Occupational exposure to solvents and risk of breast cancer.

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Abstract

Background

Occupational exposure to some organic solvents may increase risk of breast cancer.

Methods

In a population-based case-control study, 1205 women diagnosed with primary breast cancer between 2009 and 2011 were drawn from the Western Australian Cancer Registry and matched to 1789 controls from the electoral roll. Exposure to solvents was determined through telephone interviews using OccIDEAS.

Results

About a third of women were occupationally exposed to solvents. Age adjusted breast cancer risks were elevated for women who had been exposed to aliphatic solvents odds ratio (OR) 1.21 (95% CI 0.99 - 1.48) and aromatic solvents OR 1.21 (95% CI 0.97 - 1.52). For most solvents the ORs were higher for those diagnosed before menopause.

Conclusions

This study suggests that there may be an association between occupational exposure to aliphatic and aromatic solvents and the risk of breast cancer at the low levels of exposure experienced by women in this study.

Key Words: organic solvent, breast cancer, case-control study, occupational exposure, OccIDEAS.

Introduction

Solvents are volatile organic compounds that have the ability to dissolve a large array of materials, are lipophilic and are used widely in the workplace. They include compounds such as benzene and other aromatic hydrocarbons and chlorinated solvents such as methylene chloride. In 1997, it was hypothesized that organic solvents act directly as genotoxic agents or indirectly through their metabolites to cause breast cancer (Labrèche and Goldberg 1997). Evidence supporting this hypothesis is that many organic solvents have been detected in breast milk (Labrèche and Goldberg 1997; Brophy, Keith et al. 2006; Brody, Moysich et al. 2007), the majority of carcinomas occur in the lobular/duct system (Brophy, Keith et al. 2006), and some organic solvents have been shown to produce mammary gland cancer in animals (Brophy, Keith et al. 2006; Brody, Moysich et al. 2007). Since then, a number of other studies have suggested that exposure to solvents at work is associated with about a 50% increased risk of breast cancer; (Petralia, Chow et al. 1998; Hansen 1999; Band, Le et al. 2000; Rennix, Quinn et al. 2005).

A review of studies investigating occupational exposure to solvents and risk of breast cancer showed an elevated risk for jobs associated with solvent exposure, particularly chlorinated solvents, in several industries (Brody, Moysich et al. 2007). However, the authors concluded that the existing data were inadequate and criticised many of the occupational cohort studies because the follow up periods were too short and they were cancer mortality rather than incidence studies.

There is also uncertainty as to the specific type of solvent that might be associated with an increased risk of breast cancer. In general population studies, authors have suggested that there may be associations between increased risk of breast cancer and working in particular industry sectors which can result in solvent exposure. For example the metal product, wood and furniture,

printing, chemical and textile and clothing industries (Hansen 1999), automotive related industries (Brophy, Keith et al. 2006), electrical and electronic work (Peplonska, Stewart et al. 2007) or textiles, rubber and plastics product makers (Villeneuve, Favotte et al. 2011). These studies, however, may have been confounded by known breast cancer risk factors such as physical activity and reproductive history; factors likely to differ between women in the paid workforce and those who are not.(Brody, Moysich et al. 2007) In addition, the use of job title to determine exposure to solvents, may have resulted in misclassification because not all those who work in the industry sector will be exposed to the solvents under study and the type of solvents used varies widely by industry sector.

The aim of our study was to investigate the relationship between occupational exposure to specific types of solvents and the risk of breast cancer among women residing in Western Australia.

Methods

We conducted a population-based case-control study with 1205 women aged between 18 and 80 years who had a first incident invasive primary breast cancer diagnosed between 2009 and 2011 identified through the Western Australian Cancer Registry, (Fritschi, Erren et al. 2013) Women with ductal carcinoma in situ, were excluded. Cases were sent an invitation letter, consent form and questionnaire by the Cancer Registry and, if the woman consented, her details, including estrogen receptor status, were released to the study team. Information on estrogen receptor status was missing 177 cases.

We also recruited 1789 age-matched controls randomly selected from the Western Australian electoral roll. Controls were sent a letter, consent form and questionnaire by the study team. Control women with a previous diagnosis of invasive breast cancer were excluded. Other ineligibility criteria for both cases and controls were having an incorrect address or not being resident in Western Australia; too unwell to participate or having inadequate English language ability.

Fourteen days after initial contact, all women who had not yet responded were telephoned if a contact number was available. A reminder letter was sent 28 days after the initial contact to any non-respondents.

A self-administered questionnaire was used to collect demographic, reproductive and lifestyle factors as well as lifetime occupational history (detailed information on every job a woman had held for at least six months). Using the web-based application OccIDEAS (Fritschi, Friesen et al. 2009), we obtained details about job characteristics by telephone interview asking questions tailored to assess solvent exposure. The interviewer asked the participant about their job and details of the tasks carried out. For example, a driver would be asked what kind of

vehicle they drove, what fuel it used and whether they refueled the vehicle themselves. Participants were also asked about relevant exposure circumstances of some tasks, e.g. whether it was in the open air, whether there was local exhaust ventilation or whether personal protection was used. To limit respondent burden, where a woman had multiple jobs, we chose up to five of her jobs for the interview. These were usually the longest held, or most different from other jobs.

Algorithms applied to the interview answers provided automatic assessments which were manually reviewed to assess occupational exposure to the solvents. Exposure was allocated as none, possible and probable to each of the following groups of solvents: aromatic solvents excluding benzene, aliphatic solvents, chlorinated solvents and alcohols based on the answers to the questions. We also separately identified exposure to benzene.

We estimated the risk of breast cancer that was associated with having ever been probably exposed one or more of the various solvent groups. We also considered the relationship between solvents and breast cancer subtypes related to the presence of the estrogen receptor ER status, obtained from the case's pathology records because there is evidence that the risk profiles differ for these subtypes of breast cancer (Althuis, Fergenbaum et al. 2004; Nichols, Trentham-Dietz et al. 2005).

In addition the risk associated with exposure in the periods of ≤10 years, >10 to ≤20 years, >20 to ≤30 years and >30 years prior to diagnosis for cases or to recruitment for controls, was compared to the risk for those who were never exposed in regression models.

Logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (CI), adjusted for age. We also considered other known risk factors for breast cancer in the model including body mass index (BMI in their 30s), age at menarche, smoking, alcohol consumption, hormonal replacement therapy, age at first birth, parity and family history of breast

cancer. We tested the potential confounding by these factors by adding each factor to the model for each solvent and if inclusion of factors led to a change in the OR associated with the solvent by 5% or greater it was kept it the model (Wang 2007). *A priori* we hypothesized that menopause status might modify the effect of solvent exposure and we undertook a stratified analyses of the risk by menopause status. To assess the relationship between solvents and breast cancer subtypes related to the presence of the estrogen receptor ER status we used multinomial logistic regression to calculate ORs for estrogen receptor–positive (ER+)/estrogen receptor–negative (ER-) cases relative to controls. We used STATA/IC statistical software (v 13.1, StataCorp LP, College Station, TX, USA) for all analyses.

All cases and controls signed written informed consent and the research was approved by Human Research Ethics Committees of The University of Western Australia and the Department of Health, Western Australia.

Results

Of the 2084 eligible cases invited to participate, 1205 consented (57.8%), 334 refused, and 545 did not respond. Of eligible controls, 1789 (41.1%) consented to participate, 939 refused, and 1628 failed to respond. Three cases and four controls did not complete the occupational section of the questionnaire, thus were missing solvent exposure data and were excluded.

Demographic characteristics are presented in Table I. The control women who were invited to participate were frequency matched on age to the cases. A higher proportion of younger cases participated compared with the controls, so the controls were overall slightly older than the cases, and were more likely to be post-menopausal. Cases were more likely to have had higher education than controls but were similar in socioeconomic distributions and had similar BMIs at age 30. As expected, cases were more likely to have a family history of breast cancer, were slightly younger at menarche, were less likely to have had children, less likely to have breastfed and less likely to have used HRT. Cases were somewhat more likely to have ever smoked than cases. Alcohol intake was similar for cases and controls. The demographic details about the participants are discussed in more detail elsewhere (Fritschi, Erren et al. 2013).

Thirty-one percent of respondents were ever exposed to at least one organic solvent group (29.9% controls and 32.5% cases). Half of these participants (14.5% of the total) were exposed to one type of solvent, 7.8% of the total were exposed to two types and 8.6% to three or more types. OccIDEAS estimates exposure as High, Medium or Low, but there were few women that were classified as ever having experienced high exposure: benzene n=1; other aromatic solvents n=6; chlorinated solvents n=4; aliphatic solvent n=2 and alcohol n=0. A small number of women were allocated to the possible exposure category (n=46) and these were

combined with the no exposure category because exposure was not thought to be likely on reviewing their job histories.

Age-adjusted breast cancer risks were modestly elevated for exposure to alcohol (OR=1.15) and to aliphatic (OR=1.21) or aromatic solvents other than benzene (OR=1.21), the risks, however were not statistically significantly raised for any of the solvent groups. (Table II) When adjustment was made for exposure to each of the other solvents, the odds ratios were reduced (ORs= 1.11, 1.01 and 1.17 respectively) (Supplementary Table I).

The ORs for breast cancer and exposure to four of the five specific solvent groups (not alcohol exposure) were somewhat stronger for cancers occurring before menopause, although none of the odds ratios or interaction terms were statistically significant and the 95% CIs of the pre- and postmenopausal risk estimates overlapped. (Table II).

Multinomial logistic regression showed that the presence of the ER receptor did not affect risks associated with most solvent exposures but the numbers of ER positive cases are small (see Supplementary Table II). Exposure to alcohols showed limited evidence of an association.

Examining exposure with all the time windows at different time periods before diagnosis/interview in a single regression model showed that exposure to benzene and chlorinated solvents in the last 11-20 years before diagnosis was most strongly associated with risk of breast cancer but the associations were not statistically significant. (Table III)

No significant associations were observed between breast cancer and exposure before the birth of the first child to any solvents: benzene (OR=0.82, 95%CI: 0.50-1.36); other aromatic solvents (OR=1.17, 95%CI: 0.83-1.66); aliphatic solvents (OR=1.21, 95%CI: 0.88-1.68); chlorinated solvents (OR=1.34, 95%CI: 0.76-2.37); and alcohol (OR=1.03, 95%CI: 0.83-1.27).

BMI, age at menarche, smoking, alcohol consumption, hormonal replacement therapy, age at first birth, parity and family history of breast cancer had minimal effect on the solvent exposure risk estimates (<3%) so these variables were not included as adjustments of the results presented here.

Discussion

Our results suggest that about a third of women in the Australian general population have been exposed to solvents at work. When age adjusted, there is a non-statistically significantly elevated risk of breast cancer for those women exposed to solvents, the risk being more strongly associated with exposure to alcohols, aromatic and aliphatic solvents than with chlorinated solvents or benzene.

Our findings are consistent with previous reports of an elevated risk of breast cancer associated with occupations where exposure to solvents is likely. (Petralia, Chow et al. 1998; Hansen 1999; Band, Le et al. 2000; Rennix, Quinn et al. 2005). In most cases the type of solvent is not identified (Brody, Moysich et al. 2007) however a few studies identified risks associated with specific solvents or solvent groups. Exposure to aromatic hydrocarbon solvents identified from a job-exposure matrix, was associated with increased risk of post-menopausal breast cancer, the SIR for the highest of 4 exposure levels was 1.2 (confidence intervals not provided), but no convincing association with increasing exposure to chlorinated solvents was observed (Weiderpass, Pukkala et al. 1999) Another study identified that high probability of exposure to benzene was associated with an increased risk of breast cancer SIR 1.3 (95% CI 1.0 - 1.7).(Petralia, Chow et al. 1998) Women who worked in aircraft maintenance were exposed to a number of solvents. When compared to unexposed workers, several solvents were associated with rather larger increased risks of breast cancer including isopropyl alcohol relative risk (RR) 3.7 (95% CI 1.6 - 8.4), trichloroethane RR 3.3 (1.0 - 11.2), toluene RR 2.0 (0.9 - 4.2) and methyl ethyl ketone RR 2.1 (0.9 to 4.7). Exposure to several of the solvents was correlated however. (Blair, Hartge et al. 1998)

Our study suggests that the association is stronger for aliphatic and aromatic solvent exposure than for other solvent exposures. Chlorinated solvent exposure was most common in

dry cleaning while aromatic and aliphatic solvent exposure occurred when handling fuel, paints and glues. There may well have been co-exposure to several solvents, particularly for the aliphatic and aromatic solvents but our data did not show that co-exposure increased the risks of breast cancer.

We did not find an increased premenopausal-cancer risk for women exposed to alcohol at work or for women exposed to any solvent. There were fewer premenopausal cases than post-menopausal diagnosed-cases so the CIs of the premenopausal cases were wider and overlapped with those of post-menopausal cases. We did however, find that the risk was somewhat more strongly associated with premenopausal diagnosis than post-menopausal diagnosis for chlorinated, aliphatic and aromatic solvent exposures (including benzene). This is line with other studies where premenopausal breast cancers were more likely to be solvent-related than those occurring after the menopause. (Labrèche, Goldberg et al. 2010; Ekenga, Parks et al. 2014) A recent case-control study asked participants whether they had worked with "solvents, degreasers, or other cleaning agents" in each job held after the age of 18. Overall the risk of invasive breast cancer was not associated with lifetime exposure to solvents but the authors suggested that occupational exposure to solvents before the birth of the first child appeared to be a higher risk. (Ekenga, Parks et al. 2014) Examining the risk in time different time periods before diagnosis has not shown consistent results. (Labrèche, Goldberg et al. 2010; Ekenga, Parks et al. 2014)

The OccIDEAS methodology asks participants about specific tasks rather than specific exposures and most exposures are allocated automatically using predefined rules which is likely to reduce recall bias. Where expert judgment was applied, this was done without knowledge of case-status. Some non-differential bias may have occurred and this could have reduced the

observed odds ratio. (Copeland, Checkoway et al. 1977) There is less likely to be misclassification however than using a Job-Exposure matrix where all individuals with the same job would be allocated the same exposure.

This study had a relatively large number of participants who were reasonably well matched to controls. Australian citizens over the age of 18 are legally required to join the Australian electoral roll and controls could be selected according to age bands so that they were representative sample of women in Western Australia matched to the cases on age.

In Australia there is mandatory reporting of invasive cancer by pathology laboratories and other clinical sites to the state Cancer Registry. This means that all suitable cases could be approached. The advantage of an incidence study over a mortality study is that all cases can be included not just the fatal cases. In addition, the individual women could be interviewed about their solvent exposure circumstances and the potential confounders of exposure such as BMI at a standard age, smoking, parity and breast feeding.

When examined in the same model as solvent exposure, the most well documented risk factors (BMI, age at menarche, smoking, alcohol consumption, hormonal replacement therapy, age at first birth, parity and family history of breast cancer) did not greatly affect the risk estimates related to solvent exposure in this study. We used BMI at age 30, but this may be inaccurately recalled, and for 354 women this information was missing.

In this study, the risk of breast cancer following exposure to most solvents was not affected by presence of an ER genetic marker. The association with alcohol was the strongest. A previous study found that for estrogen-positive and progesterone-negative tumors, the odds ratio doubled or more for each 10-year increase in exposure to monoaromatic hydrocarbons. (Labrèche, Goldberg et al. 2010) A second study found that clinical laboratory technologists and

technicians who were ER positive and who worked with solvents were at increased risk of breast cancer, hazard ratio 2.00, (95% CI, 1.07–3.73). This finding should be treated with caution because it was the only significantly elevated risk among 44 occupations examined, non-significantly elevated risks were found for two other solvent-exposed occupations. (Ekenga, Parks et al. 2014)

ER negative breast cancers are proportionally more common among premenopausally diagnosed cases than among post-menopausal cases (Althuis, Fergenbaum et al. 2004). There were fewer pre-menopausal participants in this study, consequently there were a limited number of ER negative cases among our population.

Conclusions

The risk of breast cancer was 20% elevated for women exposed to aliphatic solvents or to aromatic hydrocarbons other than benzene. The risks were lower for those exposed to benzene and chlorinated solvents. The solvent-associated risks were not statistically significantly elevated for women in this study but they tended to be higher for breast cancer diagnosed before menopause than post-menopause, for those exposed to benzene, aliphatic and other aromatic solvents and chlorinated solvents. The small numbers in these sub-analyses resulted in wide CIs however.

Breast cancer is relatively common and the evidence is that it is likely to be multifactorial in etiology. It occurs later in life when a number of environmental exposures may have been experienced. A relatively small proportion of women are exposed to solvents at work but this and other papers suggest that solvent exposure increases risk of breast cancer. Occupational exposure is relatively easily controlled compared to other known risk factors such as genetic profile, low parity or absence of breast feeding so investigation of this could be an important source of risk reduction.

A larger study which examines several occupational exposures as well as the known personal risk factors would provide more powerful evidence about the extent to which solvent exposure is a risk factor for breast cancer and which solvents are most potent. A large case-control study is needed because of the low prevalence of exposure to solvents among women, the fact that the less common pre-menopausal breast cancers appear to be most strongly associated with solvent exposure and the likelihood that only a proportion of breast cancers are associated with solvent exposure.

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Table I. Demographic and reproductive characteristics of breast cancer cases and controls, 2009-2011

		% Controls (n = 1785)	% Cases (n = 1202)
Age group (years)	24-44	10.0	14.0
	45-49	11.4	14.6
	50-54	13.3	12.7
	55-59	17.1	15.3
	60-64	18.0	16.0
	65-69	15.2	12.2
	70-80	15.0	15.3
Status at recruitment	Postmenopausal	76.5	69.6
	Premenopausal	23.5	30.4
Socioeconomic score[a]	Advantaged	5.1	4.5
	2	13.7	12.7
	3	20.8	19.5
	4	20.1	20.5
	Disadvantaged	40.2	42.9
Education	Junior school	36.0	36.1
	Senior school	22.6	20.6
	Trade/apprenticeship	24.4	21.5
	University	17.0	21.8
Family history of breast cancer	None	71.6	60.6
	Some family history	20.9	25.0
	Clear high risk	7.3	14.1
	Unknown or missing	0.2	0.3
Age at menarche	10-11 years	18.9	19.2
	12 years	22.3	25.9
	13 years	30.0	27.7
	14+ years	27.9	26.3
	Don’t know	0.9	0.9
Age at first birth[b]	No children	10.5	13.1
	Age <20 years	9.9	10.2
	Age 20-24	36.1	35.4
	Age 25-29	29.2	24.2
	Age 30+	14.3	17.1

No. of children	0	10.5	13.1
	1	7.7	9.6
	2	38.9	38.2
	3	27.2	25.1
	4+	15.7	14.1
Breastfeeding[c]	No children	10.5	13.1
	No breastfeeding	8.6	10.5
	Breastfed ≤ 12 months	35.6	32.8
	Breastfed > 12 months	43.2	42.2
Estrogen receptor status positive			28.6
HRT Use of hormone replacement therapy			
	None	57.8	62.2
	Estrogen only	15.9	10.6
	Progesterone only	4.2	2.4
	Estrogen + progesterone	3.8	6.0
	Mixture of treatments	8.7	9.4
	Nonhormonal treatment	1.8	2.8
	Unknown treatment	7.7	6.6
BMI in 30s[d]	Underweight	8.8	8.0
	Healthy	70.8	72.5
	Overweight	15.2	13.8
	Obese	5.2	5.7
Ever Smoked[e]	Never	57.4	54.8
	Yes	42.6	45.2
Alcohol intake[f]	None	15.9	16.8
	≤3 drinks per week	36.3	34.6
	4-9 drinks per week	21.2	22.3
	10+ drinks per week	26.2	26.1

Missing values: [a]1;[b]2, [c]54, [d]354, [e]7, [f]9

Table II Breast Cancer Odds Ratios, for all women and stratified by menopausal status at time of recruitment, adjusted for age, comparing cases and controls with any probable solvent exposure to cases and controls with no or only possible exposure (Total controls 1785, total cases 1202) (7 participants were missing solvent data)

Solvent exposed?		**All participants**			**Premenopausal**			**Post menopausal**			**P-value for interaction**
		Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)	
Benzene	No	1681	1127	1.00 (ref)	399	340	1.00	1282	787	1.00	0.188
	Yes	104	75	1.08 (0.80 - 1.47)	20	26	1.53 (0.84 - 2.80)	84	49	0.96 (0.67 - 1.38)	
Other aromatic	No	1587	1045	1.00	377	316	1.00	1210	729	1.00	0.392
	Yes	197	155	1.21 (0.97 - 1.52)	42	50	1.43 (0.92 - 2.21)	156	107	1.15 (0.88 - 1.49)	
Aliphatic	No	1731	1165	1.00	368	309	1.00	1157	690	1.00	0.582
	Yes	54	37	1.21 (0.99 - 1.48)	51	57	1.33 (0.89 - 2.00)	209	146	1.16 (0.92 - 1.46)	
Chlorinated	No	1525	999	1.00	409	354	1.00	1322	811	1.00	0.372
	Yes	260	203	1.05 (0.69 - 1.61)	10	12	1.47 (0.62 - 3.45)	44	25	0.94 (0.57 - 1.54)	
Alcohol	No	1402	920	1.00	333	289	1.00	1069	631	1.00	0.611
	Yes	382	282	1.15 (0.96 - 1.37)	86	77	1.05 (0.74 - 1.49)	297	205	1.16 (0.95 - 1.43)	
Any Solvent	No	1251	811	1.00	301	254	1.00	950	557	1.00	0.977
	Yes	534	391	1.15 (0.98 - 1.35)	118	112	1.14 (0.84 - 1.56)	416	279	1.14 (0.95 - 1.37)	

Table III Breast Cancer Odds Ratios, comparing cases and controls with any probable solvent exposure to cases and controls with no or only possible exposure in the relevant time window before diagnosis, adjusting age and for exposures in other time windows

Solvent exposed?		**Exposed ⩽10 years before diagnosis**			**Exposed 11-20 years before diagnosis**			**Exposed 21-30 years before diagnosis**			**Exposed 31+ years before diagnosis**		
		Controls	Cases	Odds Ratio (95% CI)	Controls	Cases	Odds Ratio (95% CI)	Controls	Cases	Odds Ratio (95% CI)	Controls	Cases	Odds Ratio (95% CI)
Benzene	No	1746	1170	1.00	1742	1162	1.00	1737	1174	1.00	1730	1177	1.00
	Yes	37	30	1.01 (0.56-1.81)	41	38	1.66 (0.91-3.01)	46	26	0.75 (0.41-1.40)	53	23	0.70 (0.41-1.21)
Other aromatic	No	1710	1138	1.00	169	1123	1.00	1680	1128	1.00	1689	1143	1.00
	Yes	73	62	1.14 (0.75-1.74)	92	77	1.20 (0.79-1.85)	103	72	0.96 (0.65-1.43)	94	57	0.94 (0.64-1.36)
Aliphatic	No	1679	1117	1.00	1662	1111	1.00	1660	1110	1.00	1673	1123	1.00
	Yes	104	83	1.17 (0.82-1.67)	121	89	0.96 (0.66-1.40)	123	90	1.07 (0.76-1.51)	110	77	1.10 (0.79-1.52)
Chlorinated	No	1765	1186	1.00	1765	1184	1.00	1760	1189	1.00	1746	1182	1.00
	Yes	18	14	0.80 (0.29-2.18)	18	16	2.17 (0.74-6.33)	23	11	0.57 (0.23-1.42)	37	18	0.82 (0.44-1.55)
Alcohols	No	1623	1078	1.00	1595	1069	1.00	1565	1056	1.00	1521	1023	1.00
	Yes	160	122	1.19 (0.84-1.68)	188	131	0.93 (0.63-1.38)	218	144	0.89 (0.62-1.25)	262	177	1.15 (0.90–1.48)
Any solvent	No	1553	1031	1.00	1520	1011	1.00	1486	999	1.00	1445	978	1.00
	Yes	230	169	1.06 (0.80-1.41)	263	189	1.02 (0.75-1.39)	297	201	0.95 (0.72-1.25)	338	222	1.09 (0.87-1.36)

Supplementary Table I Breast Cancer Odds Ratios for all women comparing any probable solvent exposure with no or only possible exposure, adjusting for age and exposure to other solvents (Total controls 1785, total cases 1202) (7 participants were missing solvent data)

Solvent exposed?		All participants OR (95% CI)
Benzene	No	1.00 (ref)
	Yes	0.88 (0.56 - 1.31)
Other aromatic	No	1.00
	Yes	1.17 (0.79 - 1.76)
Aliphatic	No	1.00
	Yes	1.01 (0.78 - 1.58)
Chlorinated	No	1.00
	Yes	0.93 (0.59 - 1.47)
Alcohol	No	1.00
	Yes	1.11 (0.92 - 1.34)

Supplementary Table II Breast cancer subtype risk (ER positive and negative cases) associated with likelihood of exposure to any probable solvent relative to controls, adjusted for age (multinomial logistic regression)

Solvent	**Exposed?**	**Control**	**ER negative cases**		**ER positive cases**		**Overall P-value for difference between either case groups with controls**	**P-value for difference between ER+ and ER- cases**
			N	OR (95% CI)	N	OR (95% CI)		
Benzene	No	1681	156		802			
	Yes	104	13	1.35 (0.74 – 2.48)	54	1.10 (0.78 – 1.54)	0.59	0.51
Other	No	1587	145		741			
aromatic	Yes	198	24	1.34 (0.85 – 2.12)	115	1.25 (0.98 – 1.60)	0.13	0.77
Aliphatic	No	1525	140		704			
	Yes	260	29	1.24 (0.81 – 1.90)	152	**1.28 (1.03 – 1.60)**	0.07	0.89
Chlorinated	No	1731	163		828			
	Yes	54	6	1.28 (0.54 – 3.04)	28	1.12 (0.70 – 1.78)	0.80	0.76
Alcohol	No	1402	138		643			
	Yes	383	31	0.86 (0.57 – 1.29)	213	**1.24 (1.02 – 1.50)**	0.05	0.09
Any	No	1251	121		562			
Solvent	Yes	534	48	0.96 (0.68 – 1.37)	294	1.25 (1.05 – 1.48)	0.04	0.16