156 (17.4)
1–9 years	193 (39.5)	332 (37.0)
≥10 years	98 (20.0)	240 (26.8)
Menopausal status		
Premenopausal	159 (32.4)	283 (31.5)
Postmenopausal	320 (65.2)	588 (65.6)
Unknown	12 (2.4)	26 (2.9)
Number of jobs held‡		
<3	174 (35.4)	357 (39.8)
3–5	265 (54.0)	438 (48.8)
≥6	52 (10.6)	102 (11.4)
Age at first job		
<20	279 (56.8)	465 (51.8)
20–24	162 (33.0)	336 (37.5)
≥25	50 (10.2)	96 (10.7)
Duration of working life		
<15 years	69 (14.1)	130 (14.5)
15–29 years	190 (38.7)	321 (35.8)
≥30 years	232 (47.2)	446 (49.7)
Duration of longest held job		
<10 years	136 (27.7)	277 (30.9)
10–19 years	225 (45.8)	422 (47.0)
≥20 years	130 (26.5)	198 (22.1)

*Missing data: ancestry (1 case, 1 control), neighbourhood household total income (2 cases), parity (1 control), age at first birth among parous women (15 cases, 28 controls) and oral contraceptive use (2 cases).
†Data obtained from the 2016 Canadian Census of Population.
‡Jobs with distinct five-digit ISCO codes were enumerated.
PROVAQ, PRevention of OVArian Cancer in Quebec.

duration, or a probability of exposure of ≥50% for less than 2 cumulative years. Based on prevalence of exposure, we restricted our analysis to 29 occupational exposures that had at least 15 ever exposed cases and/or 15 ever exposed controls.

Among women ever exposed, duration of exposure to an agent was calculated by summing the duration of each job exposed to the agent across the participant's job history. Duration of exposure was categorised as never, <8 years and ≥8 years, where the cut-off of 8 years represented the mean of the median duration of exposure of each of the 29 agents among controls.

Cumulative exposure to an agent for women ever exposed was calculated using the following equation:

$$Cumulative\ exposure = \sum_{i=1}^{d} \left(\frac{C_i}{25} \times 100\right)\left(\frac{F_i}{40} \times 100\right)$$

where i refers to the ith year exposed, d refers to the total number of years exposed, C_i refers to the concentration of exposure in year i and F_i refers to the frequency of exposure in year i. Concentration categories of low, medium and high were assigned values of 1, 5 and 25, respectively, as suggested by the CANJEM Working Group.[21] Frequency of exposure values were halved for part-time jobs. The division of concentration and frequency of exposure estimates by their respective maximum values and multiplication by 100 attributed equal weights to each parameter and transformed estimates into percentages. The cumulative exposure variable for each agent was categorised as never, low and high, where the categories of 'low' and 'high' were created based on a cut-off at the 70th percentile of cumulative exposure among controls to identify participants with relatively high cumulative exposure.

Statistical analysis

Multivariable unconditional logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between each exposure variable separately and ovarian cancer risk. Confounders were identified using a directed acyclic graph (DAG)[22] (online supplemental figure 1). Age was forced into the DAG, as it was a frequency-matching factor. Education level was also forced, given that participation in the PROVAQ study was associated with education level,[19] and that education level is a strong predictor of employment in certain occupations, whereby more highly educated participating controls may be less exposed to occupational hazards. Between two minimally sufficient confounder sets identified by the DAG, we selected and adjusted for the more parsimonious set in all models, which included age (continuous), education level (<high school, high school, college/technical, undergraduate, postgraduate), ancestry (French Canadian, Other European, Other/Mixed), parity (nulliparous, 1, 2, ≥3 full-term births) and having ever been married or lived as married (yes, no). All analyses were performed using SAS V.9.4 (Cary, North Carolina).

RESULTS

Table 1 displays selected sociodemographic, reproductive, lifestyle and occupational characteristics of the PROVAQ study population. Cases and controls had similar distributions for age and ancestry, and only slight differences for other characteristics, except that a greater proportion of cases compared with controls had an education level of high school or less, shorter duration of oral contraceptive use and were nulliparous or had fewer children. More than 50% of participants had worked at least three jobs and had worked their first job below the age of 20. The majority of participants had a duration of working life

Table 2 Multivariable ORs (95% CIs) for the association between employment in an occupation and ovarian cancer risk, according to employment duration (<10 years, ≥10 years)

		Employment duration <10 years			Employment duration ≥10 years		
ISCO code	Occupation*	Ca	Co	OR†,‡ (95% CI)	Ca	Co	OR†,‡ (95% CI)
0–71	Professional Nurses	2	8	0.47 (0.10 to 2.30)	16	49	0.60 (0.32 to 1.09)
1–10	Accountants	8	12	1.45 (0.57 to 3.66)	21	23	2.05 (1.10 to 3.79)
1–32	Secondary Education Teachers	19	38	1.13 (0.62 to 2.04)	11	27	0.94 (0.45 to 1.98)
1–33	Primary Education Teachers	26	48	1.21 (0.73 to 2.00)	16	46	0.85 (0.46 to 1.57)
1–59	Authors, Journalists and Related Writers Not Elsewhere Classified	10	26	0.74 (0.34 to 1.59)	9	16	1.15 (0.49 to 2.71)
1–93	Social Workers	24	30	1.58 (0.90 to 2.78)	13	24	1.06 (0.53 to 2.15)
1–94	Personnel and Occupational Specialists	7	14	0.91 (0.36 to 2.32)	9	14	1.24 (0.52 to 2.96)
2–19	Managers Not Elsewhere Classified	37	51	1.48 (0.94 to 2.34)	30	60	1.05 (0.65 to 1.68)
3–00	Clerical Supervisors	11	18	1.00 (0.46 to 2.18)	10	15	1.05 (0.46 to 2.40)
3–21	Stenographers, Typists and Teletypists	60	113	1.01 (0.71 to 1.44)	65	115	1.03 (0.73 to 1.47)
3–31	Bookkeepers and Cashiers	88	121	1.31 (0.96 to 1.79)	37	78	0.83 (0.54 to 1.28)
3–39	Bookkeepers, Cashiers and Related Workers Not Elsewhere Classified	24	50	1.14 (0.67 to 1.93)	12	18	1.04 (0.49 to 2.24)
3–93	Correspondence and Reporting Clerks	36	86	0.71 (0.47 to 1.08)	35	50	1.08 (0.68 to 1.71)
3–94	Receptionists and Travel Agency Clerks	52	104	0.82 (0.57 to 1.18)	19	34	0.79 (0.44 to 1.43)
4–51	Salespeople, Shop Assistants and Demonstrators	66	98	1.17 (0.83 to 1.65)	15	18	1.45 (0.71 to 2.96)
5–32	Waitresses, Bartenders and Related Workers	35	58	0.97 (0.62 to 1.53)	12	14	1.23 (0.55 to 2.75)
5–40	Maids and Related Housekeeping Service Workers Not Elsewhere Classified	36	72	0.88 (0.57 to 1.35)	17	23	1.27 (0.66 to 2.45)
5–70	Hairdressers, Barbers, Beauticians and Related Workers	8	16	0.95 (0.40 to 2.29)	13	7	3.22 (1.25 to 8.27)
5–99	Other Service Workers	35	94	0.63 (0.42 to 0.96)	16	27	1.02 (0.53 to 1.94)
7–95	Sewers and Embroiderers	8	22	0.73 (0.31 to 1.70)	12	11	1.85 (0.77 to 4.45)

*Only the top 20 most prevalent occupations are presented.
†Adjusted for age, education level, ancestry, parity and ever been married or lived as married.
‡Reference group includes participants who had never been employed in a given occupation.

of 15 years or more, and their longest held job was for a duration of at least 10 years.

Given the low exposure prevalence for most occupations, industries and agents in the study population and the exploratory nature of this study, we highlight results for which the magnitude of the ORs suggested increased or decreased risks of 1.40 or greater, or 0.60 or less, respectively. Table 2 presents associations with ovarian cancer risk for employment durations of <10 and ≥10 years for the 20 most prevalent occupations. ORs suggesting elevated risks for ≥10 years of employment were observed for Salespeople, Shop Assistants and Demonstrators (OR=1.45; 95% CI 0.71 to 2.96), Sewers and Embroiderers (OR=1.85; 95% CI 0.77 to 4.45), Hairdressers, Barbers, Beauticians and Related Workers (OR=3.22; 95% CI 1.25 to 8.27) and Accountants (OR=2.05; 95% CI 1.10 to 3.79). The OR for employment for <10 years as an Accountant also suggested an increased ovarian cancer risk (OR=1.45; 95% CI 0.57 to 3.66). Decreased risks were suggested for Professional Nurses employed for <10 years (OR=0.47, 95% CI 0.10 to 2.30) and ≥10 years (OR=0.60, 95% CI 0.32 to 1.09). While ORs did not greatly deviate from the null for most industries (online supplemental table 2), increased risks were suggested for employment in the Retail Trade for ≥10 years (OR=1.59; 95% CI 1.05 to 2.39) and Construction for <10 years (OR=1.59; 95% CI 0.52 to 4.83) and ≥10 years (OR=2.79; 95% CI 0.52 to 4.83).

For the 29 specific occupational exposures, associations with ovarian cancer risk for ever and uncertain exposure are presented in table 3, and for duration and cumulative exposure are presented in table 4. Agents for which positive associations were suggested for ever exposure, duration of exposure ≥8 years and high cumulative exposure, with ORs ranging from 1.42 to 7.63, were: cosmetic talc, ammonia, hydrogen peroxide, hair dust, polyester fibres, cellulose, formaldehyde, propellant gases, ethanol, fluorocarbons, alkanes (C5–C17) and mononuclear aromatic hydrocarbons (MAHs). High cumulative exposure with ORs above 1.95 were observed for 6 additional agents: synthetic fibres, organic dyes and pigments, aliphatic alcohols, isopropanol, PAHs from petroleum and bleaches. Elevated ORs above 1.44 were also observed for uncertain exposure, duration of exposure <8 years and low cumulative exposure for three agents: cellulose, alkanes and PAHs from any source.

To address potential reverse-causality bias, we lagged the calculations of occupational exposure parameters by 5 years, where job history 5 years prior to the referent age (age of diagnosis for cases, age of interview for controls) were excluded, and similar results for the 29 agents were observed (results not shown). When we adjusted for the alternative confounder set identified by the DAG, which included age, education level, ancestry, parity, oral contraceptive use, endometriosis and history of tubal ligation, ORs for ovarian cancer with occupation, industry and specific occupational exposures did not appreciably differ (results not shown). When the uncertainly exposed were included in the reference group with the never exposed, ORs for ever exposure, duration of exposure and cumulative exposure for the 29 agents were similar (online supplemental table 3).

To further understand our findings for specific occupational exposures with respect to occupations, we calculated the distribution of jobs in the study population exposed to each agent.

Table 3 Multivariable ORs (95% CIs) for the association between ever and uncertain exposure to 29 agents and ovarian cancer risk

	Never exposed†			Uncertainly exposed‡			Ever exposed§		
Agent*	Ca	Co	OR (95% CI)	Ca	Co	OR¶ (95% CI)	Ca	Co	OR¶ (95% CI)
Cosmetic talc	357	639	1.00 (ref)	118	240	0.90 (0.69 to 1.17)	15	16	1.66 (0.80 to 3.46)
Calcium carbonate	275	432	1.00 (ref)	160	333	0.79 (0.61 to 1.02)	55	130	0.86 (0.59 to 1.26)
Ammonia	124	264	1.00 (ref)	343	603	1.02 (0.78 to 1.34)	23	28	1.42 (0.76 to 2.64)
Hydrogen peroxide	398	717	1.00 (ref)	74	159	0.85 (0.62 to 1.16)	18	19	1.61 (0.82 to 3.15)
Hair dust	403	739	1.00 (ref)	68	135	0.87 (0.63 to 1.21)	19	21	1.57 (0.82 to 3.00)
Synthetic fibres	104	219	1.00 (ref)	352	630	1.13 (0.85 to 1.49)	34	46	1.59 (0.91 to 2.77)
Polyester fibres	149	327	1.00 (ref)	317	534	1.24 (0.96 to 1.59)	24	34	1.58 (0.87 to 2.89)
Fabric dust	69	147	1.00 (ref)	379	696	1.12 (0.81 to 1.56)	42	52	1.70 (0.98 to 2.97)
Cotton dust	128	259	1.00 (ref)	323	585	1.07 (0.82 to 1.40)	39	51	1.54 (0.91 to 2.62)
Wool fibres	197	440	1.00 (ref)	282	437	1.35 (1.07 to 1.72)	11	18	1.39 (0.63 to 3.08)
Organic dyes and pigments	196	395	1.00 (ref)	283	482	1.21 (0.96 to 1.54)	11	18	1.14 (0.52 to 2.53)
Cellulose	81	209	1.00 (ref)	375	638	1.46 (1.08 to 1.97)	34	48	1.64 (0.97 to 2.79)
Aliphatic aldehydes	30	75	1.00 (ref)	396	723	1.20 (0.76 to 1.92)	64	97	1.42 (0.80 to 2.51)
Formaldehyde	52	129	1.00 (ref)	389	689	1.31 (0.91 to 1.88)	49	77	1.48 (0.88 to 2.51)
Propellant gases	170	299	1.00 (ref)	301	575	0.87 (0.68 to 1.12)	19	21	1.45 (0.74 to 2.84)
Organic solvents	28	51	1.00 (ref)	417	771	0.97 (0.59 to 1.60)	45	73	1.02 (0.55 to 1.91)
Aliphatic alcohols	37	77	1.00 (ref)	416	743	1.18 (0.77 to 1.80)	37	75	1.05 (0.59 to 1.88)
Ethanol	281	570	1.00 (ref)	190	304	1.16 (0.91 to 1.47)	19	21	1.71 (0.89 to 3.30)
Isopropanol	89	161	1.00 (ref)	368	679	0.89 (0.61 to 1.74)	33	55	1.03 (0.61 to 1.74)
Fluorocarbons	388	708	1.00 (ref)	83	166	0.85 (0.63 to 1.15)	19	21	1.55 (0.81 to 2.96)
Alkanes (C5-C17)	67	193	1.00 (ref)	409	686	1.67 (1.22 to 2.29)	14	16	2.14 (0.97 to 4.73)
MAHs	92	223	1.00 (ref)	383	661	1.37 (1.03 to 1.82)	15	11	2.77 (1.19 to 6.44)
PAHs from any source	27	77	1.00 (ref)	441	796	1.45 (0.90 to 2.31)	22	22	2.23 (1.04 to 4.78)
PAHs from petroleum	49	120	1.00 (ref)	425	761	1.25 (0.87 to 1.81)	16	14	2.26 (1.00 to 5.12)
Engine emissions	33	88	1.00 (ref)	422	750	1.34 (0.87 to 2.06)	35	57	1.51 (0.83 to 2.75)
Cooking fumes	181	364	1.00 (ref)	234	406	1.14 (0.89 to 1.46)	75	125	1.07 (0.75 to 1.53)
Cleaning agents	81	155	1.00 (ref)	246	444	1.08 (0.78 to 1.48)	163	296	1.00 (0.71 to 1.40)
Biocides	68	126	1.00 (ref)	322	551	1.04 (0.74 to 1.46)	100	218	0.80 (0.54 to 1.19)
Bleaches	283	540	1.00 (ref)	198	339	1.06 (0.83 to 1.35)	9	16	1.03 (0.44 to 2.42)

*Agents selected for analysis had at least 15 ever exposed cases and/or 15 ever exposed controls.
†Participants classified as never exposed to an agent have exclusively worked jobs with a probability of exposure of 0% to the agent.
‡Participants classified as uncertainly exposed to an agent have exclusively worked jobs with either a probability of exposure >0<50% to the agent at any duration or a probability of exposure ≥50% for <2 cumulative years.
§Participants classified as ever exposed to an agent have ever worked jobs with a probability of exposure of ≥50% to the agent for at least 2 cumulative years.
¶Adjusted for age, education level, ancestry, parity and ever been married or lived as married.
MAHs, mononuclear aromatic hydrocarbons; PAHs, polycyclic aromatic hydrocarbons.

The total number of occupations exposed to each agent and the top 75% occupations most frequently exposed to each agent, referenced by the three-digit ISCO unit group titles in which jobs are classified into, are displayed in table 5. Hairdressers, Barbers, Beauticians and Related Workers were the most frequently exposed occupations for 13 agents, while sewers and embroiderers were the top exposed occupation for textile-related agents. Among the 18 agents associated with increased risks when comparing high cumulative exposure versus never exposure in table 4, the occupation of Hairdressers, Barbers, Beauticians and Related Workers was the most frequent occupation exposed to 11 agents (ammonia, hydrogen peroxide, hair dust, organic dyes and pigments, formaldehyde, propellant gases, aliphatic alcohols, ethanol, isopropanol, fluorocarbons and bleaches) and the second most frequent occupation exposed to one agent (cosmetic talc).

We calculated pairwise Spearman's correlation coefficients of cumulative exposure for the 29 agents, for all study participants, as it was evident that participants working in certain occupations were exposed to multiple agents. Strong to very strong correlations were observed between many agents, with perfect correlations observed among textile-related agents and agents for which the occupation of Hairdressers, Barbers, Beauticians and Related Workers was the most or second most frequent occupation exposed. Given the very high to perfect correlations and limited sample size, methods to account for coexposures (eg, lasso and ridge regression) could not be performed. In a post hoc principal component analysis, aimed to reduce the dimensionality of the correlated data (results not shown), we observed, based on component loadings, that the first two components were heavily characterised by agents associated with the occupations of, respectively, Hairdressers, Barbers, Beauticians and Related Workers, Sewers and Embroiderers, and Tailors and Dressmakers. Therefore, the analysis of these components would not be distinct from the analysis of these occupations presented in table 2.

DISCUSSION

In this exploratory population-based case–control study examining the occupational environment in relation to ovarian cancer risk, we observed associations suggesting that women who had

Table 4 Multivariable ORs (95% CIs) for the association between duration and cumulative exposure to 29 agents and ovarian cancer risk

	Duration of exposure†						Cumulative exposure†					
	<8 years			≥8 years			Low			High		
Agent*	Ca	Co	OR‡§ (95% CI)	Ca	Co	OR‡§ (95% CI)	Ca	Co	OR‡§ (95% CI)	Ca	Co	OR‡§ (95% CI)
Cosmetic talc	11	12	1.68 (0.72 to 3.93)	4	4	1.51 (0.36 to 6.30)	8	11	1.34 (0.52 to 3.43)	7	5	2.25 (0.52 to 7.41)
Calcium carbonate	20	42	0.96 (0.54 to 1.71)	35	88	0.93 (0.57 to 1.51)	43	91	1.02 (0.66 to 1.58)	12	39	0.72 (0.35 to 1.50)
Ammonia	9	18	0.87 (0.35 to 2.15)	14	10	2.59 (1.03 to 6.47)	10	19	0.95 (0.40 to 2.25)	13	9	2.59 (1.00 to 6.69)
Hydrogen peroxide	5	11	0.70 (0.24 to 2.08)	13	8	2.75 (1.11 to 6.83)	8	13	1.02 (0.41 to 2.52)	10	6	2.65 (0.94 to 7.50)
Hair dust	5	12	0.70 (0.24 to 2.03)	14	9	2.60 (1.09 to 6.21)	8	14	1.01 (0.41 to 2.47)	11	7	2.45 (0.92 to 6.53)
Synthetic fibres	11	19	1.09 (0.46 to 2.59)	23	27	1.21 (0.53 to 2.78)	15	32	0.87 (0.40 to 1.89)	19	14	1.95 (0.77 to 4.94)
Polyester fibres	7	16	1.17 (0.45 to 3.06)	17	18	2.04 (0.88 to 4.72)	14	23	1.57 (0.72 to 3.42)	10	11	1.68 (0.62 to 4.58)
Fabric dust	15	23	0.97 (0.41 to 2.28)	27	29	0.98 (0.41 to 2.30)	25	36	0.97 (0.45 to 2.08)	17	16	0.97 (0.36 to 2.65)
Cotton dust	14	22	0.91 (0.41 to 2.02)	25	29	0.98 (0.45 to 2.16)	21	35	0.85 (0.42 to 1.74)	18	16	1.19 (0.49 to 2.89)
Wool fibres	3	10	0.67 (0.18 to 2.57)	8	8	2.00 (0.67 to 5.95)	8	12	1.48 (0.57 to 3.86)	3	6	0.85 (0.19 to 3.70)
Organic dyes and pigments	3	12	0.48 (0.13 to 1.79)	8	6	3.15 (1.03 to 9.63)	5	12	0.86 (0.29 to 2.57)	6	6	2.22 (0.68 to 7.26)
Cellulose	17	30	1.44 (0.71 to 2.95)	17	18	2.42 (1.12 to 5.24)	17	33	1.44 (0.72 to 2.88)	17	15	2.60 (1.15 to 5.84)
Aliphatic aldehydes	26	52	1.08 (0.48 to 2.40)	38	45	1.85 (0.78 to 4.38)	48	67	1.43 (0.67 to 3.05)	16	30	0.97 (0.35 to 2.64)
Formaldehyde	16	41	0.94 (0.44 to 2.03)	33	36	2.39 (1.10 to 5.21)	33	53	1.44 (0.74 to 2.83)	16	24	1.53 (0.60 to 3.90)
Propellant gases	5	12	0.65 (0.22 to 1.97)	14	9	2.16 (0.88 to 5.33)	7	14	0.79 (0.30 to 2.07)	12	7	2.32 (0.86 to 6.27)
Organic solvents	17	39	0.57 (0.23 to 1.40)	28	34	1.16 (0.49 to 2.73)	31	51	0.84 (0.37 to 1.91)	14	22	0.82 (0.31 to 2.19)
Aliphatic alcohols	16	36	0.87 (0.39 to 1.92)	21	39	1.18 (0.55 to 2.52)	20	52	0.74 (0.35 to 1.56)	17	23	1.75 (0.75 to 4.09)
Ethanol	5	12	0.82 (0.28 to 2.41)	14	9	3.27 (1.36 to 7.87)	7	14	1.05 (0.41 to 2.68)	12	7	3.43 (1.30 to 9.04)
Isopropanol	14	31	0.95 (0.45 to 2.01)	19	24	1.53 (0.73 to 3.21)	15	38	0.82 (0.40 to 1.67)	18	17	2.08 (0.94 to 4.58)
Fluorocarbons	5	12	0.72 (0.25 to 2.12)	14	9	2.69 (1.13 to 6.43)	7	14	0.92 (0.36 to 2.34)	12	7	2.78 (1.06 to 7.29)
Alkanes (C5-C17)	10	11	2.59 (0.97 to 6.96)	4	5	2.09 (0.52 to 8.43)	9	11	2.47 (0.91 to 6.70)	5	5	2.33 (0.61 to 8.88)
MAHs	9	9	2.14 (0.75 to 6.09)	6	2	7.63 (1.42 to 40.87)	10	7	3.28 (1.11 to 9.72)	5	4	2.81 (0.69 to 11.39)
PAHs from any source	18	14	2.51 (0.91 to 6.94)	4	8	0.62 (0.13 to 2.98)	16	15	2.08 (0.75 to 5.79)	6	7	1.38 (0.32 to 5.94)
PAHs from petroleum	14	9	3.14 (1.09 to 9.03)	2	5	1.23 (0.20 to 7.73)	10	9	2.51 (0.83 to 7.64)	6	5	2.63 (0.65 to 10.70)
Engine emissions	25	29	2.58 (1.22 to 5.43)	10	28	1.01 (0.41 to 2.49)	27	39	2.07 (1.02 to 4.22)	8	18	1.23 (0.45 to 3.35)
Cooking fumes	44	69	1.11 (0.71 to 1.74)	31	56	0.90 (0.54 to 1.50)	59	87	1.17 (0.78 to 1.76)	16	38	0.68 (0.35 to 1.29)
Cleaning agents	64	113	1.03 (0.67 to 1.57)	99	183	0.94 (0.64 to 1.39)	107	207	0.95 (0.66 to 1.38)	56	89	1.04 (0.66 to 1.64)
Biocides	30	76	0.67 (0.39 to 1.17)	70	142	0.90 (0.57 to 1.40)	58	152	0.66 (0.41 to 1.04)	42	66	1.23 (0.73 to 2.09)
Bleaches	2	10	0.37 (0.08 to 1.72)	7	6	2.27 (0.73 to 7.08)	2	11	0.35 (0.08 to 1.62)	7	5	2.61 (0.79 to 8.58)

*Agents selected for analysis had at least 15 ever exposed cases and/or 15 ever exposed controls.
†Duration and cumulative exposure variables were calculated for women classified as ever exposed.
‡Reference group includes participants classified as never exposed to the agent.
§Adjusted for age, education level, ancestry, parity and ever been married or lived as married.
MAHs, mononuclear aromatic hydrocarbons; PAHs, polycyclic aromatic hydrocarbons.

worked in accountancy, hairdressing, sales, sewing and related occupations and the retail trade and construction industries may have increased risks. Conversely, women working as professional nurses were suggested to have decreased risks. Elevated risks were observed for high cumulative exposure to 18 agents for which a large proportion of occupations exposed to 12 of these agents were hairdressing related. Given the presence of multiple correlated exposures, we are unable to determine whether the elevated risks observed for agents associated with hairdressing-related occupations were driven by a single agent, a combination of agents or other workplace factors.

Among four relatively recent studies on occupation and ovarian cancer,[7–10] the most similar to our study is a Canadian population-based case–control study by Le and colleagues[10] that collected lifetime occupational history and examined employment in an occupation or industry. In that study, consistent with our findings, working in accountancy-related occupations or in the retail store industry was suggestively associated with excess ovarian cancer risks. White-collar and professional occupations, including accountants, have also been associated with non-significant moderate increases in risk in other studies.[6 9] It has been hypothesised that the lifestyle factors of individuals working in such occupations, such as sedentary behaviour, may contribute to cancer risk.[10 23] In a post hoc analysis, we adjusted for physical activity to explore this potential pathway for the suggested increased risks in accountancy-related occupations, though our estimates did not change. However, our physical activity variable only considers recreational physical activity, which likely did not capture sedentary behaviour experienced at work.

Contrary to results from previous studies,[9 10 24–29] we observed a suggested decreased risk of ovarian cancer in nursing-related occupations and did not observe excess ovarian cancer risks in teaching-related occupations or educational and healthcare industries, regardless of employment duration. Many of these previous studies did not adjust for reproductive factors such as parity, lacked lifetime occupational history information and did not have histological confirmation of ovarian cancer, which may explain discrepancies with our findings.

Women working in hairdressing-related occupations are exposed to hundreds of chemicals at high concentrations, including hair dyes, shampoos, conditioners, styling and cosmetic products.[30] In our study, employment in hairdressing-related occupations and exposure to 12 agents prevalent in these

Table 5 Total number of exposed occupations and list of occupations exposed to each agent

Agent*	Total no. exposed occupations†‡	Occupations exposed to agent (% of total number of exposed occupations)§¶
Cosmetic talc	39	Other Service Workers (71.8), Hairdressers, Barbers, Beauticians and Related Workers (28.2)
Calcium carbonate	441	Primary Education Teachers (66.2), Secondary Education Teachers (24.5)
Ammonia	100	Hairdressers, Barbers, Beauticians and Related Workers (85.0)
Hydrogen peroxide	81	Hairdressers, Barbers, Beauticians and Related Workers (100.0)
Hair dust	87	Hairdressers, Barbers, Beauticians and Related Workers (100.0)
Synthetic fibres	145	Sewers and Embroiderers (50.3), Tailors and Dressmakers (25.5)
Polyester fibres	96	Sewers and Embroiderers (52.1), Tailors and Dressmakers (31.3)
Fabric dust	168	Sewers and Embroiderers (43.5), Tailors and Dressmakers (22.0), Launderers, Dry-Cleaners and Pressers (9.5)
Cotton dust	163	Sewers and Embroiderers (44.8), Tailors and Dressmakers (22.7), Launderers, Dry-Cleaners and Pressers (9.8)
Wool fibres	40	Tailors and Dressmakers (80.0)
Organic dyes and pigments	60	Hairdressers, Barbers, Beauticians and Related Workers (88.3)
Cellulose	127	Library and Filing Clerks (29.1), Dockers and Freight Handlers (24.4), Librarians, Archivists and Curators (15.8), Mail Distribution Clerks (7.1)
Aliphatic aldehydes	305	Hairdressers, Barbers, Beauticians and Related Workers (27.9), Sewers and Embroiderers (20.7), Cooks (15.4), Tailors and Dressmakers (11.8)
Formaldehyde	241	Hairdressers, Barbers, Beauticians and Related Workers (33.6), Sewers and Embroiderers (26.1), Cooks (19.1)
Propellant gases	87	Hairdressers, Barbers, Beauticians and Related Workers (100.0)
Organic solvents	229	Hairdressers, Barbers, Beauticians and Related Workers (38.0), Life Sciences Technicians (12.2), Dental Assistants (7.0), Commercial Artists and Designers (6.6), Sculptors, Painters and Related Artists (4.8), Printers and Related Workers Not Elsewhere Classified (4.4), Printing Press Operators (3.1)
Aliphatic alcohols	238	Hairdressers, Barbers, Beauticians and Related Workers (36.6), Professional Nurses (34.5), Life Sciences Technicians (11.8)
Ethanol	87	Hairdressers, Barbers, Beauticians and Related Workers (100.0)
Isopropanol	187	Hairdressers, Barbers, Beauticians and Related Workers (46.5), Professional Nurses (31.6)
Fluorocarbons	87	Hairdressers, Barbers, Beauticians and Related Workers (100.0)
Alkanes (C5-C17)	44	Printers and Related Workers Not Elsewhere Classified (18.2), Printing Press Operators (15.9), Chemists (13.6), Shoe Cutters, Lasters, Sewers and Related Workers (13.6), Salespeople, Shop Assistants and Demonstrators (11.4), Compositors and Type-Setters (9.1)
MAHs	35	Printers and Related Workers Not Elsewhere Classified (22.9), Printing Press Operators (20.0), Shoe Cutters, Lasters, Sewers and Related Workers (17.1), Chemists (14.3), Shoemakers and Shoe Repairers (5.7)
PAHs from any source	56	Waitresses, Bartenders and Related Workers (35.7), Commercial Travellers and Manufacturers' Agents (14.3), Printing Press Operators (12.5), Salespeople, Shop Assistants and Demonstrators (8.9), Motor-Vehicle Drivers (8.9)
PAHs from petroleum	36	Commercial Travellers and Manufacturers' Agents (22.2), Printing Press Operators (19.4), Salespeople, Shop Assistants and Demonstrators (13.9), Motor-Vehicle Drivers (13.9), Nursery Workers and Gardeners (8.3)
Engine emissions	135	Commercial Travellers and Manufacturers' Agents (28.9), Insurance, Real Estate and Securities Salespeople (27.4), Motor-Vehicle Drivers (11.1), Auctioneers (6.7), Technical Salespeople and Service Advisers (5.9)
Cooking fumes	378	Waitresses, Bartenders and Related Workers (43.1), Maids and Related Housekeeping Service Workers Not Elsewhere Classified (21.2), Cooks (19.8)
Cleaning agents	1192	Professional Nurses (26.0), Maids and Related Housekeeping Service Workers Not Elsewhere Classified (16.9), Other Service Workers (15.4), Waitresses, Bartenders and Related Workers (14.2), Hairdressers, Barbers, Beauticians and Related Workers (7.5)
Biocides	823	Professional Nurses (37.7), Other Service Workers (20.9), Maids and Related Housekeeping Service Workers Not Elsewhere Classified (10.7), Hairdressers, Barbers, Beauticians and Related Workers (10.6)
Bleaches	55	Hairdressers, Barbers, Beauticians and Related Workers (96.4)

*Agents selected for analysis had at least 15 ever exposed cases and/or 15 ever exposed controls.
†This column displays the total number of exposed occupations, based on ever exposure, for each agent examined.
‡The total number of exposed occupations differs for each agent depending on the linkage of jobs to CANJEM according to five-digit or three-digit ISCO codes and the time period in which the job took place.
§Occupations comprising the top 75% of the total number of exposed occupations are listed in descending order of frequency.
¶Denominator used to calculate the percentages of occupations exposed to an agent was the total no. exposed occupations. For example, for cosmetic talc, 71.8% of exposed jobs were Other Service Workers and 28.2% of exposed jobs were Hairdressers, Barbers, Beauticians and Related Workers.
MAHs, mononuclear aromatic hydrocarbons; PAHs, polycyclic aromatic hydrocarbons.

occupations were suggestively associated with increased risks of ovarian cancer. Out of the 12 agents, IARC has classified one agent as a Group 1 carcinogen (formaldehyde) and three agents as 'not classifiable as to its carcinogenicity to humans' (Group 3) (hydrogen peroxide, cosmetic talc, isopropanol).[31] The remaining agents have either not been specifically assessed by IARC or refer to mixtures or broad chemical classes. As well, IARC concluded that occupation as a hairdresser or barber entails exposures that are 'probably carcinogenic to humans' (Group 2A).[30] However, to date, the overall epidemiological evidence for this occupation remains inconsistent for ovarian cancer. Older studies, including three cohort studies[32–34] and two proportionate mortality studies,[35 36] observed increased ovarian cancer risks among hairdressers and beauticians, while newer studies, including one record-linkage study[7] and one case–control study,[10] did not observe excess risks. A potential explanation for the discordance in previous findings may be attributed to the ongoing phase out of carcinogenic substances (eg, dyes containing or metabolising to benzidine) in cosmetic and hair dye products since the 1960s.[37] However, further research is required to confirm these findings.

Synthetic fibres, polyester fibres, cellulose, alkanes (C5-C17), MAHs, and PAHs from petroleum were also potentially associated with ovarian cancer risk in our study population. Our findings of potential excess risks among sewing-related occupations, where exposure to synthetic and polyester fibres are frequent, were not concordant with results (adjusted for parity or mean number of children) from two cohort studies, which found that exposures to textile dusts were not associated with ovarian cancer risk.[38 39] For cellulose, a cohort study did not find an association with ovarian cancer for total dust exposure among pulp and paper workers,[16] while two cohort studies observed non-significant elevated risks of ovarian cancer for occupations in the paper industry.[7 38] For PAHs, one case–control study reported increased ovarian cancer risks with wide CIs.[15] A growing body of experimental research suggests that exposure to PAHs contributes to the pathogenesis of ovarian cancer.[40] We are not aware of any epidemiological studies that have specifically evaluated the relationship between alkanes (C5–C17) or MAHs and ovarian cancer.

A key strength of this study stems from the population-based study design and collection of lifetime occupational history, enabling the analysis of occupations and industries prevalent among female workers. Linking occupational history information with CANJEM allowed the evaluation of 29 agents using three exposure parameters that incorporated different dimensions of occupational exposure. Previous studies either examined occupation, industry or occupational exposure, while we sought to generate new hypotheses by evaluating all these facets of the occupational environment in relation to ovarian cancer. Unfortunately, the advantage of studying agents versus occupations could not be fully realised for some agents because of the clustering of those agents in certain occupations (eg, the highly correlated agents among Hairdressers, Barbers, Beauticians and Related Workers). Nonetheless, we present findings for many other agents not highly correlated within a single occupation. In addition, as the PROVAQ study obtained reproductive history information from participants, associations were estimated adjusting for important confounders like parity.

Despite having a relatively large study sample, few women were employed in certain occupations or had exposures to specific agents. Indeed, because of small numbers, we were not able to assess risks in certain occupations and industries (paper, printing, textile production, dry cleaning, manufacturing) or specific agents (asbestos, pesticides) previously reported as potential ovarian cancer risk factors. We acknowledge the multiple comparisons in our study, and that the CIs of most OR estimates were wide. It is likely that some statistically significant associations observed were due to chance given the number of analyses performed. Nonetheless, we did not base our interpretations on statistical significance, rather we highlighted possible associations based on the magnitude of observed ORs.

Even though we considered numerous covariates in the DAG and adjusted for the minimally sufficient confounder set in all our models, residual confounding is possible. We did not have information on participants' individual income level, and the adjustment of education level may not have fully accounted for the effects of socioeconomic status on employment in an occupation or industry, occupational exposure, ovarian cancer and other covariates. However, the inclusion of education level, which was associated with participation in the PROVAQ study[19] allowed for sources of potential selection bias to be minimised, given that we did not have a 100% participation rate and education may be associated with occupations and thus occupational exposures.

Participants' reporting of job history and coding of occupations and industries may have engendered exposure misclassification. However, this misclassification is probably non-differential as the reporting of job history is unlikely to differ according to disease status and the industrial hygienist performing the job coding was blinded to participants' case–control status. Such non-differential misclassification would bias OR estimates to the null, thereby necessitating increased statistical power given the smaller contrast in exposure. Nonetheless, we expect any such reporting error to be minimal since little is known regarding occupational risk factors for ovarian cancer, and similar distributions of number of jobs held and duration of working life were reported by cases and controls.

In summary, our results suggest that employment in certain occupations and specific occupational exposures may be associated with increased risks of ovarian cancer. Further studies are required to replicate findings. Studies with individual expert assessments of hairdressing-related occupations and larger sample sizes that can perform more advanced statistical methods accounting for coexposures may be useful in the identification of potential aetiological agents for ovarian cancer.

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Contributors AK is the principal investigator of the PROVAQ study. LL, AK and PG designed the analytical strategy and interpreted the results from this analysis. LL cleaned data, performed the statistical analysis and drafted the paper under the supervision of AK and PG. JL and JS developed CANJEM, provided access to it, consulted on the statistical analysis and reviewed the paper. AK is responsible for the overall content as the guarantor.

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