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Chemical exposures in the workplace and breast cancer risk: a prospective cohort study

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Abstract

We investigated the relationship between workplace chemical exposures and breast cancer risk among women enrolled in the Sister Study, a prospective cohort study of US and Puerto Rican women. A total of 47,640 participants reported work outside of the home. Workplace exposure to eleven agents (acids, dyes or inks, gasoline or other petroleum products, glues or adhesives, lubricating oils, metals, paints, pesticides, soldering materials, solvents, and stains or varnishes) was characterized based on self-reports of frequency and duration of use. Approximately 14% of the study population reported exposure to only one agent, and 11% reported working with two or more of the eleven agents in their lifetime. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for each agent, adjusting for established breast cancer risk factors. During follow-up, 1,966 cases of breast cancer were reported. Although there were no significant associations between ever-use of the eleven agents evaluated and breast cancer risk, women with cumulative exposure to gasoline or petroleum products at or above the highest quartile cutoff had an elevated risk of total (HR: 2.3, 95%CI: 1.1–4.9) and invasive (HR: 2.5, 95%CI: 1.1–5.9) breast cancer compared to women in the lowest quartile group (p_{trend} = 0.03). Workplace exposure to soldering materials was associated with an increased risk of premenopausal breast cancer (HR=1.8, 95% CI = 1.1–3.0). Findings support the need for further studies to elucidate the role of occupational chemicals in breast cancer etiology.

Introduction

There has been longstanding interest in the role of chemical exposures in the etiology of breast cancer [1–3]. More than 200 chemicals have been identified as potential mammary gland carcinogens and endocrine disruptors [4]. These chemicals include a variety of compounds that may be involved in carcinogenesis through direct and indirect mechanisms. Endocrine disrupting compounds, for example, can mimic or interfere with the actions of natural hormones [5–7]. The ubiquitous nature of these compounds, along with the increased prevalence of industrial chemicals in the environment during the last part of the 20th century

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[8], has led to the hypothesis that chemical exposures may explain trends in breast cancer incidence.

Epidemiologic studies have examined the association between breast cancer and exposures to compounds such as metals, organic solvents, polycyclic aromatic hydrocarbons, and polychlorinated organic compounds with inconsistent results; however, only a handful of studies [9–13] have investigated breast cancer risk associated with exposure to these compounds in the workplace, a setting with the potential for greater than background levels of exposure. The purpose of this study was to investigate the relationship between workplace exposure to potential carcinogens and endocrine disrupting compounds and breast cancer risk among women enrolled in the Sister Study, a prospective study of US and Puerto Rican women designed to examine the genetic and environmental risk factors for breast cancer.

Methods

Study Population

The Sister Study enrolled 50,884 breast cancer-free sisters of women with breast cancer between 2004 and 2009. Information on risk factors for breast cancer (e.g. demographic, lifestyle, and reproductive characteristics) and occupational exposures was collected at baseline (http://sisterstudy.niehs.nih.gov). Written informed consent was provided by study participants at enrollment. The Sister Study was approved by the institutional review boards of the National Institute of Environmental Health Sciences and Copernicus Group.

For the current study, we excluded women who were diagnosed with breast cancer before completion of baseline activities (n=99), women with missing or unknown breast cancer diagnosis dates (n=15), and women who had never worked outside of the home (n=833). We also excluded a vanguard group of women who had completed a non-comparable version of the occupational section of the baseline interview (n=2,297). The vanguard women were younger, more likely to be non-Hispanic white, and more likely to report lower levels of education and income. A total of 47,640 women were available for the present analysis.

Occupational Exposure Assessment

A comprehensive occupational exposure history was collected from each study participant during a baseline telephone interview. The baseline questionnaire was administered using a structured computer-assisted telephone interview (CATI) and included questions about workplace exposure to specific agents and materials (Supplementary material). A total of 11 of the 14 exposures included on the questionnaire were included in this analysis: acids, dyes or inks, gasoline or other petroleum products, glues or adhesives, lubricating oils, metals, paints, pesticides, soldering materials, solvents, and stains or varnishes.

Occupational data included information about lifetime (ever/never) use, frequency of use, and duration of use for each agent. For each study participant, we estimated cumulative exposure to each agent as a function of frequency and duration of use. Cumulative lifetime exposure, in total days, to an agent was determined as the product of participant-reported days per month, months per year, and total years of use. Based on the overall distribution of

cumulative lifetime exposure for each agent, quartile cutpoints were used to assign exposed study participants to categories. Participants who reported never having worked with an agent were assigned to the *Never use* category for the agent.

Follow-up of the Cohort

Participants were followed from the baseline interview until a breast cancer diagnosis, death, or end of follow-up. Incident breast cancer cases were reported by study participants through annual health updates and biennial questionnaires. When a participant reported a breast cancer diagnosis, we asked for permission to obtain related medical records and hospital reports. Agreement between self-report and medical records was better than 98% for occurrence of first primary breast cancer. Therefore, all self-reported cases of breast cancer were included in these analyses.

Data Analysis

Study participants contributed person-years from the date of completion of the baseline interview until the date of breast cancer diagnosis, death, or end of follow-up period, whichever date came first. For each agent, we used multivariable Cox proportional hazards regression, with age as the time-axis, to assess the impact of exposure on breast cancer risk. We identified potential confounders using directed acyclic graphs [14–16]. Briefly, after a review of prior scientific literature, causal diagrams were used to identify a set of factors that were potential confounders in the relation between occupational chemical exposures and breast cancer, but were not intermediates in the causal pathway. Variables whose removal altered risk estimates by 10% or more remained in the model. The following covariates were included in all multivariable models: race/ethnicity (non-Hispanic white, black, Hispanic, other), education (<High School graduate/GED, High School graduate/GED, some college, college/post graduate), income (<$50,000, $50,000–<$100,000, $100,000+), parity (nulliparous, 1, 2, 3+ births), and age at first birth (<21, 21–<24, 24–<28, 28+).

Multivariable models were fitted to estimate the breast cancer risk among women in the *Ever use* category compared with the breast cancer risk for women in the *Never use* category. Multivariable models were also fitted to compare the risk for women across exposure quartile categories, with the *Never use* category as the reference group for each agent. Adjusted hazard ratios and 95 percent confidence intervals were estimated for breast cancer overall, and by tumor subtype and hormone receptor status. We also determined hazard ratios by menopausal status at follow-up because breast cancer etiology may differ between premenopausal and postmenopausal women. Tests for trend across exposure categories were performed for each agent. All p-values for trend were two-sided. Data analysis was conducted with SAS statistical software (version 9.3; SAS Institute Inc., Cary, NC).

Results

A total of 1,966 breast cancer cases were reported during follow-up (mean follow-up 5.2 years). Baseline characteristics of breast cases and non-cases are presented in Table 1. Women diagnosed with breast cancer were more likely than non-cases to be older, non-

Hispanic white, and have a later age at first birth. Lifetime prevalences of exposure to chemical agents are displayed in Table 2. The prevalence of occupational exposure varied from two percent for *pesticides* and *stains* to eight percent for *glues or adhesives*. Approximately 14% of the study population reported exposure to only one agent, and 11% reported working with two or more of the eleven agents in their lifetime.

Table 2 shows the risk of breast cancer associated with lifetime exposure to chemicals in the workplace. There were no significant associations between ever use of any of the chemical agents and breast cancer, and risk was unrelated to total number of agents (all p-values for trend ≥ 0.30). We observed a borderline excess risk of invasive breast cancer in women ever-exposed to *dyes or inks* (HR=1.2, 95% CI = 1.0–1.6). Occupational *gasoline or other petroleum product* use was associated with a reduced risk of in situ breast cancer (HR=0.5, 95% CI = 0.2–0.9).

Exposure-response associations between cumulative days of use and the risks of overall and invasive breast cancer are presented in Table 3. We observed a significant, positive trend between *gasoline or other petroleum products* use and overall breast cancer risk (p_{trend} = 0.03). Duration of *gasoline or other petroleum products* use was also positively associated with an increased risk of invasive breast cancer (p_{trend} = 0.02). Compared with women who never used *gasoline or other petroleum products, a* non-significant elevation in breast cancer risk was observed for women with the highest quartile of *gasoline or other petroleum products* use (Total: Q4 vs Never Use: HR=1.2, 95% CI = 0.8–1.9; Invasive : Q4 vs Never Use: HR=1.4, 95% CI = 0.9–2.3). Among women who reported working with *gasoline or other petroleum products*, breast cancer risk was significantly increased for women with workplace exposure at or above the highest quartile cutoff (Total Q4 vs Q1: HR=2.3, 95% CI = 1.1–4.9; Invasive Q4 vs Q1: HR= 2.5, 95% CI = 1.1–5.9) (Supplementary Table 1). *Dye or ink* use at or above the highest quartile cutoff was associated with a borderline increase in invasive breast cancer risk (Q4 vs Never Use: HR=1.5, 95% CI = 1.0–2.3).

We evaluated the risk of breast cancer by hormone receptor status. Tumors were characterized according to joint estrogen receptor and progesterone receptor expression. Tumors that were estrogen receptor or progesterone receptor positive were characterized as hormone receptor-positive and tumors that were estrogen receptor and progesterone receptor negative were characterized as hormone receptor-negative. Although hormone receptor-negative analyses were limited by small numbers, risk estimates did not differ significantly by hormone receptor status (Table 4). Consistent with the results for overall and invasive breast cancer, women with exposure to *gasoline or other petroleum products* in the highest quartile had a non-significant increased risk of hormone receptor-positive breast cancer (Q4 vs Never Use: HR=1.4, 95% CI = 0.9–2.3; Q4 vs Q1: HR= 2.5, 95% CI = 1.0–5.8, P_{trend} = 0.06) (Supplementary Table 2). A borderline increased risk of hormone receptor-positive breast cancer was also observed for women in the highest quartile of exposure to *paints* (Q4 vs Never Use: HR=1.4, 95% CI = 1.0–2.0).

Finally, we examined the association between lifetime exposures and breast cancer risk by menopausal status (Table 5). In general, the associations between workplace chemical exposures and breast cancer were stronger for premenopausal breast cancer. Compared with

Never users, we observed a significant excess risk of breast cancer in premenopausal women exposed to *soldering materials* (HR=1.8, 95% CI = 1.1–3.0).

Discussion

In this large cohort of women, we observed a significant association between occupational exposure to gasoline or petroleum products and breast cancer incidence. Among women exposed to gasoline or petroleum products, higher levels of cumulative exposure were significantly associated with an increased risk of breast cancer. Among premenopausal women, breast cancer risk was significantly elevated for women exposed to soldering materials. There were no significant associations between the other agents in this study and breast cancer.

Although several chemical components of gasoline and gasoline exhaust such as benzene and benzo(a)pyrene have been shown to induce mammary tumors in animals [4], only a handful of epidemiologic studies have reported an association between occupational exposures and breast cancer. Job titles with potential exposure to gasoline and exhaust emissions have been associated with male breast cancer in two case-control studies. An increased breast cancer risk was reported among Danish men exposed to gasoline or combustion products [17], and a multi-center European study reported an increased in breast cancer incidence in male motor vehicle mechanics [18]. In women, a Canadian population-based study reported an increase in breast cancer risk for gasoline service station attendants [19]. In the present study of workplace chemical exposures, higher levels of self-reported use of gasoline or petroleum products were associated with a significant increase in the risk of total and invasive breast cancer.

Workplace exposure to soldering materials was associated with an increased risk of breast cancer in premenopausal women. There are known differences in breast cancer risk factors for premenopausal and postmenopausal women [20, 21], and premenopausal exposure to toxicants such as cigarette smoke [22] and benzene [23] has been associated with an increased risk of breast cancer. Soldering may involve exposure to a variety of materials including metals, alloys, and fluxes. Only a handful of epidemiologic studies have investigated the relationship between metal exposures and breast cancer incidence, with positive results associated with environmental exposure to cadmium and lead [24, 25] and occupational metalworking [12]. Our findings for premenopausal breast cancer, in combination with the results of earlier studies [12, 19, 23], indicate that studies examining the relationship between occupational chemicals and breast cancer risk should further investigate the impact of premenopausal exposure to these compounds. More epidemiologic studies with detailed exposure assessments of chemical constituents and exposure time windows are needed to clarify the relationship between workplace chemical exposures and breast cancer.

Dye exposure was associated with a borderline elevated risk of invasive breast cancer. Previous studies of occupational dye use and breast cancer in women have focused on the use of hair dyes. Although IARC has declared that occupational exposures of hairdressers and barbers as “probably carcinogenic” to humans, the epidemiologic body of evidence

suggests that hair dye exposure, in general, is not a risk factor for breast cancer [26]. Dye use outside of cosmetology settings is an understudied exposure among women. Industrial dyes are commonly used in the production of cosmetics, detergents, pharmaceuticals, leather, paper materials, printing inks and other products. Textile manufacturing is the predominant sector for industrial dye use, and common components of textile dyes such as aromatic amines and phthalates have been associated with carcinogenesis and endocrine disruption. A total of 18 dyes have been identified as chemicals that cause mammary tumors in mice [4], and several textile dyes have exhibited potential endocrine disrupting properties in vitro [27]. Our findings suggest that further analyses are warranted to evaluate the impact of occupational dye exposures on breast cancer risk.

Major strengths of our study include the large sample size and longitudinal design of the Sister Study cohort. Comprehensive information on workplace exposures and breast cancer covariates were collected during the baseline interview, and there was high agreement between breast cancer cases reported during follow-up and medical records and pathology reports. Our study had limitations. We evaluated breast cancer risk in a cohort of women who each had a sister with breast cancer, and results may not be generalizable to women without a family history of breast cancer. Workplace exposures to chemical agents were self-reported in our study. However, it is unlikely that information bias produced spurious associations in this analysis as the prospective assessment of our cases precluded breast cancer-based exposure reporting.

We examined breast cancer incidence across cumulative exposure quartiles, and although we only observed a significant trend across these categories for gasoline or petroleum product use, it is possible that a linear exposure-response model may not have been the most appropriate approach for studying chemical exposures. There is considerable evidence that low-dose and non-monotonic exposures to endocrine disrupting compounds, for example, are associated with a variety of disease outcomes [28]. We used the assessment of lifetime (ever/never) exposure as a proxy for low-dose exposure; however, our models may not have fully accounted for the strength to disrupt or for the effects of low dose exposures on breast cancer risk.

Despite the large size of our cohort, the low prevalence of exposure to some agents and the small number of breast cancer diagnoses in some exposure categories (i.e., pesticides and stains) limited the statistical power of our study. We were also statistically limited in our ability to study the effect of combined chemical exposures and mixtures. Evaluating the association with one compound of interest likely underestimated the true risk of breast cancer associated with other potential carcinogens in the workplace, and the results of our study underscore the need for more research on breast cancer risks associated with multiple exposures and mixtures of potential carcinogens and endocrine disrupting compounds. Finally, we made multiple comparisons in our analysis, and it is possible that our findings may have been due to chance alone.

In summary, the results of this analysis suggest that workplace exposure to gasoline or petroleum products is associated with an increased risk of breast cancer. To our knowledge, this prospective study is the largest, to date, to examine the relationship between chemical

agents in the workplace and breast cancer in women. Our study's focus on workplace exposures presented a unique opportunity to examine the impact of chronic exposure to chemicals on breast cancer risk. Given that gasoline and petroleum products include a mixture of potentially carcinogenic and endocrine disrupting compounds, further studies are warranted to elucidate the role of these chemicals in breast cancer etiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of breast cancer cases and non-cases

	Non-Cases N=45,674 (96%) No. (%)	Cases N=1,966 (4%) No. (%)
Age at interview		
60+ years	14,840 (32)	771 (39)
55–59 years	9,114 (20)	379 (19)
50–54 years	8,862 (19)	351 (18)
<50 years	12,858 (28)	465 (24)
Race/Ethnicity		
Non-Hispanic White	37,980 (83)	1,700 (87)
Black	4,312 (9)	148 (8)
Hispanic	2,185 (5)	64 (3)
Other	1,185 (3)	53 (3)
Education at interview		
College/Post Grad	29,819 (65)	1,360 (69)
Some College	8,881 (19)	330 (17)
High School Grad/GED	6,435 (14)	260 (13)
<High School Grad	528 (1)	15 (1)
Household income at interview		
$100,000+/year	14,795 (34)	683 (36)
$50,000–<$100,000/year	17,889 (41)	753 (40)
$<50,000/year	11,248 (26)	449 (24)
Parity		
3+ births	13,938 (31)	570 (29)
2 births	16,853 (37)	731 (37)
1 birth	6,592 (14)	305 (16)
nulliparous	8,259 (18)	360 (18)
Age at first term pregnancy*		
28+ years	9,932 (28)	467 (30)
24–<28 years	9,557 (27)	413 (27)
21–<24 years	8,393 (23)	348 (23)
<21 years	8,051 (22)	314 (20)

*Among parous women only

Note: Differences in the total numbers of cases and non-cases are due to missing values

Table 2

Hazard ratios (HR) and 95% confidence intervals (CI) for total, invasive, and *in situ* breast cancer associated with lifetime exposure

Exposure[1]	Prevalence		Total Breast Cancer		Invasive Breast Cancer[3]		*In situ* Breast Cancer[3]	
	No.	(%)	Cases n = 1,966	HR[2]	Cases n = 1,421	HR[2]	Cases n = 531	HR[2]
Acids								
Ever Use	1554	(3)	75	1.1 (0.9, 1.4)	53	1.1 (0.8, 1.4)	22	1.2 (0.8, 1.9)
Never Use	46027	(97)	1,890	1.0	1,367	1.0	509	1.0
Dyes or inks								
Ever Use	2304	(5)	98	1.1 (0.9, 1.3)	80	1.2 (1.0, 1.6)	18	0.7 (0.4, 1.2)
Never Use	45299	(95)	1,868	1.0	1,341	1.0	513	1.0
Gasoline or other petroleum products								
Ever Use	1998	(4)	66	0.8 (0.7, 1.1)	54	1.0 (0.7, 1.3)	11	**0.5 (0.2, 0.9)**
Never Use	45613	(96)	1,899	1.0	1,366	1.0	520	1.0
Glues or adhesives								
Ever Use	3626	(8)	143	0.9 (0.8, 1.1)	105	0.9 (0.8, 1.1)	37	0.9 (0.6, 1.3)
Never Use	43986	(92)	1,823	1.0	1,316	1.0	494	1.0
Lubricating oils								
Ever Use	1222	(3)	40	0.9 (0.6, 1.2)	32	1.0 (0.7, 1.5)	7	0.5 (0.2, 1.2)
Never Use	46394	(97)	1,925	1.0	1,388	1.0	524	1.0
Metals								
Ever Use	1797	(4)	64	1.0 (0.7, 1.2)	46	1.0 (0.7, 1.3)	18	1.0 (0.6, 1.6)
Never Use	45830	(96)	1,901	1.0	1,375	1.0	512	1.0
Paints								
Ever Use	2962	(6)	115	1.0 (0.8, 1.2)	88	1.1 (0.8, 1.3)	27	0.7 (0.5, 1.1)
Never Use	44668	(94)	1,850	1.0	1,332	1.0	504	1.0
Pesticides								

Exposure[1]	Prevalence		Total Breast Cancer Cases n = 1,966	HR[2]	Invasive Breast Cancer[3] Cases n = 1,421	HR[2]	*In situ* Breast Cancer[3] Cases n = 531	HR[2]
	No.	(%)						
Ever Use	725	(2)	30	1.1 (0.7, 1.5)	26	1.3 (0.9, 2.0)	4	0.4 (0.1, 1.3)
Never Use	46899	(98)	1,935	1.0	1,395	1.0	526	1.0
Soldering materials								
Ever Use	1203	(3)	48	1.1 (0.8, 1.4)	36	1.1 (0.8, 1.6)	11	0.9 (0.5, 1.7)
Never Use	46430	(97)	1,918	1.0	1,385	1.0	520	1.0
Solvents								
Ever Use	2367	(5)	105	1.1 (0.9, 1.3)	74	1.1 (0.8, 1.3)	31	1.2 (0.8, 1.7)
Never Use	44948	(95)	1,849	1.0	1,339	1.0	496	1.0
Stains								
Ever Use	953	(2)	28	0.8 (0.5, 1.1)	22	0.8 (0.5, 1.3)	6	0.6 (0.3, 1.5)
Never Use	46678	(98)	1,938	1.0	1,399	1.0	525	1.0
Total number of agents								
2+ agents	5074	(11)	195	1.0 (0.8, 1.1)	150	1.1 (0.9, 1.3)	44	0.8 (0.6, 1.1)
1 agent	6903	(14)	289	1.0 (0.9, 1.2)	215	1.1 (0.9, 1.3)	73	0.9 (0.7, 1.2)
Never Use	35663	(75)	1,482	1.0	1,056	1.0	414	1.0
			p value for trend[4]	0.30	*p* value for trend[4]	0.47	*p* value for trend[4]	0.39

[1] Lifetime exposure to agent defined as affirmative response to the question “Have you handled [agent] at least once a week in any job?"

[2] Hazard ratios are adjusted for race/ethnicity, education, income, parity and age at first birth

[3] Competing subtypes were censored at time of diagnosis; 14 subtypes unknown

[4] Test for trend among exposed only

Note: Differences in the total numbers are due to missing values

Table 3

Hazard ratios (HR) and 95% confidence intervals (CI) for total breast cancer and invasive breast cancer associated with cumulative exposure

	Total Breast Cancer		Invasive Breast Cancer	
Cumulative Exposure (Quartiles)	**Cases n=1,966**	**HR[1]**	**Cases n=1,421**	**HR[1]**
Acids				
>1456 days	21	1.3 (0.8, 2.0)	17	1.4 (0.8, 2.3)
520 – ≤1456 days	17	1.1 (0.7, 1.8)	12	1.1 (0.6, 1.9)
154 – ≤520 days	23	1.2 (0.7, 1.8)	13	0.8 (0.4, 1.5)
<154 days	13	0.9 (0.5, 1.6)	10	1.0 (0.6, 1.8)
Never Use	1,890	1.0	1,367	1.0
p value for trend[2]		0.32		0.21
Dyes or inks				
>1560 days	26	1.2 (0.8, 1.8)	23	1.5 (1.0, 2.3)
520 – ≤1560 days	22	1.2 (0.8, 1.8)	15	1.1 (0.7, 1.8)
130 – ≤520 days	28	1.0 (0.7, 1.5)	27	1.3 (0.9, 2.0)
<130 days	22	1.1 (0.7, 1.5)	15	1.0 (0.6, 1.7)
Never Use	1,868	1.0	1,341	1.0
p value for trend[2]		0.47		0.31
Gasoline or other petroleum products				
>1300 days	23	1.2 (0.8, 1.9)	19	1.4 (0.9, 2.3)
468 – ≤1300 days	17	0.9 (0.6, 1.5)	15	1.1 (0.7, 1.9)
139 – ≤468 days	13	0.6 (0.4, 1.2)	10	0.7 (0.4, 1.3)
<139 days	12	0.6 (0.3, 1.1)	9	0.7 (0.3, 1.3)
Never Use	1,899	1.0	1,366	1.0
p value for trend[2]		**0.03**		**0.02**
Glues or adhesives				
>1612 days	37	0.9 (0.7, 1.3)	28	1.0 (0.6, 1.4)
520 – ≤1612 days	32	0.8 (0.6, 1.2)	22	0.8 (0.5, 1.3)
180 – ≤520 days	31	0.7 (0.5, 1.1)	22	0.8 (0.5, 1.2)
<180 days	43	1.2 (0.9, 1.6)	33	1.3 (0.9, 1.8)
Never Use	1,823	1.0	1,316	1.0
p value for trend[2]		0.53		0.52
Lubricating oils				
>1872 days	8	0.8 (0.4, 1.6)	8	1.1 (0.5, 2.2)
624 – ≤1872 days	8	0.7 (0.3, 1.5)	6	0.9 (0.4, 1.9)
208 – ≤624 days	14	1.2 (0.7, 2.2)	12	1.6 (0.9, 2.8)
<208 days	9	0.8 (0.4, 1.5)	5	0.6 (0.3, 1.5)

	Total Breast Cancer		Invasive Breast Cancer	
Cumulative Exposure (Quartiles)	**Cases n=1,966**	**HR[1]**	**Cases n=1,421**	**HR[1]**
Never Use	1926	1.0	1,389	1.0
p value for trend[2]		0.69		0.65
Metals				
>1716 days	21	1.3 (0.9, 2.1)	15	1.3 (0.8, 2.2)
607 – ≤1716 days	16	0.8 (0.5, 1.4)	12	1.0 (0.6, 1.8)
195 – ≤607 days	12	0.9 (0.5, 1.5)	8	0.8 (0.4, 1.6)
<195 days	15	0.8 (0.5, 1.4)	11	0.8 (0.4, 1.5)
Never Use	1,901	1.0	1,375	1.0
p value for trend[2]		0.19		0.26
Paints				
>1170 days	40	1.3 (0.9, 1.8)	26	1.1 (0.8, 1.7)
360 – ≤1170 days	25	0.9 (0.6, 1.4)	20	1.0 (0.7, 1.6)
104 – ≤360 days	20	0.8 (0.5, 1.2)	16	0.9 (0.5, 1.5)
<104 days	30	0.9 (0.6, 1.4)	26	1.2 (0.8, 1.8)
Never Use	1,850	1.0	1,332	1.0
p value for trend[2]		0.08		0.65
Pesticides				
>780 days	7	1.1 (0.5, 2.3)	6	1.3 (0.6, 2.9)
240 – ≤780 days	8	1.2 (0.5, 2.4)	6	1.4 (0.9, 3.1)
60 – ≤240 days	9	1.2 (0.6, 2.3)	8	1.4 (0.7, 3.0)
<60 days	5	0.8 (0.3, 1.9)	5	1.1 (0.5, 2.7)
Never Use	1,936	1.0	1,396	1.0
p value for trend[2]		0.70		0.95
Soldering materials				
>990 days	15	1.3 (0.8, 2.3)	10	1.4 (0.8, 2.6)
312 – ≤990 days	8	0.8 (0.4, 1.7)	6	0.9 (0.4, 1.9)
96 – ≤312 days	10	0.7 (0.4, 1.4)	9	0.9 (0.4, 1.8)
<96 days	14	1.3 (0.8, 2.2)	10	1.3 (0.7, 2.4)
Never Use	1,918	1.0	1,385	1.0
p value for trend[2]		0.85		0.90
Solvents				
>1300 days	26	1.1 (0.7, 1.7)	19	1.1 (0.7, 1.8)
438 – ≤1300 days	19	0.8 (0.5, 1.2)	16	0.9 (0.5, 1.5)
120 – ≤438 days	37	**1.6 (1.2, 2.3)**	21	1.3 (0.9, 2.1)
<120 days	22	0.9 (0.6, 1.4)	17	0.9 (0.5, 1.5)
Never Use	1,849	1.0	1,339	1.0

Cumulative Exposure (Quartiles)	Total Breast Cancer Cases n=1,966	Total Breast Cancer HR[1]	Invasive Breast Cancer Cases n=1,421	Invasive Breast Cancer HR[1]
p value for trend[2]		0.87		0.89
Stains				
>576 days	4	0.5 (0.2, 1.2)	3	0.5 (0.2, 1.5)
180 – ≤576 days	5	0.6 (0.2, 1.4)	5	0.8 (0.3, 2.5)
52 – ≤180 days	10	1.3 (0.7, 2.5)	9	1.6 (0.8, 3.2)
<52 days	9	1.0 (0.5, 1.9)	5	0.7 (0.3, 1.8)
Never Use	1,938	1.0	1,399	1.0
p value for trend[2]		0.13		0.42

[1] Hazard ratios are adjusted for race/ethnicity, education, income, parity and age at first birth

[2] Test for trend among exposed only

Note: Differences in the total numbers of cases are due to missing values

Table 4

Hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer associated with lifetime exposure by hormone receptor status

	HR+ Breast Cancer		HR− Breast Cancer	
	Cases n = 1,442	HR[1]	Cases n = 261	HR[1]
Acids				
Ever Use	55	1.1 (0.8, 1.5)	9	0.9 (0.4, 1.9)
Never Use	1,386	1.0	252	1.0
Dyes or inks				
Ever Use	73	1.1 (0.8, 1.4)	16	1.4 (0.9, 2.4)
Never Use	1,369	1.0	245	1.0
Gasoline or other petroleum products				
Ever Use	53	1.0 (0.7, 1.3)	7	0.6 (0.3, 1.4)
Never Use	1,388	1.0	254	1.0
Glues or adhesives				
Ever Use	106	1.0 (0.8, 1.2)	22	1.1 (0.7, 1.7)
Never Use	1,336	1.0	239	1.0
Lubricating oils				
Ever Use	29	0.9 (0.6, 1.3)	7	1.0 (0.5, 2.3)
Never Use	1,412	1.0	254	1.0
Metals				
Ever Use	48	1.0 (0.7, 1.3)	7	0.8 (0.4, 1.7)
Never Use	1,394	1.0	254	1.0
Paints				
Ever Use	93	1.1 (0.9, 1.3)	13	0.8 (0.5, 1.5)
Never Use	1,348	1.0	248	1.0
Pesticides				
Ever Use	24	1.2 (0.8, 1.8)	4	1.1 (0.4, 3.0)
Never Use	1,417	1.0	257	1.0
Soldering materials				
Ever Use	33	1.1 (0.7, 1.5)	9	1.2 (0.6, 2.6)
Never Use	1,409	1.0	252	1.0
Solvents				
Ever Use	80	1.1 (0.9, 1.4)	16	1.2 (0.7, 2.0)
Never Use	1,354	1.0	244	1.0
Stains				

	HR+ Breast Cancer		HR− Breast Cancer	
	Cases n = 1,442	**HR[1]**	**Cases n = 261**	**HR[1]**
Ever Use	19	0.7 (0.4, 1.1)	6	1.3 (0.6, 2.9)
Never Use	1,423	1.0	255	1.0
Total number of agents				
2+ agents	149	1.0 (0.9, 1.2)	30	1.1 (0.7, 1.6)
1 agent	214	1.1 (0.9, 1.2)	38	1.0 (0.7, 1.4)
Never Use	1,079	1.0	193	1.0
		p value for trend[2] 0.49		*p* value for trend[2] 0.86

[1]Hazard ratios are adjusted for race/ethnicity, education, income, parity and age at first birth

[2]Test for trend among exposed only

Note: Differences in the total numbers are due to missing values

Table 5

Hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer associated with lifetime exposure by menopause status

	Pre-menopausal Breast Cancer		Post-menopausal Breast Cancer	
	Cases n = 450	HR[1]	Cases n = 1,505	HR[1]
Acids				
Ever Use	24	1.3 (0.9, 2.1)	51	1.0 (0.8, 1.4)
Never Use	425	1.0	1,454	1.0
Dyes or inks				
Ever Use	26	1.4 (0.9, 2.1)	72	1.0 (0.8, 1.3)
Never Use	424	1.0	1,433	1.0
Gasoline or other petroleum products				
Ever Use	19	0.7 (0.4, 1.2)	45	0.9 (0.6, 1.2)
Never Use	430	1.0	1,460	1.0
Glues or adhesives				
Ever Use	34	1.1 (0.8, 1.6)	109	0.9 (0.7, 1.1)
Never Use	416	1.0	1,396	1.0
Lubricating oils				
Ever Use	7	0.6 (0.3, 1.3)	33	1.0 (0.7, 1.5)
Never Use	443	1.0	1,471	1.0
Metals				
Ever Use	20	1.2 (0.8, 2.0)	44	0.9 (0.6, 1.2)
Never Use	430	1.0	1,460	1.0
Paints				
Ever Use	28	1.0 (0.6, 1.4)	86	1.0 (0.8, 1.2)
Never Use	422	1.0	1,418	1.0
Pesticides				
Ever Use	12	1.5 (0.8, 2.7)	18	0.9 (0.6, 1.5)
Never Use	438	1.0	1,486	1.0
Soldering materials				
Ever Use	15	1.8 (1.1, 3.0)	33	1.4 (0.9, 2.1)
Never Use	435	1.0	1,472	1.0
Solvents				
Ever Use	32	1.3 (0.9, 1.9)	73	1.0 (0.8, 1.3)
Never Use	414	1.0	1,424	1.0
Stains				

	Pre-menopausal Breast Cancer		Post-menopausal Breast Cancer	
	Cases n = 450	**HR[1]**	**Cases n = 1,505**	**HR[1]**
Ever Use	8	1.1 (0.6, 2.2)	20	0.7 (0.5, 1.1)
Never Use	442	1.0	1,485	1.0
Total number of agents				
2+ agents	58	1.2 (0.9, 1.6)	137	0.9 (0.7, 1.1)
1 agent	70	1.1 (0.8, 1.5)	216	1.0 (0.9, 1.2)
Never Use	322	1.0	1,152	1.0
		p value for trend[2] 0.69		*p* value for trend[2] 0.18

[1]Hazard ratios are adjusted for race/ethnicity, education, income, parity and age at first birth

[2]Test for trend among exposed only

Note: Differences in the total numbers are due to missing values