Published in final edited form as:
Cancer Res. 2014 June 1; 74(11): 3076–3083. doi:10.1158/0008-5472.CAN-13-2430.

Breast cancer risk after occupational solvent exposure: the influence of timing and setting

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Abstract

Organic solvents are ubiquitous in occupational settings where they may contribute to risks for carcinogenesis. However, there is limited information on organic solvents as human breast carcinogens. We examined the relationship between occupational exposure to solvents and breast cancer in a prospective study of 47,661 women with an occupational history in the Sister Study cohort. Occupational solvent exposure was categorized using self-reported job-specific solvent use collected at baseline. Multivariable Cox regression analyses were used to assess breast cancer risk, adjusting for established breast cancer risk factors. A total of 1,798 women were diagnosed with breast cancer during follow-up, including 1,255 invasive cases. Overall, the risk of invasive breast cancer was not associated with lifetime exposure to solvents (HR: 1.04; 95% CI = 0.88–1.24). Parous women who worked with solvents prior to their first full-term birth had an increased risk of estrogen receptor-positive invasive breast cancer compared to women who never worked with solvents (HR: 1.39; 95% CI = 1.03–1.86). A significantly elevated risk for estrogen receptor-positive invasive breast cancer was associated with solvent exposure among clinical laboratory technologists and technicians (HR: 2.00; 95%CI: 1.07–3.73). Occupational exposure to solvents prior to first birth, a critical period of breast tissue differentiation, may result in increased vulnerability for breast cancer. Our findings suggest a need for future studies in this area to focus on exposure time windows and solvent types in different occupational settings.

Introduction

Organic solvents are chemicals that are ubiquitous in occupational settings. Solvents are present in the workplace through the use of adhesives, paints, degreasing agents, and cleaning products. Solvents are also used in industrial processes, including the manufacturing of computer components, plastics, pharmaceuticals, and textiles. In the United States, millions of workers are exposed to solvents on a daily basis [1]. Solvents such as benzene and trichloroethylene have been recognized by the International Agency for

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The authors disclose no potential conflicts of interest.

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Research on Cancer (IARC) and the US National Toxicology Program (NTP) as known human carcinogens; however there is limited data on solvents as human breast carcinogens [2, 3].

Animal studies have provided strong evidence for an association between organic solvents and breast cancer [4]. Benzene, methylene chloride, styrene, and vinyl chloride have been shown to cause mammary tumors in mice [5], and different mechanisms for breast carcinogenesis have been hypothesized. Solvents are lipophilic compounds that can accumulate in the adipose tissue of the breast where they are stored, biotransformed, and excreted into the parenchyma of the breast. If present in the parenchyma for a considerable amount of time, solvents or their metabolites can initiate or promote carcinogenesis through genotoxic mechanisms [6]. Several chemicals used as solvents have exhibited endocrine disrupting properties [7–9]. Endocrine disrupting chemicals can bind to estrogen receptors, disrupt estrogen-mediated pathways, and alter gene expression, thus making the mammary gland more vulnerable to tumor cell proliferation [10, 11].

Several epidemiologic studies have reported associations between occupational exposure to solvents and increased breast cancer risk [12–17]. In general, these studies have assessed risk associated with overall lifetime exposures. A few studies have observed elevated breast cancer risks among women who were occupationally exposed to solvents at young ages [12, 17], suggesting that early solvent exposure, prior to full differentiation of breast tissue, may result in increased vulnerability for breast cancer.

In this study, we examined the relationship between occupational exposure to solvents and breast cancer among women enrolled in the Sister Study, a large prospective cohort of women from the United States and Puerto Rico who have a family history of breast cancer. We used detailed occupational histories to study the risk of breast cancer among women who were occupationally exposed to solvents prior to their first full-term birth, a critical period of breast tissue differentiation. In order to study the impact of occupation-specific exposures, we also examined the relationship between self-reported exposure to solvents and breast cancer risk by occupation.

Materials and Methods

Study population

The Sister Study is a prospective cohort study of environmental and genetic risk factors for breast cancer [18]. The cohort consists of 50,884 initially breast cancer-free sisters of women who had been diagnosed with breast cancer. Participants enrolled in the study between 2003 and 2009. Baseline activities included a computer-assisted telephone interview and self-administered questionnaires that included questions about suspected risk factors for breast cancer. The Sister Study was approved by the institutional review boards at the National Institute of Environmental Health Sciences and Copernicus Group. Written informed consent was provided by study participants.

Exposure assessment

Lifetime occupational history and self-reported information on occupational exposures on each job were collected during the baseline interview. After excluding a vanguard group of women with incomplete occupational data (n=2,297), women without an occupational history (n=832), and women who were diagnosed with breast cancer prior to the baseline interview (n=94), the present analysis included 47,661 women who reported ever working at least one job. For each job held after the age of 18, study participants were asked whether they had worked with "solvents, degreasers, or other cleaning agents" (hereafter referred to as "solvents") on the job, and the first and last date of employment for each job.

In addition to lifetime solvent job exposure, several measures of exposure were determined for each participant who reported working with solvents: the duration of solvent job exposure in years, the weekly frequency of exposure to solvents, the time period of first solvent job, the age at first solvent job, and the time in years since last solvent job at baseline interview. For parous women, we determined the timing of first solvent job relative to first full-term birth, and for those women who reported working at a solvent job prior to their first full-term birth, we determined the duration of solvent job exposure prior to the birth.

The most commonly reported solvent-exposed occupations (minimum 50 study participants with self-reported solvent exposure) were classified and assigned into the following major occupational categories according to the 2010 United States Standard Occupational Classification (SOC) system: *Building and grounds cleaning and maintenance*; *Education, training, and library*; *Food preparation and serving related*; *Healthcare practitioner and technical*; *Management*; *Office administrative and support*; and *Production* occupations.

Follow-Up

Study participants reported incident breast cancer diagnoses via annual health updates and biennial self- or telephone-administered questionnaires. If a study participant reported a breast cancer diagnosis, we followed up with the participant about diagnostic details such as tumor subtype and estrogen receptor status and requested permission to contact their physician for medical records and pathology reports. We used data from self-report breast cancer characteristics only when medical record or pathology report data were not available. Participants were followed prospectively from baseline until date of invasive breast cancer diagnosis. Women reporting *in situ* breast cancer were censored at time of diagnosis. Women lost to follow-up or deceased from other causes were censored as appropriate.

Statistical Analysis

Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for invasive breast cancer and estrogen-receptor tumor subtypes were estimated using multivariable Cox proportional hazards regressions models with the study participant's age as the time scale. We used directed acyclic graphs (DAGs) to identify potential confounders [19]. Briefly, through a review of the literature, we identified potential confounders that were associated with both occupational solvent exposure and breast cancer, but were not direct descendants of both or in the causal pathway [20, 21]. The final multivariable model adjusted for 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+). Where appropriate, trends in incidence were examined across exposure categories.

To explore exposures within occupations, proportional hazards regressions analyses were carried out separately for each occupation with women who had never worked in the occupation as a reference group. For each occupation, hazard ratios were determined for two groups: solvent-exposed women and solvent-unexposed women. The statistical software package SAS (version 9.3, SAS Institute) was used for all analyses.

Results

A total of 1,798 breast cancer diagnoses were reported during the follow-up period (mean follow-up of 4.7 years). Among women with available information about tumor subtypes, approximately 70% (n=1,255) of breast cancer tumors were invasive, and 77% (n=968) of invasive tumors were estrogen-receptor positive. Characteristics of invasive breast cancer cases and the remainder of the cohort are displayed in Table 1. Women diagnosed with invasive breast cancer were more likely than non-cases to be older, non-Hispanic white, have higher educational attainment and income, and have a later age at first term pregnancy.

The hazard ratios for invasive breast cancer associated with solvent job exposure are shown in Table 2. Overall, there was no increased risk of invasive breast cancer among women exposed occupationally to solvents (HR = 1.04; 95% CI = 0.88–1.24). Longer duration of work and more frequent work with solvents and in solvent jobs were not associated with an increased risk of breast cancer. The breast cancer risk for women whose first solvent job was before 1980 was not different from the risk among women who first solvent job was in 1980 or later (a time period after regulatory interventions in the late 1970s). In latency analyses, the risk for women whose last solvent job was five or more years before the baseline interview was not significantly different from women who were recently exposed to solvents.

We evaluated the risk of invasive breast cancer associated with occupational solvent exposure for different periods of initial exposure. Age of first solvent exposure was not associated with breast cancer risk. Women who were exposed to solvents prior to their first birth had a non-significant increased risk of breast cancer (HR = 1.24; 95% CI = 0.95–1.63). Among parous women, there was a significant positive trend for duration of solvent work prior to first birth and breast cancer (P_{trend} = 0.04).

Results by estrogen receptor status are presented in Table 3. The overall association between any occupational exposure to solvents and invasive breast cancer incidence was elevated, but non-significant, for estrogen-receptor positive tumors (HR = 1.15; 95% CI = 0.95–1.39). Estrogen-receptor positive breast cancer was not associated with either frequency or duration of solvent exposure. There was, however, an increased risk for estrogen-receptor positive breast cancer among women whose first solvent job was prior to1980 (HR = 1.28; 95% CI = 1.01–1.62).

Compared to women who were never exposed to solvents, women who were exposed to solvents prior to their first birth had an increased risk of estrogen-receptor positive breast cancer (HR = 1.39; 95% CI = 1.03–1.86). Women who started working in solvent jobs after their first birth (HR = 1.05; 95% CI = 0.79–1.40) and nulliparous women with solvent job exposure (HR = 1.03; 95% CI = 0.69–1.54) did not have an increased risk for estrogen-receptor positive breast cancer. Parous women who were exposed to solvents for more than 5 years prior to their first birth had a borderline excess risk for developing estrogen-receptor positive breast cancer compared to women who were never exposed to solvents (HR = 1.56; 95% CI = 0.97–2.50). No statistically significant associations were observed between solvent exposure and estrogen-receptor negative breast cancer risk.

A total of 44 occupations had 50 or more women who were exposed to solvents. The results for women in occupations with a minimum of five breast cancer cases are presented in the supplementary table. A significant increase in estrogen receptor-positive breast cancer risk was observed among *clinical laboratory technologists and technicians* who worked with solvents (HR: 2.00; 95%CI: 1.07–3.73). Non-significant elevated risks were also observed for solvent-exposed *maids and housekeeping cleaners* (HR: 1.82; 95%CI: 0.90–3.67) and solvent-exposed women in *production* occupations (HR: 1.66; 95%CI: 0.86–3.22). Additional adjustment for alcohol consumption, environmental tobacco smoke exposure, smoking, and work at night did not have an impact on occupation-specific point estimates (data not shown).

Discussion

In this large cohort of women, there was no overall association between occupational exposure to solvents and invasive breast cancer risk. We observed an elevated risk of estrogen receptor-positive tumors among women who were exposed to solvents prior to their first full term birth, independent of known confounding factors. Our findings support the hypothesis that chemical exposure prior to breast tissue differentiation may be a risk factor for breast cancer.

This study examined the association between an occupational exposure prior to first birth and breast cancer. An increased risk associated with pre-birth occupational exposure to solvents is biologically plausible. The years prior to the first birth of a child have been identified as a critical period of exposure for breast tissue susceptibility [22]. Furthermore, studies of women exposed to cigarette smoke [23–25], DDT [26], ionizing radiation [27, 28], and traffic-related polycyclic aromatic hydrocarbons (PAH) [29] have reported elevated risks among younger women, providing evidence that developing breast tissue may be more vulnerable to potential carcinogens. We did not observe an association between solvent exposure and breast cancer among nulliparous women. Our results suggest that solvent exposure prior to and in combination with the proliferative changes that occur during pregnancy may play a role in breast cancer development.

We are aware of only one other study that reported an association between occupational chemical exposures before first full-term pregnancy and breast cancer risk. In a recent case-control study with 1005 cases, Brophy et al. observed an increased risk for Canadian women who worked with automotive plastics between menarche and the first full-term pregnancy [30]. Two previous case-control studies of women occupationally exposed to solvents have reported increased breast cancer risks for women exposed at young ages. A Danish study reported an elevated risk of breast cancer among women aged 55 or younger in solvent-using industries [12], and a Canadian study reported an increased risk for breast cancer among women who worked with solvents before the age of 36 [17]. Our study is the first with a cohort design to report an association between early solvent exposure and breast cancer risk.

Null results for lifetime solvent exposure may reflect our assessment of solvents as a group of chemicals, rather than individual compounds or mixtures. Occupational studies of breast cancer risk in women have reported significant associations with several types of solvents. A significant exposure-response breast cancer trend was observed in a cohort of Finnish women exposed to aromatic hydrocarbon solvents [13]. In a large study of active duty military women, women in occupations with moderate-high volatile organic compound (VOC) exposure had significantly higher incidence rates for breast cancer compared to low-unexposed VOC exposure [31]. Trichloroethylene, but not any of the other organic solvents assessed in a cohort of civilian maintenance workers, was associated with a non-significant excess risk for breast cancer [32].

Several studies have reported inconsistent associations between occupational solvent exposure and breast cancer by hormone receptor status. One study, comprised of 2383 incident cases, found that solvent exposure was significantly associated with 120 estrogen- and progesterone-receptor negative tumors [16]. Others have reported no difference in risk among hormone receptor types associated with lifetime solvent [17] and benzene [16] exposure. A case-control study with 556 cases reported increased risks for estrogen receptor-positive and progesterone receptor-negative tumors in women who were exposed before age 36 years [17], and another study of only 56 cases and 35 controls found a greater risk for estrogen receptor-positive tumors among premenopausal women exposed to benzene [33]. We had limited power to evaluate results jointly by both estrogen receptor and progesterone receptor status in this study; however risk estimates tended to be higher for estrogen receptor-positive tumors compared to estrogen receptor-negative tumors.

We identified occupations that had elevated breast cancer risks associated with solvent exposure. A significantly elevated risk for estrogen receptor-positive breast cancer was associated with solvent exposure among *clinical laboratory technologists and technicians*. Studies of breast cancer among laboratory workers have produced inconsistent results, primarily due to incomplete information about reproductive and lifestyle characteristics, but also because of incomplete information about workplace exposures. In addition to laboratory solvents, clinical laboratory workers may be exposed to elevated levels of solvents and degreasers through routine tasks like applying topical cleansers and antiseptics, sterilizing instruments, and other general cleaning activities. Other possible explanations for the observed excess risk could include inadequate personal protection measures or unmeasured confounding due to exposure to potentially carcinogenic or endocrine disrupting compounds in the workplace.

Solvent exposed *maids and housekeeping cleaners* had an elevated, non-significant risk for breast cancer. Although shift work and work at night is common in this population, only those reporting solvent exposure had an increased breast cancer risk; thus, irregular work schedule is an unlikely explanation for our observation. *Maids and housekeeping cleaners* are an understudied population that may be at risk for breast cancer. Women in this occupation are exposed to a variety of chemicals, including solvent-containing cleaning products and disinfectants. Cleaning product use has been associated with increased breast cancer risk in women [34].

A non-significant increase in breast cancer risk was also observed among solvent-exposed women in *production* occupations. Previous epidemiologic studies have reported elevated breast cancer risks in manufacturing occupations such as automotive plastics manufacturing, rubber and plastic manufacturers, metal work, and textile workers [30, 31, 35]. Women in these settings may have had concurrent exposure to solvents, metals, dusts and other potential carcinogens. This study, like many previous occupational studies, was unable to evaluate the impact of chemical mixtures on breast cancer risk.

The major strengths of this study include its large sample size, comprehensive occupational history data, and extensive information on important breast cancer covariates. We were able to prospectively examine the association between occupational solvent exposures and breast cancer risk, adjusting for established demographic, socioeconomic, and reproductive risk factors. This study had a sizeable proportion of working women with detailed individual information about exposure to solvents, and we used these data to evaluate the exposure-response relationship between duration of occupational solvent exposure and breast cancer incidence. In addition, we were able to evaluate the impact of solvent exposure during a critical period of breast development in women. The results of this study support a more biologically-based exposure assessment approach to studies of chemical exposures and breast cancer.

Our study has several potential limitations associated with exposure assessment. We assessed solvent exposure via self-report, and participants may have had difficulty recalling solvent exposures in their workplace. Any misclassification of lifetime solvent exposure, however, is likely to be nondifferential, thus leading to an underestimation of effect. Similarly, unmeasured household or environmental solvent exposures would not explain the elevated risks we observed as it is unlikely that residential or environmental exposures differed by occupational solvent exposure status.

We combined self-reported exposures and occupational coding of job titles to create a composite index of solvent exposure and identify occupations that had elevated breast cancer risks associated with solvent exposure. Although this composite measure reduced the potential for solvent exposure misclassification, our results by occupation should be interpreted with caution as they involved multiple comparisons and relatively small numbers of breast cancer cases for some occupations. Adjusting for alcohol use, smoking, environmental tobacco smoke, and work at night did not alter our occupation-specific results. Nevertheless, because these data were based on retrospective self-reports, we cannot fully rule out the potential confounding effects of these risk factors or other unmeasured socioeconomic factors that may act as negative confounders. Also, in spite of the size of our cohort, some occupational groups with elevated solvent-exposed risks may not have been identified due to small group sizes and low exposure prevalence.

In this study, we did not control for simultaneous exposures to other potential occupational carcinogens in the workplace that could have been associated with breast cancer. Additional exposure studies focusing on the high-risk occupations identified in this study may yield new insights into the types of solvents used across different occupational settings and the role of other occupational exposures as carcinogens potentially associated with breast cancer.

Our results suggest that occupational exposure to solvents prior to first full-term birth is associated with an increased risk of breast cancer. Further large-scale epidemiological studies are warranted to explore the relationship between the timing of occupational chemical exposures and breast cancer incidence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support: This research was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences, (Z1A ES044005).

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Table 1

Selected characteristics of invasive breast cancer cases and non-cases at time of enrollment

	Non-Cases[a] N=46,381 (97%) No. (%)	Cases[b] N=1,255 (3%) No. (%)
Age at interview		
60+ years	15,091 (33)	518 (41)
55–59 years	9,240 (20)	253 (20)
50–54 years	9,011 (19)	201 (16)
<50 years	13,039 (28)	283 (23)
Race/Ethnicity		
Non-Hispanic White	38,577 (83)	1,100 (88)
Black	4,388 (9)	72 (6)
Hispanic	2,199 (5)	49 (4)
Other	1,205 (3)	33 (3)
Education at interview		
College/Post Grad	30,323 (65)	854 (68)
Some College	8,992 (19)	218 (17)
High School Grad/GED	6,520 (14)	174 (14)
<High School Grad	535 (1)	8 (1)
Household income at interview		
$100,000+/year	15,061 (34)	416 (35)
$50,000–<$100,000/year	18,162 (41)	479 (40)
$<50,000/year	11,397 (26)	298 (25)
Parity		
3+ births	14,134 (30)	372 (30)
2 births	17,124 (37)	458 (36)
1 birth	6,693 (14)	203 (16)
nulliparous	8,398 (18)	222 (18)
Age at first term pregnancy[c]		
28+ years	10,095 (28)	302 (30)
24–<28 years	9,706 (27)	262 (26)
21–<24 years	8,511 (23)	227 (23)
<21 years	8,162 (22)	204 (21)

[a]Non-invasive cases were censored at the date of diagnosis

[b]Excluding 25 cases missing information on date of diagnosis date

[c]Among parous women only

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

Table 2

Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for breast cancer associated with solvent job exposure

	Person-years	Cases[a] N=1,255 No. (%)	Adjusted HR[b], (95% CI)
Solvent job			
Ever	30,386	163 (13)	1.04 (0.88,1.24)
Never	195,219	1092 (87)	Ref
Total duration of solvent job(s) exposure			
10+ years	12,597	77 (6)	1.14 (0. 90, 1.45)
5 – <10 years	7,368	36 (3)	0.96 (0.68, 1.35)
1 – <5 years	10,422	50 (4)	0.98 (0.74, 1.32)
Never	195,219	1092 (87)	Ref
Trend[c]			p=0.35
Frequency of solvent exposure			
1+/week	6,666	37 (3)	0.97 (0.69, 1.37)
<1/week	23,034	123 (10)	1.07 (0.88, 1.30)
Never	195,219	1092 (87)	Ref
Time period of first solvent job			
Prior to 1980	14,898	98 (8)	1.16 (0.93, 1.44**)**
1980 and after	15,448	65 (5)	0.91 (0.70, 1.18)
Never	195,219	1092 (87)	Ref
Time since last solvent job at baseline interview			
5+ years	20,177	113 (9)	1.05 (0.86, 1.29)
Current − <5 years	10,170	50 (4)	1.03 (0.77, 1.38)
Never	195,219	1092 (87)	Ref
Age at first solvent job at baseline interview			
35+ years	7,328	41 (3)	1.04 (0.76, 1.44)
25 – <35 years	8,457	42 (3)	0.97 (0.70, 1.34)
20 – <25 years	7,903	39 (3)	0.95 (0.68, 1.32)
<20 years	6,658	41 (3)	1.27 (0.92, 1.75)
Never	195,219	1092 (87)	Ref
Trend[c]			p=0.73
Timing of first solvent job			
Prior to first birth	9,613	57 (5)	1.24 (0.95, 1.63)
After first birth	14,509	75 (6)	0.98 (0.76, 1.26)
Nulliparous	6,189	31 (2)	0.92 (0.63, 1.33)
Never	195,219	1092 (87)	Ref
Duration of solvent job(s) exposure relative to first birth[d]			
5+ years before first birth	3,046	21 (2)	1.42 (0.92, 2.20)
3 – <5 years before first birth	2,763	18 (2)	1.30 (0.80, 2.10)

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	Person-years	Cases[a] N=1,255 No. (%)	Adjusted HR[b], (95% CI)
<3 years before first birth	3,804	18 (2)	0.92 (0.57, 1.49)
After first birth	14,509	75 (7)	0.97 (0.75, 1.25)
Never	159,720	901 (87)	Ref
Trend[c]			**p=0.04**

[a]Excluding 25 cases missing information on date of diagnosis

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

[c]Test for trend among solvent-exposed only

[d]Among parous women only

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

Table 3

Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for breast cancer associated with solvent job exposure by estrogen receptor status

	ER+ Tumors			ER− Tumors		
	Person-years	Cases[a] N=968 No. (%)	Adjusted HR[b], (95% CI)	Person-years	Cases[a] N=197 No. (%)	Adjusted HR[b], (95% CI)
Solvent job						
Ever	30,373	132 (14)	1.15 (0.95, 1.39)	30,373	27 (14)	0.91 (0.58,1.43)
Never	194,930	836 (86)	Ref	194,930	170 (86)	Ref
Total duration of solvent job(s) exposure						
10+ years	12,584	59 (6)	1.20 (0.92, 1.57)	12,584	14 (7)	1.07 (0.58, 1.97)
5 – <10 years	7,368	32 (3)	1.20 (0.83, 1.71)	7,368	4 (2)	0.35 (0.09, 1.40)
1 – <5 years	10,422	41 (4)	1.06 (0.77, 1.46)	10,422	9 (5)	1.11 (0.57, 2.19)
Never	194,930	836 (86)	Ref	194,930	170 (86)	Ref
Trend[c]			p=0.62			p=0.75
Frequency of solvent exposure						
1+/week	6,661	31 (3)	1.12 (0.77, 1.63)	6,661	5 (3)	0.55 (0.18, 1.74)
<1/week	23,027	98 (10)	1.16 (0.94, 1.44)	23,027	22 (11)	1.05 (0.65, 1.70)
Never	194,930	836 (87)	Ref	194,930	170 (86)	Ref
Time period of first solvent job						
Prior to 1980	14,893	80 (8)	**1.28 (1.01, 1.62)**	14,893	16 (8)	1.01 (0.57, 1.79)
1980 and after	15,440	52 (5)	1.00 (0.75, 1.34)	15,440	11 (6)	0.80 (0.40, 1.57)
Never	194,930	836 (86)	Ref	194,930	170 (86)	Ref
Time since last solvent job at baseline interview						
5+ years	20,169	96 (10)	1.22 (0.98, 1.51)	20,169	16 (8)	0.74 (0.41, 1.34)
Current − <5 years	10,164	36 (4)	1.01 (0.72, 1.42)	10,164	11 (6)	1.27 (0.66, 2.42)
Never	194,930	836 (86)	Ref	194,930	170 (86)	Ref
Age at first solvent job at baseline interview						
35+ years	7,328	33 (3)	1.14 (0.80, 1.62)	7,328	7 (4)	1.00 (0.44, 2.27)
25 – <35 years	8,445	32 (3)	1.00 (0.70, 1.45)	8,445	8 (4)	1.02 (0.48, 2.19)
20 – <25 years	7,903	34 (4)	1.14 (0.80, 1.62)	7,903	4 (2)	0.32 (0.08, 1.30)

	ER+ Tumors			ER− Tumors		
	Person-years	Cases[a] N=968 No. (%)	Adjusted HR[b], (95% CI)	Person-years	Cases[a] N=197 No. (%)	Adjusted HR[b], (95% CI)
<20 years	6,658	33 (3)	1.38 (0.97, 1.97)	6,658	8 (4)	1.40 (0.65, 2.99)
Never	194,930	836 (86)	Ref	194,930	170 (86)	Ref
Trend[c]			p=0.54			p=0.68
Timing of first solvent job						
Prior to first birth	9,612	48 (5)	**1.39 (1.03, 1.86)**	9,612	8 (4)	1.00 (0.47, 2.15)
After first birth	14,497	57 (6)	1.06 (0.79, 1.41)	14,497	15 (8)	0.90 (0.48, 1.68)
Nulliparous	6,189	27 (3)	1.03 (0.69, 1.54)	6,189	4 (2)	0.82 (0.29, 2.29)
Never	194,930	836 (86)	Ref	194,930	170 (86)	Ref
Duration of solvent job(s) exposure relative to first birth[d]						
5+ years before first birth	3,045	18 (2)	1.56 (0.97, 2.50)	3,045	2 (1)	0.91 (0.22, 3.73)
3 – <5 years before first birth	2,763	13 (2)	1.28 (0.74, 2.23)	2,763	5 (3)	1.98 (0.73, 5.37)
<3 years before first birth	3,804	17 (2)	1.14 (0.70, 1.88)	3,804	1 (1)	0.33 (0.05, 2.38)
After first birth	14,497	57 (7)	1.05 (0.79, 1.40)	14,497	15 (9)	0.88 (0.47, 1.65)
Never	159,475	689 (87)	Ref	159,475	141 (86)	Ref
Trend[c]			p=0.05			p=0.76

[a] Excluding cases missing information on estrogen receptor status

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

[C] Test for trend among solvent-exposed only

[D] Among parous women only

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