Original article

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Postmenopausal breast cancer and occupational exposure to chemicals

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Objectives The aim of this study was to investigate if exposure to chemicals in the workplace was associated with an increased risk of postmenopausal breast cancer.

Methods The study comprised women born 1923–1950 living in Malmö city, Sweden, 1991–1996, and enrolled for a prospective population cohort study. Occupational exposure to various chemicals was assessed from job-exposure matrices. An extensive set of individual data on hormonal breast cancer risk factors were collected via a baseline questionnaire and used for confounding control. First time diagnoses of invasive breast cancer were identified through the Swedish Cancer Registry until end of follow-up on 31 December 2013.

Results Of 16 084 women, 1011 were diagnosed with breast cancer. Women exposed to chemicals in their occupational environment had a statistically significant increased risk [adjusted hazard ratio (HR_{adj}) 1.26, 95% confidence interval (CI) 1.02–1.54] of breast cancer, and the risk correlated with duration of exposure. Investigation of risk in association with specific chemicals showed a non-significantly elevated risk after exposure to organic solvents. More than ten years of exposure to diesel exhaust was associated with an increased risk (HR_{adj} 1.69, 95% CI 1.01–2.82). Occupational chemical exposures account for 2% of the breast cancer cases in this population.

Conclusions Occupational exposure to chemicals in general was associated with an elevated risk of breast cancer. A slight elevation of risk was seen after exposure to organic solvents. A statistically significant elevation of risk after >10 years of exposure to diesel exhaust was an unexpected finding.

Key terms cohort study; confounding; invasive breast cancer; JEM; job-exposure matrix; occupational environment; tumor; population attributable fraction.

Breast cancer is the most common cancer among women worldwide, accounting for 25% of all cancer cases (1). Many established risk factors for breast cancer in women are associated with hormonal factors related to reproduction, such as early menarche, late menopause, hormone replacement therapy (HRT) and oral contraceptive use, while protective factors are early first-time pregnancy and multiparity (2). Alcohol consumption is a strong risk factor for breast cancer (3), while no increased risk was found in association with smoking (2). Family history of breast cancer (4) and high body mass index (BMI) (2) are other risk factors.

Previous studies suggest a link between chemical exposure and breast cancer, acting through three different mechanisms: (i) genotoxic action, (ii) alteration of mammary gland development or hormone responsiveness, or (iii) hormonal tumour promotion (5). Endocrine disrupting chemicals (EDC) can both alter the breast development and increase the susceptibility to breast cancer but also promote tumour growth through oestrogen- or progesterone mediated pathways (5). Even though the interest for studies, especially on EDC and breast cancer, have increased through the years, there is still a need for good quality epidemiological studies investigating the relationship between chemical exposure and the risk of breast cancer.

One of the most studied groups of chemicals in respect to breast cancer is organic solvents. Goldberg et

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al's review (6) noted an increased risk of breast cancer in occupations with potential exposure to organic solvents, like dry cleaners, painters and laboratory technicians. This association has further been supported by a few other studies (7–11). Lifetime cumulative exposure to organic solvents has also been linked to an increased risk of male breast cancer (12). Organic solvents are absorbed systemically from the upper and lower airways but may also be absorbed through the skin and are then distributed throughout the body via the bloodstream (13). It can then, due to their lipophilic properties be stored in the surrounding fat tissue of the breast and migrate into the lobules and be transported to the ductular system (13). The mechanism for organic solvents could possibly be similar to the one for alcohol and breast cancer, since alcohol is an organic solvent (14). It is thought that organic solvents cause breast cancer by acting directly as a genotoxic agent or indirectly through their metabolites (5, 13).

Diesel and gasoline exhaust have shown to increase the risk of cancer in the lung and urinary bladder, however studies on breast cancer are inconsistent (15). Two studies have found an increased risk of breast cancer among women exposed to engine exhaust with a risk ratio of 1.53 [95% confidence interval (CI) 1.00-2.33] (16) and odd ratio of 2.57 (95% CI 1.16-5.69) (17) while three studies have found no increased risk (18–20). However many of the studies had methodological problems such as few participants, not enough data on confounders such as reproductive factors or a low validity on exposure data (16, 18, 19). The relationship between diesel and gasoline exhaust and breast cancer needs to be investigated further.

A meta-analysis has found a small but significant increased risk of breast cancer among hairdressers which might be related to the exposure to hair dyes which contain substances that are suspected carcinogenic, like solvents (21).

Although some studies, as mentioned above, indicate an increased risk of breast cancer related to chemical exposure, the results were inconsistent and could potentially be influenced by uncontrolled confounding. Many studies lack detailed information on reproductive factors such as age at first pregnancy and parity, confounding factors that decrease the risk of breast cancer for occupational groups that have a higher parity and are younger at first term pregnancy, which is more common in manual labour where the exposure to chemicals might be higher. Since reproductive factors are crucial risk factors for breast cancer, it is important to have detailed individual reproductive data in order to conduct a good quality study. The aim of this study was to investigate if exposure to chemicals in the workplace were associated with an increased risk of postmenopausal breast cancer, while adjusting for individual data on important potential confounders.

Methods

The Malmö Diet and Cancer Study (MDCS) is a population-based prospective cohort study (22, 23). A total of 74 138 persons living in Malmö, Sweden, between 1991–1996 and 41–73 years old were invited to participate in the study, of which 24 851 did not respond or had unknown address, 16 942 declined to participate and 4247 were excluded due to language problems, leaving 28 098 participants (17 035 women) in MDCS. Exclusion criteria for the present study were women (i) with breast cancer before baseline (N=576), (ii) who had not been employed in an occupation for ≥1 year (N=247), and (iii) who remained premenopausal until the end of follow up (N=128). Premenopausal women were excluded due to the low number of premenopausal breast cancer cases in the cohort and the difficulty to analyse these due to different risk factors in pre- and postmenopausal breast cancer (24). High BMI increases the risk for postmenopausal breast cancer while it seems to decrease the risk in premenopausal women (24).Menopausal status was defined by medical records and questionnaire data. A woman was classified as postmenopausal if: (i) she had undergone bilateral oophorectomy, (ii) the above criteria was absent and she confirmed that her menstruation had ceased two years prior to baseline, or (iii) the above criteria was absent and she was ≥55 years of age. A total of 16 084 women were included in this study. At baseline, each participant filled out an extensive questionnaire containing questions on lifestyle, working history and reproductive factors. Questions on each woman's three latest occupations and the time period for these were asked as well as detailed questions on the woman's specific work tasks. Only retrospective occupational data were collected from baseline. Questions on alcohol consumption were asked as regard to the last 30 days using the validated questionnaire AUDIT (25). Health care personnel measured height and weight for each person.

Exposure to chemicals was assessed through the Scandinavian job-exposure matrices (JEM) NOCCA and FINJEM, adapted for Swedish working conditions (26, 27). Chemicals of interest for our study that were available in NOCCA included: 1,1,1-trichloroethane, benzene, benzo(a)pyrene, bitumen fumes, diesel exhaust, gasoline, methylene chloride, perchloroethylene, toluene, and trichloroethylene. Chemicals used from FINJEM included: aliphatic and alicyclic hydrocarbon solvents (ALHC), aromatic hydrocarbon solvents (ARHC), chlorinated hydrocarbon solvents (CHC), other organic solvents (other than defined in ALHC, ARHC, CHC, including alcohols, ketones, esters, glycol ethers), fungicides, herbicides, insecticides, polycyclic aromatic hydrocarbons (PAH), gasoline exhaust, and

oil mist. The job-exposure matrices specify two measurements for each chemical and occupational group; intensity level for the exposed individuals and proportion exposed in the specific occupation. The matrices are also divided into time-periods since the exposure to chemicals change over time due to regulations, new methods that influences the usage of certain chemicals or safety precautions affecting the exposure. Being ever exposed to chemicals in our study were defined as having worked in an occupation where ≥5% of the employees were, according to the matrices, exposed to any of these chemicals.

First time diagnoses of invasive breast cancer in 1991−2013 were identified through the Swedish Cancer Registry (28). Breast cancer cases were identified as International Classification of Diseases, 7th Revision (ICD7) code 170. Death and migration status were retrieved from the Swedish National Tax Board.

Statistical analyses

Confounding variables were selected based on *a priori* knowledge from the literature including age (45–49, 50–54, 55–59, 60–64, 65–69, 70–74 years), parity (0, 1, 2, 3, ≥4), age at first term pregnancy (<20, 20–24, 25–29, 30–34, ≥35 years), months of breastfeeding per child (0, 1–5, 6–12, ≥13), hormone replacement therapy (HRT) (no treatment, oestrogen, progesterone, combined treatment), physical activity at work (quartiles), alcohol consumption (0, 1–14, 15–30, >30 g/day), height (<160, 160–169, ≥170 cm) and BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2).

BMI categorization was made according to the World Health Organization standard (29). Physical activity was measured with several questions estimating the time of physical activity performed outside of work and multiplied with an intensity factor for each activity (30). Months of breastfeeding were reported for each child and a mean number was calculated. Imputations were made on breastfeeding data for women who had data for at least one child but missing for another, using the mean number as imputation.

Chi-square tests were used to compare the distribution of risk factors for chemically exposed and non-exposed women. Cox proportional hazard model was used to estimate the hazard ratio (HR) for breast cancer in chemically exposed/never chemically exposed women and in duration analysis of 1–10 and >10 years. The underlying time variable was follow-up time from baseline to event or censoring. Minimally adjusted estimates were adjusted for age only while the fully adjusted model included age, parity, age at first term pregnancy, months of breastfeeding/child, HRT, physical activity, alcohol consumption, height, and BMI. We also performed a sensitivity analysis considering the HR for breast cancer by exposure duration, restricted to women who were pre-menopausal at baseline. Cumulative exposure was calculated as intensity level stated in JEM × proportion exposed according to JEM × years worked in that occupation (26, 27). The women were then divided dichotomously at the median and analysed using Cox proportional hazard model. Trend tests in tables 2 and 3 were calculated using Cox proportional hazard model, creating a variable assigning the unexposed group a value of 0, the low or short-term exposed group a value of 1, and the high or long-term exposed group a value of 2, using the unexposed group as a reference. Pearson correlation analysis was used to investigate correlations between chemical agents and chemical groups (31). Population attributable fraction (PAF) was calculated using the formula AF=proportion of cases exposed to risk factor × (RR-1/RR) (32). All women who were postmenopausal were considered at risk from baseline until a breast cancer diagnosis, death, migration, or end of follow-up at 31 December 2013, whichever occurred first. If premenopausal at baseline, the woman was considered at risk from the time she became postmenopausal according to the earlier specified criteria for postmenopause. Statistical analyses were performed using STATA version 13.0 (StataCorp, College Station, TX, USA) with an α-level for significance tests at 0.05 (33).

Results

The cohort comprised 16 084 women, of which 1011 women were diagnosed with breast cancer during the study period, and 1492 women were exposed to any of the chemicals we included in the analysis.

Distribution of risk factors for breast cancer among women exposed to chemicals and non-exposed women are presented in table 1. Women who were ever exposed to chemicals were older and had higher BMI (positive confounding) compared to unexposed women. Women ever exposed also had more children, were younger at first term pregnancy, and drank less alcohol (negative confounding) compared to unexposed women. These differences were all statistically significant.

Table 2 shows that women being exposed to any of the included chemicals had a higher risk of breast cancer compared to unexposed women (HR 1.26, 95% CI 1.02–1.54). Analysis by duration of exposure indicated that the risk increased with duration in the occupation, with a HR of 1.43 (95% CI 1.10–1.85) for women exposed >10 years compared to non-exposed women. The P-for-trend test showed a significant result with a P-value of 0.01. Calculation of PAF indicated that 2% of the breast cancer cases in this specific population could be attributed to occupational exposure to chemicals.

Table 1. Distribution of potential risk factors for breast cancer in the present population of 1492 exposed and 14 592 non-exposed women.

	Exposed [a] (N=1492)	%	Non-exposed (N=14 592)	%
Age [b] (years)				
45–49	318	21.3	3712	25.4
50–54	291	19.5	2817	19.3
55–59	243	16.3	2482	17.0
60–64	318	21.3	2682	18.4
65–69	174	11.7	1571	10.8
70–74	148	9.9	1328	9.1
Parity				
0	172	11.5	1870	12.8
1	318	21.3	3095	21.2
2	583	39.1	6061	41.5
3	274	18.4	2409	16.5
≥4	129	8.7	901	6.2
Missing values	16	1.1	256	1.8
Age at first term pregnancy				
<20	239	16.0	1468	10.1
20–24	550	36.9	4898	33.6
25–29	382	25.6	4244	29.1
30–34	93	6.2	1408	9.7
≥35	38	2.6	440	3.0
No children	172	11.5	1870	13.0
Missing values	18	1.2	264	1.8
Months of breastfeeding/child				
0	67	4.5	600	4.1
1–5	770	51.6	7649	52.4
6–12	364	24.4	3604	24.7
≥13	28	1.9	149	1.0
No children	172	11.5	1870	12.8
Missing values	91	6.1	720	4.9
Hormone replacement therapy				
No treatment	1 247	83.6	11 808	80.9
Estrogen	92	6.2	953	6.5
Progesterone	7	0.5	93	0.6
Estrogen & progesterone	142	9.5	1696	11.6
Missing values	4	0.3	42	0.3
Physical activity (percentile)				
0–25	404	27.1	3519	24.1
25–50	346	23.2	3603	24.7
50–75	358	24.0	3763	25.8
75–100	374	25.1	3628	24.9
Missing values	10	0.7	79	0.5
Alcohol (g/day)				
0	182	12.2	994	6.8
1–14	1141	76.5	11 107	76.1
15–30	141	9.5	2129	14.6
>30	26	1.7	349	2.4
Missing values	2	0.1	13	0.1
Height (cm)				
<160	483	32.4	3450	23.6
160–169	836	56.0	8620	59.1
≥170	170	11.4	2502	17.2
Missing values	3	0.2	20	0.1
Body mass index (kg/m^2)				
<18.5 underweight	16	1.1	223	1.5
18.5–24.9 normal weight	661	44.3	7637	52.3
25–29.9 overweight	538	36.1	4812	33.0
≥30 obese	274	18.4	1900	13.0
Missing values	3	0.2	20	0.1

[a] Exposed in the work environment to at least one of the following chemicals; aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, chlorinated hydrocarbon solvents, other organic solvents, fungicides, herbicides, insecticides, polycyclic aromatic hydrocarbons, bitumen fumes, diesel exhaust, gasoline exhaust, oil mist, benzene, trichloroethylene, toluene, perchloroethylene, 1,1,1-trichloroethane, gasoline, benzo(a)pyrene, methylene chloride

[b] Age at baseline.

The analysis by duration of exposure, also in table 2, showed statistically significantly increased risk of breast cancer for women being exposed >10 years to fumes [polycyclic aromatic hydrocarbons (PAH), bitumen fumes, diesel exhaust and gasoline exhaust] with a HR of 1.57 (95% CI 1.01–2.42), while no increased risk was found for women exposed 1–10 years. The P-for-trend test was non-significant. Among the components in fumes, specifically exposure to diesel exhaust showed a statistically increased risk for women being exposed >10 years (HR 1.69, 95% CI 1.01–2.82). The sensitivity analysis restricted to pre-menopausal women at baseline showed similar associations as in the full model (not shown).

The risk of breast cancer in relation to the cumulative exposure to each chemical agent is presented in table 3. The trend of increased risk of breast cancer with cumulative exposure to chemicals showed no clear association, with non-significant HR both in the minimally adjusted (for age) and the fully adjusted analysis. Since the results were essentially the same in the minimally and fully adjusted model, only the latter is presented in table 3.

Discussion

This study showed that women exposed to chemicals in their occupation were at an increased risk of breast cancer compared to women who never had been exposed. Women working longer time in an occupation with chemical exposure had higher risk of breast cancer compared to women working shorter time. Specifically women exposed to diesel exhaust for >10 years seemed to have an increased risk of breast cancer; 2% of the breast cancer cases in this population could be attributed to occupational exposure to chemicals.

The main analysis showed an increased risk of breast cancer for women who had been working in an occupation with exposure to any of the included chemicals. This result included increased HR in organic solvents, methylene chloride, other organic solvents, pesticides, fumes, and diesel exhaust, although all non-significant when evaluated individually.

The previous literature indicates that organic solvents could increase the risk of breast cancer (6–11). Even though our results showed a small increased risk, the HR were not statistically significant.

Women exposed to diesel exhaust for >10 years had a significantly increased risk of breast cancer (HR 1.69 95% CI 1.01–2.82). Breast cancer also seemed to increase with cumulative dose of diesel exposure, however those results were statistically non-significant. Not surprisingly, a quite strong correlation was found between diesel and gasoline

Table 2. Hazard ratios (HR) for invasive breast cancer by exposure duration; ever exposed, 1–10 years and >10 years of exposure. [CI=confidence interval.]

Chemical agents	N total	N cases	Ever exposed Minimally adjusted [a]		Ever exposed Fully adjusted [b]		N cases	1-10 year exposure Fully adjusted [b]		N cases	>10 year exposure Fully adjusted [b]		Trend test
			HR	95% CI	HR	95% CI		HR	95% CI		HR	95% CI	P-value
Any of the included chemicals [c]	1492	109	1.21	0.99–1.47	1.26	1.02–1.54	43	1.05	0.77–1.45	66	1.43	1.10–1.85	0.01
Organic solvents [d]	957	67	1.16	0.90–1.48	1.15	0.89–1.50	34	1.14	0.80–1.63	33	1.18	0.81–1.71	0.28
Aliphatic and alicyclic hydrocarbon solvents	284	13	0.74	0.42–1.28	0.85	0.49–1.47	5	0.55	0.23–1.32	8	1.28	0.64–2.58	0.93
Aromatic hydrocarbon solvents	524	35	1.08	0.77–1.51	1.10	0.77–1.55	19	0.99	0.62–1.58	16	1.26	0.75–2.09	0.47
Benzene	567	37	1.04	0.75–1.44	1.06	0.76–1.49	23	1.24	0.82–1.87	14	0.84	0.47–1.48	0.97
Toluene	259	15	0.94	0.56–1.56	1.00	0.60–1.67	8	0.90	0.45–1.81	7	1.15	0.55–2.42	0.87
Chlorinated hydrocarbon solvents	628	42	1.08	0.79–1.47	1.12	0.82–1.55	21	1.09	0.70–1.70	21	1.17	0.74–1.84	0.45
Methylene chloride	208	17	1.44	0.90–2.34	1.39	0.83–2.32	6	1.03	0.46–2.31	11	1.80	0.93–3.49	0.11
1,1,1-trichloroethane	198	11	0.93	0.51–1.68	0.97	0.53–1.76	6	0.94	0.42–2.10	5	1.01	0.42–2.44	0.96
Other organic solvents [e]	292	24	1.37	0.92–2.06	1.34	0.87–2.06	13	1.31	0.74–2.31	11	1.38	0.71–2.67	0.20
Pesticides [f]	150	10	1.08	0.58–2.02	1.17	0.62–2.18	3	0.89	0.29–2.77	7	1.34	0.64–2.83	0.52
Fumes [g]	466	35	1.21	0.86–1.69	1.25	0.89–1.76	14	0.94	0.54–1.63	21	1.57	1.01–2.42	0.09
Polycyclic aromatic hydrocarbons	175	11	1.02	0.56–1.84	1.07	0.59–1.94	6	1.00	0.45–2.24	5	1.16	0.48–2.79	0.78
Diesel exhaust	303	24	1.27	0.85–1.91	1.33	0.88–2.01	9	0.95	0.47–1.92	15	1.69	1.01–2.82	0.08
Oil mist	395	19	0.76	0.48–1.20	0.89	0.56–1.40	9	0.71	0.37–1.37	10	1.14	0.61–2.13	0.87

[a] Adjusted for age.

[b] Adjusted for age, parity, age at first term pregnancy, months of breastfeeding per child, hormonal replacement therapy, physical activity, alcohol consumption, height and BMI.

[c] Exposed in the work environment to at least one of the following chemicals; aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, chlorinated hydrocarbon solvents, other organic solvents, fungicides, herbicides, insecticides, polycyclic aromatic hydrocarbons, bitumen fumes, diesel exhaust, gasoline exhaust, oil mist, benzene, trichloroethylene, toluene, perchloroethylene, 1,1,1-trichloroethane, gasoline, benzo(a)pyrene, methylene chloride.

[d] Aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, chlorinated hydrocarbon solvents, other organic solvents

[e] Includes alcohols, ketones, esters, glycol ethers etc.

[f] Fungicides, herbicides, insecticides.

[g] Polycyclic aromatic hydrocarbons, bitumen fumes, diesel exhaust, gasoline exhaust.

exhaust (r=0.64) indicating that the results should be interpreted cautiously. Our findings have some support in previous studies; a cohort study in the US found increased risk of breast cancer (RR 1.53, 95% CI 1.00–2.33) associated with self-reported occupational exposure to engine exhaust (16). Another study found increased risk of breast cancer (OR 2.57, 95% CI 1.16–5.69) for women exposed to motor vehicle exhaust (17). Nevertheless, most previous studies on diesel exhaust found no increased risk of breast cancer (18–20). Animal studies have shown possible mechanisms for gasoline exposure and breast cancer by either mimicking oestrogen to promote tumour growth, directly damaging DNA or promoting cancer cell proliferation. The International Agency for Research on Cancer (IARC) have classified diesel exhaust as carcinogenic to humans based on sufficient evidence linking it to an increased risk of lung cancer and urinary bladder cancer, but lacking enough quality studies on breast cancer (15). The findings of diesel exhaust and increased risk of breast cancer is a clear finding in our study but needs to be investigated further.

Exposure to methylene chloride showed a non-significant increased risk of breast cancer, and with no indication of dose–response. Most previous epidemiological studies have found little or no association between breast cancer and methylene chloride (34, 35) although an US study found an increased risk of breast cancer mortality for women exposed to methylene chloride (36). Animal studies have found increased mammary tumour in mice exposed to methylene chloride (37). The IARC recently classified methylene chloride as 2A carcinogenic to humans (cancer of the biliary tract and non-Hodgkin lymphoma) (38).

The analysis by duration of exposure (table 2) showed a clearer trend than cumulative analysis using the full FINJEM/NOCCA JEM (table 3). This is an unexpected result, but could be due to the misclassification of exposure that is inherent to using JEM. Since duration of exposure is measured at an individual level (self-reported) but intensity and proportion exposed are measured and estimated on group level, this adds inaccuracy to the estimate. A non-differential misclassification of exposure is therefore likely, resulting in an attenuation of the HR.

It has been suggested that exposure to chemicals can affect the risk of adverse outcomes differentially depending on at what age the women are exposed (39). During pregnancy there is a shift in the breast tissue of more stem cells to a stage where they become less sensitive (39). Our data contained women exposed both before and after menopause, however the majority of exposure took place before menopause, in reproductive age. Sensitivity analysis showed essentially the same results for women exposed only before menopause and those exposed before and after. The loss in power made the CI wider, but the point estimates remained

Table 3. Hazard ratios (HR) for invasive breast cancer by high/low cumulative exposure to chemicals. [CI=confidence interval.]

Chemical agents	Mean cumulative exposure in class	N total	N cases	Fully adjusted [a]		Trend test
				HR	95% CI	P-value
Organic solvents [b] (ppm-years)						
Unexposed	0	15 127	944	1		0.42
>0–17.74	5.97	474	35	1.26	0.89–1.79	
17.78–2802.58	140.38	483	32	1.05	0.72–1.54	
Aliphatic and alicyclic hydrocarbon solvents (ppm–years)						
Unexposed	0	15 800	998	1		0.70
>0–20.00	9.20	140	5	0.70	0.29–1.68	
20.34–487.92	106.53	144	8	0.98	0.49–1.97	
Aromatic hydrocarbon solvents (ppm–years)						
Unexposed	0	15 560	976	1		0.78
>0–3.13	0.68	259	21	1.21	0.77–1.91	
3.34–1253.36	95.83	265	14	0.97	0.57–1.65	
Benzene (ppm–years)						
Unexposed	0	15 517	974	1		0.55
>0–1.43	0.57	280	16	0.92	0.55–1.53	
1.45–16.85	4.08	287	21	1.20	0.77–1.88	
Toluene (ppm–years)						
Unexposed	0	15 825	996	1		0.64
>0–11.70	4.24	124	10	1.42	0.76–2.66	
12.00–770.00	85.53	135	5	0.63	0.26–1.52	
Chlorinated hydrocarbon solvents (ppm–years)						
Unexposed	0	15 456	969	1		0.59
>0–8.11	3.63	311	21	1.20	0.77–1.87	
8.26–285.00	25.83	317	21	1.05	0.67–1.66	
Methylene chloride (ppm–years)						
Unexposed	0	15 876	994	1		0.33
>0–8.40	4.26	99	8	1.62	0.81–3.27	
8.50–84.00	18.94	109	9	1.19	0.56–2.51	
1,1,1–trichloroethane (ppm–years)						
Unexposed	0	15 886	1000	1		0.95
>0–3.90	1.83	98	5	0.84	0.35–2.03	
4.00–108.75	11.95	100	6	1.12	0.50–2.50	
Other organic solvents [c] (ppm–years)						
Unexposed	0	15 792	987	1		0.42
>0–23.21	10.69	144	14	1.70	0.98–2.95	
23.86–1053.39	118.78	148	10	0.99	0.49–1.99	
Pesticides [d] (mg–years/m3)						
Unexposed	0	15 934	1001	1		0.61
>0–0.74	0.16	74	5	1.11	0.46–2.68	
0.77–7.28	2.36	76	5	1.23	0.51–2.96	
Fumes [e] (mg–years/m3)						
Unexposed	0	15 618	976	1		0.18
>0–1.13	0.43	232	17	1.16	0.71–1.91	
1.15–397.11	44.94	234	18	1.34	0.84–2.14	
Polycyclic aromatic hydrocarbons (µg–years/m3)						
Unexposed	0	15 909	1000	1		0.51
>0–1.17	0.39	84	3	0.60	0.19–1.87	
1.23–397.11	24.87	91	8	1.50	0.75–3.02	
Diesel exhaust (mg–years/m3)						
Unexposed	0	15 781	987	1		0.11
>0–0.42	0.23	151	10	1.09	0.58–2.03	
0.43–3.57	0.89	152	14	1.61	0.93–2.79	
Oil mist (mg–years/m3)						
Unexposed	0	15 689	992	1		0.67
>0–0.70	0.34	200	9	0.84	0.44–1.63	
0.72–78.00	7.19	195	10	0.93	0.50–1.74	

[a] Adjusted for age, parity, age at first child, months of breastfeeding per child, hormonal replacement therapy, physical activity, alcohol consumption, height and BMI. The crude model gave essentially the same results as the fully adjusted model and was therefore not included in the table.

[b] Aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, chlorinated hydrocarbon solvents, other organic solvents.

[c] Includes alcohols, ketones, esters, glycol ethers etc.

[d] Fungicides, herbicides, insecticides.

[e] Polycyclic aromatic hydrocarbons, bitumen fumes, diesel exhaust, gasoline exhaust.

close to the original. However, there was a significant increase in risk for women exposed to pesticides; from a non-significant HR for the full cohort to a significant increased risk for women only exposed before menopause (HR 2.90 95% CI 1.43–5.86). Pesticides have been researched increasingly over the last years and there is an indication that exposure to pesticides in early life might increase the risk of breast cancer (40), however the research is far from consistent (37, 41). The sensitivity analysis indicates a possible increased risk if exposed in reproductive years and the relationship between pesticides and breast cancer should be investigated further.

Aside from the correlation between diesel exhaust and gasoline exhaust, low correlations were found between individual chemical agents (r=0.01–0.47) and between main chemical groups (r=0.01–0.23).

This study has some other weaknesses and strengths that need to be considered. Occupational data were only available and measured until the day of enrolment in the study. However, the participants were quite old at recruitment and many were close to retirement, leaving an almost complete occupational exposure history for each participant. Another weakness is the power of this study. As we find predominantly positive but non-significant associations, several of these might have been significant with a better power. Since the exposure is quite rare, especially regarding specific chemical agents, we would have needed a larger sample in order to observe an effect for many of the chemical agents. This is especially true when analysing duration and cumulative exposure. This study lacks information on the estrogen-receptor status of breast cancer, which may play a role in the development of breast cancer. Strength of this study is the extensive individual data on hormonal and reproductive factors allowing for a good confounder control. However, there is always a possibility of residual confounding that need to be considered. Night-shift work is a possible confounder that is strongly associated with occupation and seems to be associated with increased risk of breast cancer (42). It might explain the increased risk seen in occupations where exposure to chemicals and night-shift work exist, eg, among bus drivers or nurses. However, most of the results in this study are probably attenuated towards HR 1.00 due to the misclassification of exposure described earlier.

A strength of this study is that the design used a prospective cohort with a follow-up of >20 years. Outcome data on breast cancer cases are close to 100% coverage in the Swedish Cancer Registry.

Occupational chemical exposure is a risk factor that can be regulated and eliminated if found to be harmful, and is therefore important to investigate thoroughly. This paper indicates that chemical exposure is associated with an increased risk of breast cancer and that 2% of the breast cancer cases in this specific population could be attributed to occupational chemical exposure. This is equivalent to approximately 20 of the 1011 cases. However, this figure should be interpreted cautiously due to the risk of residual confounding discussed above.

In conclusion, women exposed to chemicals in their occupational environment had a statistically significant increased risk of breast cancer compared to women who were not exposed. The risk tended to be higher after >10 years of exposure than after 1–10 years of exposure for many of the studied exposures. Specifically women exposed to diesel exhaust for >10 years had a statistically significant increased risk of breast cancer. Further research is needed to identify associations between exposure to individual chemicals and breast cancer.

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Competing interest

Authors declare no conflicts of interest

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Ethical approval

Lund ethical review board approved the MDCS study (LU 51-90), and the Stockholm ethical review board approved the present study (Dnr 2014/233-31/4). All participants gave informed consent before taking part in this study.

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