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## Occupational exposure to organic solvents and breast cancer in women

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### Abstract

**Background**—Although studies in rodents suggest possible associations between exposure to organic solvents and breast cancer, the evidence in humans is limited.

**Methods**—We evaluated job histories of 2383 incident breast cancer cases diagnosed during 2000–2003, and 2502 controls who participated in a large population-based case-control study in Poland. Industrial hygienists reviewed occupational histories and developed exposure metrics for total organic solvents and benzene. Unconditional logistic regression analyses estimated odds ratios (ORs) and 95% confidence intervals (CIs) as the measure of association with breast cancer, controlling for breast cancer risk factors. Stratified analyses examined the potential modification by known breast

Competing Interest: None to declare.

What this paper adds

- Studies in rodents suggest possible associations between exposure to organic solvents and breast cancer, but the evidence in humans is limited.
- Our study provides weak evidence for an association between occupational exposure to organic solvents (as a class of chemicals) and breast cancer risk.
- The study also suggests that these chemicals might play a more important role for estrogen and progesterone negative breast cancer.

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cancer risk factors. Associations were also evaluated by estrogen (ER) and progesterone receptor (PR) status and by other clinical characteristics of the tumours using polytomous regression analyses.

**Results**—Women who ever worked at jobs with organic solvents exposure had a small, non-significant increase in breast cancer risk (OR=1.16; 95% CI 0.99 to 1.4). A significant association was present for ER and PR negative tumors (OR 1.40; 95% CI 1.1 to 1.8), but there was no association with tumors with both positive receptors (OR 0.97; 95% CI 0.8 to 1.2 (p-heterogeneity: 0.008)). We did not observe trends with increasing level of exposure. Known breast cancer risk factors did not modify the association with organic solvents and breast cancer risk. No association with breast cancer was found for benzene exposure (OR 1.00; 95% CI 0.8 to 1.3).

**Conclusion**—Our study provides weak evidence for a possible association between occupational exposure to organic solvents as a class and breast cancer risk. The association might be limited to hormone receptor negative tumors.

## Keywords

breast cancer; organic solvents

## Introduction

Several organic solvents have been associated with mammary gland tumors in rodents. A comprehensive compilation of data from animal studies, including assessments performed by the International Agency on Cancer (IARC) and the U.S. National Toxicology Program (NTP) lists thirty organic solvents that have caused malignant mammary gland tumors[1]. Among these chemicals, only benzene has been classified by IARC as a Group 1 human carcinogen, and this was based on its established links with acute myelogenous leukaemia rather than breast cancer. Five solvents have been classified as Group 2A, Group 2B (16 chemicals), and Group 3 (2 chemicals), but for most, the epidemiologic data are quite meager. Six have not been evaluated by IARC.

Epidemiological studies of breast cancer and organic solvents have been summarized in several reviews[2–5]. Increased breast cancer risk has been reported among women employed in jobs and industrial settings that entailed potential exposure to organic solvents, including dry cleaners [6], hair dressers[7,8], metal working[9], aircraft maintenance[10], textiles[11,12], leather and fur processing [13], and electronics manufacturing[14], and among enlisted women in the army with potentially moderate/heavy exposure to solvents[15]. A record linkage study in Denmark found the risk of breast cancer increased two-fold in women employed for more than 10 years in jobs entailing extensive exposure to solvents[16]. Most of these studies have used job/industry title groupings as a surrogate for exposure, and few attempted to quantify exposures and relate breast cancer risk to exposure levels [11,17–19]. Only one epidemiological study evaluated the risk of breast cancer from exposure to benzene by estrogen receptor status[17], a characteristic that could be important because the hypothesized mechanism for organic solvents in breast carcinogenesis involves action through their estrogenic properties[20]. Further, no epidemiological data are available on the association between organic solvents and breast cancer and other tumor pathologic characteristics, including histology, stage and grade. Although it has been shown that established breast cancer risk factors differ by tumour features[21], no epidemiological data are available on the association between organic solvents and breast cancer and other tumor pathologic characteristics, including histology, stage and grade.

The potential modification of the associations between breast cancer with organic solvents by traditional breast cancer risk factors has not been evaluated before. Nevertheless, it could be hypothesized that susceptibility to these chemicals might be modified by factors that underlie

the hormonal milieu - total lifetime estrogen dose or are proxy measures of other underlying (possibly genetic) characteristics. Modification by alcohol consumption might be of particular interest, since its chronic consumption has been shown to induce CYP2E1[22,22,23,23], the enzyme that activates a variety of procarcinogens including some organic solvents (e.g., benzene and halogenated solvents)[24,25].

To investigate further the relationship between organic solvents, and in particular, benzene, and breast cancer risk, we evaluated job histories of women in a large population-based case-control study conducted in Poland during 2000–2003[26]. An expert-based exposure assessment also was conducted to evaluate breast cancer risk by organic solvents level. We addressed the issue of potential modification of organic solvents effects by stratifying for menopausal status, age, family history of breast cancer, BMI (body mass index), parity, age at menarche, and alcohol consumption. We also assessed organic solvents and breast cancer relationships by estrogen and progesterone receptor status and by other clinical characteristics of the tumours.

## Material and methods

The study has been previously described[21]. In brief, cases for this population-based case-control study were female residents of Warsaw and Lodz, Poland, aged 20–74, newly diagnosed with cytologically or histologically confirmed *in situ* or invasive breast cancer from January 2000 through January 2003. Cases were identified through a rapid case ascertainment system organized in the participating hospitals, supplemented by a regular review of the records of regional population-based cancer registries. Potential eligible controls were randomly selected using the Polish Electronic System of Population Evidence, which keeps records on the entire population in Poland. Controls were matched to the cases by city of residence and age within five-year age groups. The study was approved by the institutional review boards at the National Cancer Institute (NCI), each of the participating Polish institutions, and the NCI contractor (Westat, Inc.). A signed informed consent was obtained from each study participant.

A structured questionnaire was administered during in-person interviews. The questionnaire response rates were 79% for the cases and 69% for the controls. Data were collected on known and suspected breast cancer risk factors and included detailed job histories on all jobs held at least six months.

Pathology information on cases was obtained from medical record and pathology forms. Pathology forms and tissue blocks were collected for 87% of cases. Estrogen receptor and progesterone receptor status was determined for 83% and 83% of the cases, respectively. In ~59% of cases, receptors status was determined by immunohistochemistry and AQUA analysis [27]. For the remaining, 91% were performed using immunohistochemistry and the remainder by biochemical methods[28–30]. As many as 52% of cancers were ductal; 14%, were lobular; and 23%, were other types. Information was missing on histological type for 10% of the cases. Information on tumor size was available for 84% of cases and on grade for 86% of invasive cases. More details have been presented in a previous publication[21]

## Exposure information

The occupational data collected from the questionnaires were examined by Polish industrial hygienists (J.G, S.B), who assessed occupational exposure to organic solvents and to benzene in particular, for all jobs held by the study participants. The assessors were blinded with respect to case/control status. The first step was to assess whether the job might have entailed exposure to organic solvents or benzene. For each exposed job, four exposure indices were created, i.e. intensity, frequency, probability, and confidence. Organic solvents was the general term used to describe any organic solvent, including aromatic, aliphatic, chlorinated hydrocarbons,

ketones, organic acid esters, petroleum distillates (including leaded and unleaded gasoline, white spirit, etc.). Carbon disulfide were not considered an organic solvent for the purpose of this work.

Because the group of organic solvents comprises several tens of solvents, because solvents are often interchangeable, and because allowable exposure limits for the various solvents are set based on different critical health effects, it was problematic to assess the group relative to varying exposure levels or limits, as is often done for specific substances. For this reason, the intensity of exposure to organic solvents was assessed based on the likely quantity of organic solvents used at the job per month, using the following scale for total organic solvents: 1: <1 liter (L)/mo; 2: 1–10 L/mo; 3: >10–100 L/mo; and 4: >100 L/mo. For assessment of intensity of benzene exposure, air concentrations were estimated using the following categories: 1: <1 mg/m<sup>3</sup>; 2: 1–10 mg/m<sup>3</sup>, and 3: >10 mg/m<sup>3</sup>. Due to the small number of women exposed to more than 10 mg/m<sup>3</sup>, the categories 3 and 2 were combined. Frequency represented the average amount of exposed time for a job and was estimated as: 1: <2 hrs/wk; 2: 2–10 hrs/wk; 3: >10–<20 hrs/wk; and 4: ≥20 hrs/wk. A frequency of <1 hr/wk was considered unexposed.

Probability of exposure reflected the percentage of workers in the job/industry likely to be exposed, i.e., 1: <10%; 2: 10–<50%; 3: 50–<90%; and 4: ≥90%. A probability <1 % was considered unexposed. Confidence was the relative confidence of the industrial hygienist in the evaluation of intensity, frequency, and probability and was largely based on the availability of information in the literature. For example, low confidence (category 1) indicated that little information was available for any of the three measures; moderate confidence (category 2), indicated that information was available for one of the measures but not for the other two; and high confidence (category 3) indicated that information was available for at least two measures. Air monitoring data from records of the Nofer Institute of Occupational Medicine and from regional units of the State Sanitary Inspectorate, as well as publications in the Polish literature, were considered. If such data were not available appropriate to a particular job, international data were used or scientific publications (e.g., the ILO Encyclopaedia of Occupational Health and Safety or W.A. Burgess: Recognition of Health Hazards. A Review of Materials and Processes, Industrial Hygiene Aspects of Plant Operations).

The duration of exposure was calculated in years. All of the other metrics were based on the scores assigned to the intensity, frequency, and probability. Intensity, frequency, and probability were analyzed both as the crude scores and the scores weighted by duration. Average crude intensity was expressed as the cumulative score over exposed jobs (sum of scores) divided by the number of exposed jobs. The weighted average for intensity for an individual was calculated as the sum of the products of all the jobs' intensity score and the respective duration of exposure divided by the total exposed duration for the individual. Average frequency and probability were calculated in a similar manner. Cumulative exposure was the product of the scores for intensity, frequency, and duration, summed across all jobs. The odds ratios for the crude scores and the scores weighted by duration were similar, so that in the tables of the stratified analyses, only results for the crude exposure metrics are presented. The highest intensity calculated as the product of the highest intensity and its respective frequency was also analyzed. Analyses were conducted both including all exposed women, irrespective of the confidence score, and women who held only jobs with a confidence score of 1 as unexposed. Latency was defined as time since first exposure.

### Statistical analysis

We performed unconditional logistic regression analyses to estimate odds ratios (ORs) and 95% confidence intervals (95% CI) as the measure of association between the various metrics of exposure to organic solvents, and benzene in particular, and breast cancer risk. Women never exposed to organic solvents (or never exposed to benzene in the benzene-specific analyses)

served as the referent. Trend tests were conducted for organic solvents (or benzene) by entering levels of exposure as ordinal values.

Multivariate models included adjustment for known breast cancer risk factors. Potential confounders were evaluated by univariate and multivariate analyses and covariates included in the models were statistically significant ( $p < 0.05$ ) in the univariate analyses. All covariates except study center, age at first birth and breastfeeding remained significant in the multivariate analyses. These were kept in the models for consistency of reporting. All the covariates were treated as categorical variables, with the following categories: study site (Warsaw, Lodz), age (20–24; 25–29; ... 70–74), education (< high school; high school; some college, professional training; college degree), age at menarche ( $\leq 12$ ; 13–14;  $\geq 15$ ), menopausal status (premenopausal; postmenopausal), age at menopause (<45; 45–54;  $\geq 55$ ), age at first full-term birth (<20; 20–24; 25–29;  $\geq 30$ ), number of full-term births ( $\leq 1$ ; 2;  $\geq 3$ ), breastfeeding (ever, never), BMI (<25; 25–29;  $\geq 30$ ), breast cancer in first degree relatives (yes; no), and previous screening mammography (yes; no).

Three women with missing information on family history of breast cancer were excluded from the analysis. For six women lacking information on menopausal status, we classified their menopausal status based on their age and the average age at menopause for the study population (two were classified as premenopausal and four as postmenopausal). There was missing information on covariates in 161 other women. Subjects with unknown values for covariates were included by incorporating the unknown as a separate category of the indicator variable. The final analytic dataset consisted of 2383 cases and 2502 controls.

To explore potential modifying effects we analyzed the data stratified by menopausal status (premenopausal, postmenopausal); age (<50,  $\geq 50$ ); parity (nulliparous, parous), family history of breast cancer (yes, no), age at menarche ( $\leq 12$ ,  $> 12$ ), BMI (<25,  $\geq 25$ ), alcohol consumption (never vs ever consumed) and number of drinks consumed per week (0; 1–4,  $\geq 5$ ). Statistical significance of the effect modifiers was tested using the likelihood ratio test comparing appropriate likelihood statistics between models with and without interaction terms.

We also assessed associations between exposure and breast cancer by tumour characteristics, including estrogen and progesterone status (separately and together), as well as by histological type of breast cancer (invasive ductal NOS-Not Otherwise Specified and invasive lobular), tumour size ( $\leq 2$ cm,  $> 2$  cm), and in invasive cancers, grade (well, moderately, and poorly differentiated). Polytomous logistic regression models were fitted to estimate risk of breast cancer subtypes relative to control group. Equality of coefficients of exposure variables for cancer subtypes was tested using Wald test.

All analyses were performed using STATA version 9.2 (StataCorp LP).

## Results

The distribution of the commonly recognized breast cancer risk factors in this population has been described in previous publications [21,26] and was consistent with existing knowledge. In our study almost all women (99.7%) had held at least one job for 6 months or longer and 17.7% of cases and slightly fewer controls (16.4%) had ever held a job entailing exposure to organic solvents. Similar frequencies of cases and controls (4.8%) ever had held jobs with possible exposure to benzene (tables 1,2).

Overall, women who ever worked at jobs with possible exposure to organic solvents exposure had breast cancer risk of OR=1.16; 95% CI 0.99–1.4 (table 1). None of the exposure metrics showed evidence of an exposure-response risk of breast cancer. There was a statistically significant increase of breast cancer among those with the least frequent exposure, i.e., 1 – <2



hrs/wk (OR 1.91; 95% CI 1.1–3.4) and the corresponding category when weighted by duration (OR 2.00; 95% CI 1.1–3.5). Insignificant increases were found in the lowest exposure categories of crude intensity (OR 1.18; 95% CI 0.99–1.4), cumulative exposure (OR 1.19; 95% CI 0.96 to 1.5) and “highest intensity” (OR 1.19; 95% CI 0.99–1.4). There was no indication of increased breast cancer risk in women who had a longer latency period (more than 15 years) as compared to women exposed more recently.

We observed no association or exposure-response gradient between benzene and risk of breast cancer (table 2). A small, but insignificant, increase of breast cancer was noted for women with an average (crude or weighted) exposure intensity above 1 mg/m<sup>3</sup> (OR 1.21; 95% CI 0.7–2.2).

In the dataset there were 182 women with a low confidence score, indicating that little or no information was available for any of the exposure measures. The overall results did not materially change when these women were treated as unexposed (data not shown).

The results of the analyses stratified by selected breast cancer risk factors and for breast cancer subtypes are included in table 3. The analysis by menopausal status showed an insignificant increase in breast cancer risk in both pre- and postmenopausal women ever exposed to organic solvents (OR 1.21; 95% CI 0.9–1.6 and OR 1.15 95% CI 0.96–1.4 respectively). A significant trend was found for duration of exposure to organic solvents in premenopausal women (p trend = 0.026) but not in postmenopausal women (p-trends heterogeneity-0.012); and an insignificant increase was found in the highest cumulative exposure in premenopausal (OR 1.57; 95% CI 0.99–2.5) (e-table I). We did not find any significant exposure-response relationships either in younger (<50 yrs) or older women (≥50 yrs) (data not shown). Neither pre- nor post menopausal women or women younger or older than 50 yrs showed significant associations with benzene exposure in the stratified analyses.

The risk of breast cancer was significantly elevated in women with exposure to organic solvents who have reported no family history of breast cancer (OR 1.18; 95% CI 1.0–1.4), but not in women with family history. None of the exposure metrics showed significant trends in either group, and no significant heterogeneity of the effect by family history of breast cancer was found (data not shown). No significant results were found in the analysis by exposure to benzene and family history status. Only 10 cases and 10 controls ever exposed to benzene reported family history of breast cancer, which precluded further analyses by the various exposure metrics.

No modification of the relationships between organic solvents exposure and breast cancer risk was found by age at menarche, BMI, and parity. There was a slight suggestion of modification of the benzene exposure effect by parity, where an insignificant increase in breast cancer risk was found in nulliparous women (OR 1.94; 95% CI 0.9–4.1) but not in parous (OR 0.88; 95% CI 0.7–1.2). Some increased risk estimates were observed in women ever exposed to benzene with a BMI of less than 25, but not in overweight (BMI ≥25) women, but the results did not reach statistical significance.

The risk of breast cancer exposed to organic solvents was significantly increased in never drinkers (OR 1.22; 95% CI 1.0–1.5), but not among ever drinkers (OR 1.11; 95% CI 0.9–1.4). Several categories of the various metrics were statistically significantly elevated among abstainers, in particular for the medium category of crude average intensity (OR 1.56; 95% CI 1.1–2.3) and the highest category for the product of intensity and frequency (OR 1.45; 95% CI 1.0–2.1). Number of drinks per week did not affect the risk of breast cancer among exposed women (data not shown).

In analyses of the associations with organic solvents exposure by pathological features of breast cancer, we found a small, insignificant increase of risk in ductal breast cancer (OR 1.18; 95%

CI 0.98–1.4). For this type of cancer, statistically significant associations occurred in the category of women with >5–10 years exposure duration and who, on average, used >10–100 liters of organic solvents per month (OR 1.50; 95% CI 1.0–2.2 and OR 1.49; 95% CI 1.0–2.2, respectively) (data not shown). None of the estimates reached statistical significance in lobular cancers and risk estimates were close to unity for most exposure measures (data not shown). The risk did not differ significantly by tumor size, although a significant increase was observed in larger tumors in the category of highest probability of exposure to organic solvents (OR 1.88; 95% CI 1.1–3.4) (data not shown). Insignificant associations were found for well and moderately differentiated tumors (OR 1.42; 95% CI 0.98–2.10 and OR 1.20; 95% CI 0.99–1.4, respectively) but no positive exposure-response gradient was found in any of the analyzed exposure metrics. A marginally significant positive trend was observed in poorly differentiated tumors for probability of exposure ( $p$  for trend 0.047) with an OR=0.83; 1.02, 1.21 and 2.17 for increasing probability categories, respectively. The formal statistical test did not confirm any significant modification of the effect by tumor grade (data not shown). No effect was seen for benzene and these pathologic features (data not shown).

The results of the analysis for total organic solvents by estrogen/progesterone (ER/PR) receptor status are presented in table 4. ORs were significantly increased for total organic solvents exposure in cases with negative receptors (OR 1.40; 95% CI 1.1–1.8), but not in cases having both ER/PR positive receptors (OR 0.97; 95% CI 0.8–1.2) ( $p$ -heterogeneity: 0.008). Although not statistically significant, the OR of 1.27; 95% CI 0.95–1.7 (in ER+/PR-) cases suggests that solvent exposure might be associated with PR negative cases rather than with ER negative cases. The associations between exposure to total organic solvents and breast cancer risk were consistent across most exposure metrics in ER/PR negative cases, although no significant exposure-response gradient was observed.

The analyses of associations between benzene and risk of breast cancer subtypes did not reveal any statistically significant differences although numbers for this analysis were quite small (data not shown).

## Discussion

We observed a weak marginally significant association between exposure to organic solvents and breast cancer risk. Several previous epidemiological studies have also reported such associations[11,14–19]. The most pronounced finding occurred among estrogen and progesterone negative breast cancer cases, but not among estrogen and progesterone positive cancers. However, no exposure-response gradient was detected for the associations observed. Heterogeneity of the effect by receptor status was statistically significant.

In only one previous report has the association of breast cancer with benzene exposure by estrogen receptor status been addressed in premenopausal women, and no apparent difference in risk between ER- positive and ER-negative breast tumor cases was found[17]. However, no other individual solvents or organic solvents, as a category, were analyzed in this study. Organic solvents have some similarities with organochlorines with respect to their lipophilicity and potential role in breast cancer etiology. Organochlorines have been investigated by hormone receptor status by several authors, but the results have been inconsistent [31–34]. Similar to our finding, a Canadian study found selected PCBs to relate most strongly with negative estrogen receptor breast cancers, even though these substances are dioxin-like and potentially antiestrogenic[35].

We did not find a statistically significant heterogeneity in the associations between exposure to organic solvents and breast cancer risk by well-established breast cancer risk factors including menopause, family history status, age, age at menarche, parity, and BMI. Several

metrics of solvent exposure were associated with breast cancer and abstinent drinker, but not with drinkers. Similarly, breast cancer and some organic solvent metrics were associated with cancer type and tumor size, but there was no statistical heterogeneity. The only significant heterogeneity that we found was for benzene exposure and parity, where there was an increased risk in nulliparous but not in parous women. However, the number of nulliparous women ever exposed to benzene was small (n=38) and none of the results for nulliparous reached statistical significance.

Contrary to one previous report,[17], we did not observe significant associations between breast cancer risk and benzene. Benzene exposure among women in our study, however, was relatively low. Only 1% of women rated as ever exposed to benzene had an estimated benzene intensity of more than 1 mg/m<sup>3</sup>. This may be due to the fact that work in an environment entailing exposure to benzene exceeding the Maximal Allowable Concentration (MAC) has been banned for women since 1951 (the MAC in Poland for benzene was 100 mg/m<sup>3</sup> since 1956 and 30 mg/m<sup>3</sup> since 1976). Exposure to benzene among women in Poland, thus, has been mainly due to exposure to other solvents with benzene impurities, resulting in a low benzene intensity. Thus, although our study concluded that low levels of exposure to benzene was not associated with breast cancer risk, we had only limited power to elucidate effects of high intensity exposures.

Strengths of our study include a large sample size, a high response rate, and detailed information on lifetime job histories, established breast cancer risk factors, and tumor characteristics, including ER and PR status. The expert-based case-by-case assessment of occupational exposures allowed us to evaluate associations by various exposure metrics while adjusting for known breast cancer risk factors.

As in several other studies, we were unable to distinguish exposures to specific organic solvents, other than for benzene. This was because these chemicals are generally used as a mixture of variable and undeterminable composition. The effect of grouping a large number of solvents into a single category of organic solvents might have resulted in attenuation of the risk, because the potential effect of an undetermined single compound that might have been truly associated with breast cancer might have been obscured by “mixing” it with other substances not related to cancer risk.

Assessment of organic solvents as a group, without knowing the specific organic solvents present, is often done in epidemiologic studies. Typically, airborne exposures are assessed, but how investigators have estimated a mixture of unknown solvents has not been described. The process is problematic because the assessment requires estimating an exposure level received from an unknown solvent or what could be a mixture of unknown solvents. Because the solvent (s) will vary from subject to subject and each solvent has its own vapor pressure, the exposure levels will also vary. In this study, we chose to estimate the quantity of the solvent used by an individual or present in a workplace. This approach has the same problems as the first approach, i.e., unknown solvents with different vapor pressures. It is not clear, therefore, that estimating quantity of solvents used per month by an individual is a better indicator of the exposure level than estimating an airborne intensity, but it is more easily estimated by raters.

In our study we relied on the data from work histories provided by study subjects. We recognize that these data might have been a subject to recall bias, which is a concern of case-control studies. We also were unable to perform a validity or reliability evaluation of the exposure assessment in our study, since no hygienic measurements or biomarkers of exposure were available for the study subjects. However, an evaluation of exposure misclassification in a multicentre case-control study[36], in which a similar exposure assessment approach was used and in which the same exposure assessors in this study participated, found that attenuation of



relative risks could occur even if the sensitivity and specificity are high. Exposure misclassification in this study is likely to be non-differential with respect to case-control status because there has been little public attention in Poland of potential effects of occupational exposures on breast cancer risk.

Stratified analyses in this report were limited by small number of subjects, particularly those relating to benzene exposures.

Finally, results should be interpreted with caution because of the large number of comparisons made, particularly for subgroup associations.

In summary, our study provides weak evidence for an association between occupational exposure to organic solvents and breast cancer risk. There was some suggestion that these chemicals might play a more important role for estrogen and progesterone negative breast cancer.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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table 1

Breast cancer risk by exposure to organic solvents in a breast cancer case-control study

Exposure metrics	Cases n= 2383 n (%)	Controls n = 2502 n (%)	OR <sup>d</sup> (95%CI)
Ever exposed to organic solvents			
Never	1961 (82.3)	2093 (83.6)	
Ever	422 (17.7)	409 (16.4)	1.16 (0.99–1.4)
Duration of exposure (in yrs) <sup>b</sup>			
>0 – 5	123 (5.2)	124 (5.0)	1.17 (0.9–1.5)
>5 – 10	82 (3.4)	72 (2.9)	1.27 (0.9–1.8)
>10	217 (9.1)	213 (8.5)	1.13 (0.9–1.4)
<i>p trend</i> <sup>e</sup>			0.847
Crude average intensity (quantity used in L/mo) <sup>b</sup>			
≥1–≤10	337 (14.2)	313 (12.5)	1.18 (0.99–1.4)
>10–≤100	77 (3.2)	77 (3.1)	1.23 (0.9–1.7)
>100	8 (0.3)	19 (0.8)	0.61 (0.3–1.4)
<i>p trend</i> <sup>e</sup>			0.368
Intensity weighted by duration (in L/mo) <sup>b</sup>			
≥1–≤10	336 (14.1)	317 (12.7)	1.16 (0.98–1.4)
>10–≤100	78 (3.3)	73 (2.9)	1.31 (0.9–1.8)
>100	8 (0.3)	19 (0.8)	0.61 (0.3–1.4)
<i>p trend</i> <sup>e</sup>			0.590
Crude average frequency (hrs/wk) <sup>b</sup>			
≥1 – <2	33 (1.4)	20 (0.8)	1.91 (1.1–3.4)
≥2 – ≤10	133 (5.6)	110 (4.4)	1.16 (0.9–1.5)
>10 – <20	169 (7.1)	185 (7.4)	1.06 (0.8–1.3)
≥20	87 (3.6)	94 (3.8)	1.23 (0.9–1.7)
<i>p trend</i> <sup>e</sup>			0.368
Average frequency weighted by duration <sup>b</sup> (hrs/wk)			
≥1–<2	35 (1.5)	20 (0.8)	2.00 (1.1–3.5)
≥2 – ≤10	134 (5.6)	112(4.5)	1.16 (0.9–1.5)
>10 – <20	165 (6.9)	182 (7.3)	1.05 (0.8–1.3)
≥20	88 (3.6)	95 (3.8)	1.23 (0.9–1.7)
<i>p trend</i> <sup>e</sup>			0.305
Average latency (yrs)			
0–15	41 (1.7)	34 (1.4)	1.48 (0.9–2.4)
>15	381 (16.0)	375 (15.0)	1.14 (0.97–1.3)
<i>p trend</i> <sup>e</sup>			0.266
Cumulative exposure(hrs*L*yr/wk*mo) <sup>b,c</sup>			
>0–39	213 (8.9)	206 (8.2)	1.19 (0.96–1.5)

Exposure metrics	Cases n= 2383 n (%)	Controls n = 2502 n (%)	OR <sup>a</sup> (95%CI)
>39	209 (8.8)	202 (8.1)	1.15 (0.9–1.4)
<i>p trend</i> <sup>e</sup>			0.741
Highest intensity*frequency(L*hrs/mo*wk) <sup>b,d</sup>			
I level	321 (13.5)	298 (11.9)	1.19 (0.99–1.4)
II level	101 (4.2)	111 (4.5)	1.12 (0.8–1.5)
<i>p trend</i> <sup>e</sup>			0.776
Crude average probability <sup>b</sup>			
≥1 – <10%	130 (5.5)	128 (5.1)	1.13 (0.9–1.5)
≥10 – <50%	148 (6.2)	134 (5.7)	1.19 (0.9–1.5)
≥50 – <90%	109 (4.6)	113 (4.5)	1.14 (0.9–1.5)
≥90%	35 (1.5)	34 (1.4)	1.31 (0.8–2.2)
<i>p trend</i> <sup>e</sup>			0.728
Average probability weighted by duration <sup>b</sup>			
≥1 – <10%	130 (5.5)	128 (5.1)	1.13 (0.9–1.5)
≥10 – <50%	146 (6.1)	131 (5.2)	1.19 (0.9–1.5)
≥50 – <90%	108 (4.5)	116 (4.6)	1.11 (0.8–1.5)
≥90%	38 (1.6)	34 (1.4)	1.44 (0.9–2.3)
<i>p trend</i> <sup>e</sup>			0.674

<sup>a</sup> Adjusted for age, study site, education, BMI, age at menarche, menopausal status, age at menopause (in postmenopausal women), number of full term births, age at first full term birth, breastfeeding, family history of breast cancer and previous screening mammography

<sup>b</sup> Never exposed to organic solvents used as referent

<sup>c</sup> Cumulative exposure: product of frequency, intensity, and duration of exposure summed across all jobs. Cutpoint=median in exposed controls

<sup>d</sup> Product of scores for intensity\*frequency: level I=≤4, level II= >4

<sup>e</sup> p for trend in ever exposed to organic solvents



table 2

## Breast cancer risk by exposure to benzene in a breast cancer case-control study

Exposure metrics	Cases n= 2383 n (%)	Controls n = 2502 n (%)	OR <sup>a</sup> (95%CI)
Ever exposed to benzene			
Never	2268 (95.2)	2382 (95.2)	
Ever	115 (4.8)	120 (4.8)	1.00 (0.8–1.3)
Duration of exposure (in yrs) <sup>b</sup>			
>0 – 5	42 (1.8)	41 (1.6)	1.07 (0.7–1.7)
>5 – 10	25 (1.0)	19 (0.8)	1.36 (0.7–2.5)
>10	48 (2.0)	60 (2.4)	0.82 (0.6–1.2)
<i>p trend</i> <sup>e</sup>			0.691
Crude average intensity (concentration in air) (mg/m <sup>3</sup> ) <sup>b</sup>			
>0 – <1	92 (3.9)	99 (4.0)	0.95 (0.7–1.3)
≥1	23 (0.9)	21 (0.8)	1.21 (0.7–2.2)
<i>p trend</i> <sup>e</sup>			0.849
Intensity weighted by duration (mg/m <sup>3</sup> ) <sup>b</sup>			
>0 – 1	92 (3.9)	99 (3.9)	0.95 (0.7–1.3)
>1	23 (0.9)	21 (0.9)	1.21 (0.7–2.2)
<i>p trend</i> <sup>e</sup>			0.849
Crude average frequency (hrs/wk) <sup>b</sup>			
>1 – ≤10	33 (1.4)	28 (1.1)	0.93 (0.5–1.6)
>10 – <20	48 (2.0)	46 (1.8)	1.10 (0.7–1.7)
≥20	34 (1.4)	46 (1.8)	0.93 (0.6–1.5)
<i>p trend</i> <sup>e</sup>			0.962
Average frequency weighted by duration (hrs/wk) <sup>b</sup>			
>1 – ≤10	34 (1.4)	28 (1.1)	0.96 (0.5–1.6)
>10 – <20	47 (2.0)	46 (1.8)	1.08 (0.7–1.6)
≥20	34 (1.4)	46 (1.8)	0.93 (0.6–1.5)
<i>p trend</i> <sup>e</sup>			0.940
Average latency (yrs) <sup>b</sup>			
0 – 20	10 (0.4)	12 (0.5)	0.94 (0.4–2.2)
>20	105 (4.4)	108 (4.3)	1.00 (0.8–1.3)
<i>p trend</i> <sup>e</sup>			0.991
Cumulative exposure(hrs*mg*yr/wk*m <sup>3</sup> ) <sup>b,c</sup>			
>0 – 33	58 (2.4)	59 (2.4)	1.00 (0.7–1.5)
>33	57 (2.4)	61 (2.4)	0.99 (0.7–1.4)
<i>p trend</i> <sup>e</sup>			0.960
Highest intensity*frequency(L*hrs/mo*wk) <sup>b,d</sup>			
I level	95 (4.0)	102 (4.1)	0.96 (0.7–1.3)

Exposure metrics	Cases n= 2383 n (%)	Controls n = 2502 n (%)	OR <sup>a</sup> (95% CI)
II level	20 (0.8)	18 (0.7)	1.21 (0.6–2.3)
<i>p trend</i> <sup>e</sup>			0.872
Crude average probability <sup>b</sup>			
≥1 – <10%	63 (2.6)	54 (2.2)	1.28 (0.9–1.9)
≥10 – <50%	36 (1.5)	44 (1.8)	0.73 (0.5–1.2)
≥50 – <90%	11 (0.5)	17 (0.7)	0.77 (0.4–1.7)
≥90%	5 (0.2)	5 (0.2)	1.20 (0.3–4.3)
<i>p trend</i> <sup>e</sup>			0.565
Average probability weighted by duration <sup>b</sup>			
≥1 – <10%	63 (2.6)	54 (2.2)	1.28 (0.9–1.9)
≥10 – <50%	37 (1.6)	44 (1.8)	0.76 (0.5–1.2)
≥50 – <90%	15 (0.5)	17 (0.7)	0.71 (0.3–1.6)
≥90%	5 (0.2)	5 (0.2)	1.20 (0.3–4.3)
<i>p trend</i> <sup>e</sup>			0.542

<sup>a</sup> Adjusted for age, study site, education, BMI, age at menarche, menopausal status, age at menopause (in postmenopausal women), number of full term births, age at first full term birth, breastfeeding, family history of breast cancer and previous screening mammography

<sup>b</sup> Never exposed to benzene used as referent

<sup>c</sup> Product of scores for intensity\*frequency: level I=≤4, level II=>4

<sup>d</sup> Cumulative exposure: product of frequency, intensity, and duration of exposure summed across all jobs. Cutpoint=median in exposed controls

<sup>e</sup> p for trend in ever exposed to benzene

Breast cancer risk in women ever exposed to organic solvents or ever exposed to benzene by selected breast cancer risk factors and risk of breast cancer subtypes

table 3

Factor	Ever exposed to total organic solvents OR <sup>ab</sup> ; 95%CI		Ever exposed to benzene OR <sup>ac</sup> ; 95%CI	
	pre- (104/121)	post- (318/288)	pre- (21/31)	post- (94/89)
Menopause(n cases/controls)				
<i>p</i> -heterogeneity	1.21 (0.9–1.6)	1.15 (0.96–1.4)	0.78 (0.4–1.4)	1.06 (0.8–1.4)
Age(n cases/controls)				
<i>p</i> -heterogeneity		0.74		0.58
Age(n cases/controls)	<50 (121/122)	≥50 (301/287)	<50 (25/28)	≥50 (90/92)
<i>p</i> -heterogeneity	1.13 (0.8–1.5)	1.20 (0.99–1.5)	0.90 (0.5–1.6)	1.04 (0.8–1.4)
Family history of breast cancer (n cases/controls)				
<i>p</i> -heterogeneity		0.73		0.71
Family history of breast cancer (n cases/controls)	yes (49/28)	no (373/381)	yes (10/10)	no (105/110)
<i>p</i> -heterogeneity	1.08 (0.6–1.9)	1.18 (1.0–1.4)	0.49 (0.2–1.3)	1.07 (0.8–1.4)
Age at menarche <sup>e</sup> (n cases/controls)				
<i>p</i> -heterogeneity		0.67		0.11
Age at menarche <sup>e</sup> (n cases/controls)	≤12 (132/91)	>12 (289/312)	≤12 (37/32)	>12 (78/86)
<i>p</i> -heterogeneity	1.25 (0.9–1.7)	1.15 (0.96–1.4)	0.88 (0.5–1.5)	1.09 (0.8–1.5)
BMI <sup>e</sup> (n cases/controls)				
<i>p</i> -heterogeneity		0.16		0.44
BMI <sup>e</sup> (n cases/controls)	<25 (155/129)	≥25 (266/277)	<25 (49/33)	≥25 (65/86)
<i>p</i> -heterogeneity	1.16 (0.9–1.5)	1.19 (0.98–1.4)	1.33 (0.8–2.2)	0.85 (0.6–1.2)
Parity(n cases/controls)				
<i>p</i> -heterogeneity		0.94		0.19
Parity(n cases/controls)	nulliparous (59/41)	parous (363/368)	nulliparous (26/12)	parous (89/108)
<i>p</i> -heterogeneity	1.22 (0.8–1.9)	1.17 (0.99–1.4)	1.94 (0.9–4.1)	0.88 (0.7–1.2)
Alcohol consumption <sup>e</sup> (n cases/controls)				
<i>p</i> -heterogeneity		0.81		0.04
Alcohol consumption <sup>e</sup> (n cases/controls)	abstainers (267/252)	ever consumers (155/157)	abstainers (80/79)	ever consumers (35/42)
<i>p</i> -heterogeneity	1.22 (1.0–1.5)	1.11 (0.9–1.4)	1.12 (0.8–1.6)	0.83 (0.5–1.3)
Pathomorphological breast cancer feature				
<i>p</i> -heterogeneity		0.49		0.29
Pathomorphological breast cancer feature	ductal NOS (222)	lobular (55)	ductal NOS (61)	lobular(14)
Cancer type(n of cases)	1.18 (0.98–1.4)	1.05 (0.8–1.4)	1.00 (0.7–1.4)	0.83 (0.5–1.5)
<i>p</i> -heterogeneity		0.48		0.55
Tumor size(n of cases)	≤2cm (200)	> 2cm (156)	≤2cm (47)	> 2cm (47)
<i>p</i> -heterogeneity	1.20 (0.99–1.5)	1.15 (0.9–1.4)	0.84 (0.6–1.2)	1.08 (0.8–1.5)

Factor	Ever exposed to total organic solvents OR <sup>ab</sup> ; 95%CI	Ever exposed to benzene OR <sup>ac</sup> ; 95%CI
<i>p</i> -heterogeneity	0.74	0.26
Grade(n of cases)	well differentiated (42) 1.42 (0.98–2.0)	poorly (84) 1.10 (0.8–1.4)
	moderately (220) 1.20 (0.99–1.4)	well differentiated (14) 1.50 (0.8–2.7)
		moderately (54) 0.88 (0.6–1.2)
<i>p</i> -heterogeneity	0.38 <sup>d</sup>	0.09 <sup>d</sup>
		0.21 <sup>d</sup>

<sup>a</sup> Adjusted for age, study site, education, BMI, age at menarche, menopausal status, age at menopause (in postmenopausal women), number of full term births, age at first full term birth, breastfeeding, family history of breast cancer and previous screening mammography

<sup>b</sup> Never exposed to organic solvents used as referent

<sup>c</sup> Never exposed to benzene used as referent

<sup>d</sup> compared to well differentiated

<sup>e</sup> there was missing information for age at menarche in 1 case and 6 controls exposed to organic solvents and 2 controls exposed to benzene; BMI (in 1 case and 3 controls exposed to organic solvents and 1 case and 1 control exposed to benzene)

Breast cancer risk by exposure to organic solvents and joint estrogen/progesterone status in breast cancer case-control study

table 4

Status of the receptors Exposure metrics	ER-/PR-			ER-/PR+			ER+/PR+			
	n controls	n cases	OR <sup>a</sup>	95%CI	n cases	OR <sup>a</sup>	95%CI	n cases	OR <sup>a</sup>	95%CI
Exposed to organic solvents										
Never	2093	449	1.0		301	1.0		98	1.0	
Ever	409	120	1.40(1.1-1.8)		71	1.27(0.95-1.7)		20	1.11(0.7-1.8)	
<i>p</i> -heterogeneity <sup>e</sup>						0.56			0.40	
Duration of exposure (in yrs) <sup>b</sup>										
>0-5	124	37	1.45(0.98-2.1)		16	1.06(0.6-1.8)		7	1.22(0.5-2.7)	
>5-10	72	18	1.17(0.7-2.0)		17	1.71(1.0-3.1)		3	0.90(0.3-2.9)	
>10	213	65	1.46(1.1-2.0)		38	1.23(0.8-1.8)		10	1.14(0.6-2.2)	
<i>p</i> trend <sup>d</sup>				0.82			0.76			0.63
<i>p</i> -heterogeneity of trends <sup>e</sup>						0.91			0.58	
Crude intensity (quantity used in L/mo) <sup>b</sup>										
≥1-10	313	95	1.43(1.1-1.8)		54	1.22(0.9-1.7)		17	1.20(0.7-2.0)	
>10-100	77	24	1.55(0.96-2.5)		15	1.58(0.9-2.8)		3	0.99(0.3-3.2)	
>100	19	1	0.31(0.04-2.3)		2	1.02(0.2-4.5)		0		
<i>p</i> trend <sup>d</sup>				0.33			0.97			0.43
<i>p</i> -heterogeneity of trends <sup>e</sup>						0.47			0.68	
Crude average frequency (hrs/wk) <sup>b</sup>										
≥1-<2	20	9	2.20(0.98-4.9)		5	1.70(0.6-4.7)		2	2.62(0.6-11.3)	
≥2-≤10	110	35	1.40(0.9-2.1)		15	0.79(0.4-1.4)		8	1.59(0.7-3.4)	
>10-<20	185	46	1.23(0.9-1.7)		39	1.64(1.1-2.4)		6	0.74(0.3-2.8)	
≥20	94	30	1.59(1.0-2.5)		12	1.23(0.6-2.3)		4	0.98(0.3-2.8)	
<i>p</i> trend <sup>d</sup>				0.59			0.24			0.14
<i>p</i> -heterogeneity of trends <sup>e</sup>						0.176			0.24	
Average latency (yrs) <sup>b</sup>										
0-15	34	15	1.98(1.0-3.7)		4	1.39(0.5-4.0)		2	1.05(0.2-4.5)	
										0.40
										0.92
										0.39
										0.65
										0.58
										0.99(0.8-1.3)
										1.04(0.6-1.7)
										0.21(0.03-1.6)
										2.05(1.0-4.2)
										1.06(0.7-1.5)
										0.76(0.5-1.1)
										1.00(0.6-1.6)
										0.10
										0.40
										1.40(0.7-2.6)



Status of the receptors Exposure metrics	ER-/PR-			ER-/PR+			ER+/PR+			ER+/PR-			
	n controls	n cases	OR <sup>a</sup>	95%CI	n cases	OR <sup>a</sup>	95%CI	n cases	OR <sup>a</sup>	95%CI	n cases	OR <sup>a</sup>	95%CI
>15	375	105	1.35 (1.1–1.7)	0.26	67	1.26 (0.9–1.7)	0.94	18	1.13 (0.7–1.9)	0.39	121	0.94 (0.7–1.2)	0.19
<i>p</i> trend <sup>d</sup>													
<i>p</i> - heterogeneity of trends <sup>e</sup>													
Cumulative exposure (hrs*L*yr/wk*mo) <sup>b,c</sup>													
>0–39	206	61	1.42 (1.0–1.9)	0.29	29	1.08 (0.7–1.6)	0.73	9	0.95 (0.5–1.9)	0.91	75	1.05 (0.8–1.4)	0.91
>39	203	59	1.39 (1.0–1.9)	0.42	42	1.44 (1.0–2.1)	0.74	11	1.30 (0.7–2.5)	0.85	62	0.88 (0.7–1.2)	0.38
<i>p</i> trend <sup>d</sup>													
<i>p</i> - heterogeneity of trends <sup>e</sup>													
Highest intensity*frequency (L*hrs/mo*wk) <sup>b,c</sup>													
level I	298	92	1.46 (1.1–1.9)	0.53	53	1.25 (0.9–1.7)	0.75	12	0.90 (0.5–1.7)	0.67	107	1.01 (0.8–1.3)	0.67
level II	111	28	1.25 (0.8–1.9)	0.18	18	1.36 (0.8–2.3)	0.51	8	1.77 (0.8–3.7)	0.23	30	0.86 (0.6–1.3)	0.67
<i>p</i> trend <sup>d</sup>													
<i>p</i> - heterogeneity of trends <sup>e</sup>													
Crude average probability <sup>b</sup>													
≥1–<10%	128	37	1.31 (0.9–1.9)	0.22	22	1.23 (0.6–2.0)	0.61	7	1.20 (0.5–2.7)	0.47	106	1.06 (0.7–1.5)	0.47
≥10–<50%	134	39	1.40 (0.96–2.0)	0.24	24	1.20 (0.8–1.9)	0.61	5	0.86 (0.3–2.2)	0.49	98	0.98 (0.7–1.4)	0.47
≥50–<90%	113	27	1.21 (0.8–1.9)	0.23	23	1.60 (0.99–2.6)	0.61	8	1.64 (0.8–3.5)	0.31	83	0.83 (0.5–1.3)	0.47
≥90%	34	17	2.44 (1.3–4.5)	0.43	2	0.54 (0.1–2.3)	0.77	0		0.10	99	0.99 (0.5–2.0)	0.47
<i>p</i> trend <sup>d</sup>													
<i>p</i> - heterogeneity of trends <sup>e</sup>													

<sup>a</sup> Adjusted for age, study site, education, BMI, age at menarche, menopausal status, age at menopause (in postmenopausal women), number of full term births, age at first full term birth, breastfeeding, and family history of breast cancer

<sup>b</sup> Never exposed to organic solvents used as referent

<sup>c</sup> For definitions see e-table I

<sup>d</sup> *p* for trend in ever exposed to organic solvents

<sup>e</sup> compared to ER-/PR- cases