EDITOR'S CHOICE

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 ORs and 95% CIs as the measure of association with breast cancer, controlling for breast cancer risk factors. Stratified analyses examined the potential modification by known breast cancer risk factors. Associations were also evaluated by oestrogen and progesterone receptor 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 oestrogen receptor- and progesterone receptor-negative tumours (OR 1.40; 95% CI 1.1 to 1.8), but there was no association with tumours 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 between 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 tumours.

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 oestrogen- and progesterone-negative breast cancer.

INTRODUCTION

Several organic solvents have been associated with mammary gland tumours in rodents. A comprehensive compilation of data from animal studies, including assessments performed by the International Agency for Research on Cancer (IARC) and the U.S. National Toxicology Program lists 30 organic solvents that have caused malignant mammary gland tumours.[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 (two chemicals), but for most, the epidemiological data are quite meagre. Six have not been evaluated by IARC.

Epidemiological studies of breast cancer and organic solvents have been summarised 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 twofold in women employed for more then 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 oestrogen receptor status,[17] a characteristic that could be important because the hypothesised mechanism for organic solvents in breast carcinogenesis involves action through their oestrogenic properties.[20] Further, no epidemiological data are available on the association between organic solvents and breast cancer and other tumour 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 tumour pathological 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 hypothesised that susceptibility to these chemicals might be modified by factors that underlie the hormonal milieu — total lifetime oestrogen 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 23] the enzyme that activates a variety of procarcinogens including some organic solvents (eg, 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 solvent level. We addressed the issue of potential modification of organic solvent effects by stratifying for menopausal status, age, family history of breast cancer, body mass index (BMI), parity, age at menarche, and alcohol consumption. We also assessed organic solvents and breast cancer relationships by oestrogen and progesterone receptor status and by other clinical characteristics of the tumours.

MATERIALS 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 to January 2003. Cases were identified through a rapid case ascertainment system organised 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 5-year age groups. The study was approved by the institutional review boards at the National Cancer Institute, each of the participating Polish institutions, and the National Cancer Institute 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 for at least 6 months.

Pathology information on cases was obtained from medical record and pathology forms. Pathology forms and tissue blocks were collected for 87% of cases. Oestrogen receptor and progesterone receptor status were 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 tumour 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, that is, 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 disulphide was 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 litre (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^3; 2: 1–10 mg/m^3, and 3: >10 mg/m^3. Due to the small number of women exposed to more than 10 mg/m^3, the categories 3 and 2 were combined. Frequency represented the average amount of exposed time for a job and was estimated as: 1: <2 h/wk; 2: 2–10 h/wk; 3: >10–<20 h/wk; and 4: ≥20 h/wk. A frequency of <1 h/wk was considered unexposed.

Probability of exposure reflected the percentage of workers in the job/industry likely to be exposed, that is, 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 (eg, 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 analysed 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 ORs 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 analysed. 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 ORs and 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 centre, 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 (≤12; 13–14; ≥15), menopausal status (premenopausal; postmenopausal), age at menopause (<45; 45–54; ≥55), age at first full-term birth (<20; 20–24; 25–29; ≥30), number of full-term births (≤1; 2; ≥3), breastfeeding (ever, never), BMI (<25; 25–29; ≥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 analysed the data stratified by menopausal status (premenopausal, postmenopausal); age (<50, ≥50); parity (nulliparous, parous); family history of breast cancer (yes, no); age at menarche (≤12, >12), BMI (<25, ≥25); alcohol consumption (never vs ever consumed); and number of drinks consumed per week (0, 1–4, ≥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 oestrogen 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 (≤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 V.9.2 (StataCorp LP).

RESULTS

The distribution of the commonly recognised 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 and 2).

Overall, women who ever worked at jobs with possible exposure to organic solvents had breast cancer risk of OR 1.16; 95% CI 0.99 to 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, that is, 1–<2 h/wk (OR 1.91; 95% CI 1.1 to 3.4) and the corresponding category when weighted by duration (OR 2.00; 95% CI 1.1 to 3.5). Insignificant increases were found in the lowest exposure categories of crude intensity (OR 1.18; 95% CI 0.99 to 1.4), cumulative exposure (OR 1.19; 95% CI 0.96 to 1.5) and 'highest intensity' (OR 1.19; 95%CI 0.99 to 1.4). There was no indication of increased breast cancer risk in women who had a longer latency period (more then 15 years) as compared with 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^3 (OR 1.21; 95% CI 0.7 to 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 to 1.6 and OR 1.15; 95% CI 0.96 to 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 to 2.5) (e-table I). We did not find any significant exposure-response relationships either in younger (<50 years) or older women (≥50 years) (data not shown). Neither pre- nor postmenopausal women or women younger or older than 50 years showed significant associations with benzene exposure in the stratified analyses (data not shown).

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 to 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

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* (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 to 1.4)
Duration of exposure (in years)†			
>0–5	123 (5.2)	124 (5.0)	1.17 (0.9 to 1.5)
>5–10	82 (3.4)	72 (2.9)	1.27 (0.9 to 1.8)
>10	217 (9.1)	213 (8.5)	1.13 (0.9 to 1.4)
p Trend¶			*0.847*
Crude average intensity (quantity used in l/mo)†			
≥1–≤10	337 (14.2)	313 (12.5)	1.18 (0.99 to 1.4)
>10–≤100	77 (3.2)	77 (3.1)	1.23 (0.9 to 1.7)
>100	8 (0.3)	19 (0.8)	0.61 (0.3 to 1.4)
p Trend¶			*0.368*
Intensity weighted by duration (in l/mo)†			
≥1–≤10	336 (14.1)	317 (12.7)	1.16 (0.98 to 1.4)
>10–≤100	78 (3.3)	73 (2.9)	1.31 (0.9 to 1.8)
>100	8 (0.3)	19 (0.8)	0.61 (0.3 to 1.4)
p Trend¶			*0.590*
Crude average frequency (h/wk)†			
≥1–<2	33 (1.4)	20 (0.8)	1.91 (1.1 to 3.4)
≥2–≤10	133 (5.6)	110 (4.4)	1.16 (0.9 to 1.5)
>10–<20	169 (7.1)	185 (7.4)	1.06 (0.8 to 1.3)
≥20	87 (3.6)	94 (3.8)	1.23 (0.9 to 1.7)
p Trend¶			*0.368*
Average frequency weighted by duration (h/wk)†			
≥1–<2	35 (1.5)	20 (0.8)	2.00 (1.1 to 3.5)
≥2–≤10	134 (5.6)	112 (4.5)	1.16 (0.9 to 1.5)
>10–<20	165 (6.9)	182 (7.3)	1.05 (0.8 to 1.3)
≥20	88 (3.6)	95 (3.8)	1.23 (0.9 to 1.7)
p Trend¶			*0.305*
Average latency (years)†			
0–15	41 (1.7)	34 (1.4)	1.48 (0.9 to 2.4)
>15	381 (16.0)	375 (15.0)	1.14 (0.97 to 1.3)
p Trend¶			*0.266*
Cumulative exposure (h*l*years/wk*mo)†,‡			
>0–39	213 (8.9)	206 (8.2)	1.19 (0.96 to 1.5)
>39	209 (8.8)	203 (8.1)	1.15 (0.9 to 1.4)
p Trend¶			*0.741*
Highest intensity*frequency (l*h/mo*wk)†,§			
I level	321 (13.5)	298 (11.9)	1.19 (0.99 to 1.4)
II level	101 (4.2)	111 (4.5)	1.12 (0.8 to 1.5)
p Trend¶			*0.776*
Crude average probability†			
≥1–<10%	130 (5.5)	128 (5.1)	1.13 (0.9 to 1.5)
≥10–<50%	148 (6.2)	134 (5.7)	1.19 (0.9 to 1.5)
≥50–<90%	109 (4.6)	113 (4.5)	1.14 (0.9 to 1.5)
≥90%	35 (1.5)	34 (1.4)	1.31 (0.8 to 2.2)
p Trend¶			*0.728*
Average probability weighted by duration†			
≥1–<10%	130 (5.5)	128 (5.1)	1.13 (0.9 to 1.5)
≥10–<50%	146 (6.1)	131 (5.2)	1.19 (0.9 to 1.5)
≥50–<90%	108 (4.5)	116 (4.6)	1.11 (0.8 to 1.5)
≥90%ss	38 (1.6)	34 (1.4)	1.44 (0.9 to 2.3)
p Trend¶			*0.674*

*Adjusted for age, study site, education, body mass index (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.
†Never exposed to organic solvents used as referent.
‡Cumulative exposure: product of frequency, intensity, and duration of exposure summed across all jobs. Cutpoint=median in exposed controls.
§Product of scores for intensity*frequency: I level=≤4, II level=>4.
¶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* (95% CI)
Ever exposed to benzene			
Never	2268 (95.2)	2382 (95.2)	
Ever	115 (4.8)	120 (4.8)	1.00 (0.8 to 1.3)
Duration of exposure (in years)†			
>0–5	42 (1.8)	41 (1.6)	1.07 (0.7 to 1.7)
>5–10	25 (1.0)	19 (0.8)	1.36 (0.7 to 2.5)
>10	48 (2.0)	60 (2.4)	0.82 (0.6 to 1.2)
p Trend¶			*0.691*
Crude average intensity (concentration in air) (mg/m^3)†			
>0–<1	92 (3.9)	99 (4.0)	0.95 (0.7 to 1.3)
≥1	23 (0.9)	21 (0.8)	1.21 (0.7 to 2.2)
p Trend¶			*0.849*
Intensity weighted by duration (mg/m^3)†			
>0–1	92 (3.9)	99 (3.9)	0.95 (0.7 to 1.3)
>1	23 (0.9)	21 (0.9)	1.21 (0.7 to 2.2)
p Trend¶			*0.849*
Crude average frequency (h/wk)†			
>1–≤10	33 (1.4)	28 (1.1)	0.93 (0.5 to 1.6)
>10–<20	48 (2.0)	46 (1.8)	1.10 (0.7 to 1.7)
≥20	34 (1.4)	46 (1.8)	0.93 (0.6 to 1.5)
p Trend¶			*0.962*
Average frequency weighted by duration (h/wk)†			
>1–≤10	34 (1.4)	28 (1.1)	0.96 (0.5 to 1.6)
>10–<20	47 (2.0)	46 (1.8)	1.08 (0.7 to 1.6)
≥20	34 (1.4)	46 (1.8)	0.93 (0.6 to 1.5)
p Trend¶			*0.940*
Average latency (years)†			
0–20	10 (0.4)	12 (0.5)	0.94 (0.4 to 2.2)
>20	105 (4.4)	108 (4.3)	1.00 (0.8 to 1.3)
p Trend¶			*0.991*
Cumulative exposure (h*mg*years/wk*m^3)†,‡			
>0–33	58 (2.4)	59 (2.4)	1.00 (0.7 to 1.5)
>33	57 (2.4)	61 (2.4)	0.99 (0.7 to 1.4)
p Trend¶			*0.960*
Highest intensity*frequency (mg*h/m^3*wk)†,§			
I level	95 (4.0)	102 (4.1)	0.96 (0.7 to 1.3)
II level	20 (0.8)	18 (0.7)	1.21 (0.6 to 2.3)
p Trend¶			*0.872*
Crude average probability†			
≥1–<10%	63 (2.6)	54 (2.2)	1.28 (0.9 to 1.9)
≥10–<50%	36 (1.5)	44 (1.8)	0.73 (0.5 to 1.2)
≥50–<90%	11 (0.5)	17 (0.7)	0.77 (0.4 to 1.7)
≥90%	5 (0.2)	5 (0.2)	1.20 (0.3 to 4.3)
p Trend¶			*0.565*
Average probability weighted by duration†			
≥1–<10%	63 (2.6)	54 (2.2)	1.28 (0.9 to 1.9)
≥10–<50%	37 (1.6)	44 (1.8)	0.76 (0.5 to 1.2)
≥50–<90%	10 (0.5)	17 (0.7)	0.71 (0.3 to 1.6)
≥90%	5 (0.2)	5 (0.2)	1.20 (0.3 to 4.3)
p Trend¶			*0.542*

*Adjusted for age, study site, education, body mass index (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.
†Never exposed to benzene used as referent.
‡Cumulative exposure: product of frequency, intensity, and duration of exposure summed across all jobs. Cutpoint=median in exposed controls: I level=≤4, II level=>4.
§Product of scores for intensity*frequency: I level=≤4, II level=>4.
¶p For trend in ever exposed to benzene.

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.

Table 3 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

Factor	Ever exposed to total organic solvents OR*, †; 95% CI			Ever exposed to benzene OR*, ‡; 95% CI		
Menopause (n cases/controls)	Pre- (104/121)	Post- (318/288)		Pre- (21/31)	Post- (94/89)	
	1.21 (0.9 to 1.6)	1.15 (0.96 to 1.4)		0.78 (0.4 to 1.4)	1.06 (0.8 to 1.4)	
p Heterogeneity		*0.74*			*0.58*	
Age (n cases/controls)	<50 (121/122)	≥50 (301/287)		<50 (25/28)	≥50 (90/92)	
	1.13 (0.8 to 1.5)	1.20 (0.99 to 1.5)		0.90 (0.5 to 1.6)	1.04 (0.8 to 1.4)	
p 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)	
	1.08 (0.6 to 1.9)	1.18 (1.0 to 1.4)		0.49 (0.2 to 1.3)	1.07 (0.8 to 1.4)	
p Heterogeneity		*0.67*			*0.11*	
Age at menarche¶ (n cases/controls)	≤12 (132/91)	>12 (289/312)		≤12 (37/32)	>12 (78/86)	
	1.25 (0.9 to 1.7)	1.15 (0.96 to 1.4)		0.88 (0.5 to 1.5)	1.09 (0.8 to 1.5)	
p Heterogeneity		*0.16*			*0.44*	
BMI¶ (n cases/controls)	<25 (155/129)	≥25 (266/277)		<25 (49/33)	≥25 (65/86)	
	1.16 (0.9 to 1.5)	1.19 (0.98 to 1.4)		1.33 (0.8 to 2.2)	0.85 (0.6 to 1.2)	
p Heterogeneity		*0.94*			*0.19*	
Parity (n cases/controls)	Nulliparous (59/41)	Parous (363/368)		Nulliparous (26/12)	Parous (89/108)	
	1.22 (0.8 to 1.9)	1.17 (0.99 to 1.4)		1.94 (0.9 to 4.1)	0.88 (0.7 to 1.2)	
p Heterogeneity		*0.81*			*0.04*	
Alcohol consumption (n cases/controls)	Abstinents (267/252)	Ever consumers (155/157)		Abstinents (80/78)	Ever consumers (35/42)	
	1.22 (1.0 to 1.5)	1.11 (0.9 to 1.4)		1.12 (0.8 to 1.6)	0.83 (0.5 to 1.3)	
p Heterogeneity		*0.49*			*0.29*	
Pathomorphological breast cancer feature						
Cancer type (n cases)	Ductal NOS (222)	Lobular (55)		Ductal NOS (61)	Lobular (14)	
	1.18 (0.98 to 1.4)	1.05 (0.8 to 1.4)		1.00 (0.7 to 1.4)	0.83 (0.5 to 1.5)	
p Heterogeneity		*0.48*			*0.55*	
Tumour size (n cases)	≤2 cm (200)	>2 cm (156)		≤2 cm (47)	>2 cm (47)	
	1.20 (0.99 to 1.5)	1.15 (0.9 to 1.4)		0.84 (0.6 to 1.2)	1.08 (0.8 to 1.5)	
p Heterogeneity		*0.74*			*0.26*	
Grade (n cases)	Well differentiated (42)	Moderately (220)	Poorly (84)	Well differentiated (14)	Moderately (54)	Poorly (25)
	1.42 (0.98 to 2.0)	1.20 (0.99 to 1.4)	1.10 (0.8 to 1.4)	1.50 (0.8 to 2.7)	0.88 (0.6 to 1.2)	0.97 (0.6 to 1.5)
p Heterogeneity		*0.38*§	*0.24*§		*0.09*§	*0.21*§

*Adjusted for age, study site, education, body mass index (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.
†Never exposed to organic solvents used as referent.
‡Never exposed to benzene used as referent.
§Compared with well differentiated.
¶There was missing information for age at menarche in one case and six controls exposed to organic solvents and two controls exposed to benzene; BMI (in one case and three controls exposed to organic solvents and one case and one control exposed to benzene).

No modification of the relationships between organic solvent 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 to 4.1) but not in parous (OR 0.88; 95% CI 0.7 to 1.2). Some increased risk estimates were observed in women ever exposed to benzene with a BMI of <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 to 1.5), but not among ever drinkers (OR 1.11; 95% CI 0.9 to 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 to 2.3) and the highest category for the product of intensity and frequency (OR 1.45; 95% CI 1.0 to 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 solvent 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 to 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 l of organic solvents per month (OR 1.50; 95% CI 1.0 to 2.2 and OR 1.49; 95% CI 1.0 to 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 tumour size, although a significant increase was observed in larger tumours in the category of highest probability of exposure to organic solvents (OR 1.88; 95% CI 1.1 to 3.4) (data not shown). Insignificant associations were found for well and moderately differentiated tumours (OR 1.42; 95% CI 0.98 to 2.10 and OR 1.20; 95% CI 0.99 to 1.4, respectively) but no positive exposure-response gradient was found in any of the analysed exposure metrics. A marginally significant positive trend was observed in poorly differentiated tumours for probability of exposure (p 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 tumour grade (data not shown). No effect was seen for benzene and these pathological features (data not shown).

The results of the analysis for total organic solvents by oestrogen/progesterone (ER/PR) receptor status are presented in table 4. ORs were significantly increased for total organic solvent exposure in cases with negative receptors (OR 1.40; 95% CI 1.1

Table 4 Breast cancer risk by exposure to organic solvents and joint oestrogen/progesterone receptor status in breast cancer case-control study

Status of the receptors		ER−/PR−		ER+/PR−		ER−/PR+		ER+/ PR+	
Exposure metrics	n controls	n cases	OR* 95% CI	n cases	OR* 95% CI	n cases	OR* 95% CI	n cases	OR*, 95% CI
Exposed to organic solvents									
Never	2093	449	1.0	301	1.0	98	1.0	778	1.0
Ever	409	120	1.40 (1.1 to 1.8)	71	1.27 (0.95 to 1.7)	20	1.11 (0.7 to 1.8)	137	0.97 (0.8 to 1.2)
p Heterogeneity ¶					*0.56*		*0.40*		*0.008*
Duration of exposure (years)†									
>0−5	124	37	1.45 (0.98 to 2.1)	16	1.06 (0.6 to 1.8)	7	1.22 (0.5 to 2.7)	41	0.99 (0.7 to 1.4)
>5−10	72	18	1.17 (0.7 to 2.0)	17	1.71 (1.0 to 3.1)	3	0.90 (0.3 to 2.9)	29	1.14 (0.7 to 1.8)
>10	213	65	1.46 (1.1 to 2.0)	38	1.23 (0.8 to 1.8)	10	1.14 (0.6 to 2.2)	67	0.90 (0.7 to 1.2)
p Trend§			*0.82*		*0.76*		*0.63*		*0.65*
p Heterogeneity of trends¶					*0.91*		*0.58*		*0.58*
Crude intensity (quantity used in l/mo)†									
≥1−10	313	95	1.43 (1.1 to 1.8)	54	1.22 (0.9 to 1.7)	17	1.20 (0.7 to 2.0)	111	0.99 (0.8 to 1.3)
>10−100	77	24	1.55 (0.96 to 2.5)	15	1.58 (0.9 to 2.8)	3	0.99 (0.3 to 3.2)	25	1.04 (0.6 to 1.7)
>100	19	1	0.31 (0.04 to 2.3)	2	1.02 (0.2 to 4.5)	0		1	0.21 (0.03 to 1.6)
p Trend§			*0.33*		*0.97*		*0.43*		*0.39*
p Heterogeneity of trends¶					*0.47*		*0.68*		*0.92*
Crude average frequency (h/wk)†									
≥1−<2	20	9	2.20 (0.98 to 4.9)	5	1.70 (0.6 to 4.7)	2	2.62 (0.6 to 11.3)	14	2.05 (1.0 to 4.2)
≥2−≤10	110	35	1.40 (0.9 to 2.1)	15	0.79 (0.4 to 1.4)	8	1.59 (0.7 to 3.4)	49	1.06 (0.7 to 1.5)
>10−<20	185	46	1.23 (0.9 to 1.7)	39	1.64 (1.1 to 2.4)	6	0.74 (0.3 to 1.7)	47	0.76 (0.5 to 1.1)
≥20	94	30	1.59 (1.0 to 2.5)	12	1.23 (0.6 to 2.3)	4	0.98 (0.3 to 2.8)	27	1.00 (0.6 to 1.6)
p Trend§			*0.59*		*0.24*		*0.14*		*0.10*
p Heterogeneity of trends¶					*0.18*		*0.24*		*0.40*
Average latency (years)†									
0−15	34	15	1.98 (1.0 to 3.7)	4	1.39 (0.5 to 4.0)	2	1.05 (0.2 to 4.5)	16	1.40 (0.7 to 2.6)
>15	375	105	1.35 (1.1 to 1.7)	67	1.26 (0.9 to 1.7)	18	1.13 (0.7 to 1.9)	121	0.94 (0.7 to 1.2)
p Trend§			*0.26*		*0.94*		*0.39*		*0.19*
p Heterogeneity of trends¶					*0.49*		*0.73*		*0.91*
Cumulative exposure (h*l*years/wk*mo)†,‡									
>0−39	206	61	1.42 (1.0 to 1.9)	29	1.08 (0.7 to 1.6)	9	0.95 (0.5 to 1.9)	75	1.05 (0.8 to 1.4)
>39	203	59	1.39 (1.0 to 1.9)	42	1.44 (1.0 to 2.1)	*11*	1.30 (0.7 to 2.5)	62	0.88 (0.7 to 1.2)
p Trend§			*0.74*		*0.30*		*0.85*		*0.38*
p Heterogeneity of trends¶					*0.26*		*0.75*		*0.67*
Highest intensity*frequency (l*h/mo*wk)†,‡									
I level	298	92	1.46 (1.1 to 1.9)	53	1.25 (0.9 to 1.7)	12	0.90 (0.5 to 1.7)	107	1.01 (0.8 to 1.3)
II level	111	28	1.25 (0.8 to 1.9)	18	1.36 (0.8 to 2.3)	8	1.77 (0.8 to 3.7)	30	0.86 (0.6 to 1.3)
p Trend§			*0.51*		*0.95*		*0.23*		*0.67*
p Heterogeneity of trends¶					*0.61*		*0.15*		*0.84*
Crude average probability†									
≥1−<10%	128	37	1.31 (0.9 to 1.9)	22	1.23 (0.6 to 2.0)	7	1.20 (0.5 to 2.7)	47	1.06 (0.7 to 1.5)
≥10−<50%	134	39	1.40 (0.96 to 2.0)	24	1.20 (0.8 to 1.9)	5	0.86 (0.3 to 2.2)	49	0.98 (0.7 to 1.4)
≥50−<90%	113	27	1.21 (0.8 to 1.9)	23	1.60 (0.99 to 2.6)	8	1.64 (0.8 to 3.5)	31	0.83 (0.5 to 1.3)
≥90%	34	17	2.44 (1.3 to 4.5)	2	0.54 (0.1 to 2.3)	0		10	0.99 (0.5 to 2.0)
p Trend§			*0.43*		*0.77*		*0.56*		*0.47*
p Heterogeneity of trends¶					*0.80*		*0.38*		*0.22*

*Adjusted for age, study site, education, body mass index (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.
†Never exposed to organic solvents used as referent.
‡For definitions see e-table I.
§p For trend in ever exposed to organic solvents.
¶Compared with ER−/PR− cases.

to 1.8), but not in cases having both ER/PR-positive receptors (OR 0.97; 95% CI 0.8 to 1.2) (p heterogeneity 0.008). Although not statistically significant, the OR of 1.27; 95% CI 0.95 to 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 oestrogen- and progesterone-negative breast cancer cases, but not among oestrogen- 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 oestrogen receptor status been addressed in premenopausal women, and no apparent difference in risk between ER-positive and ER-negative breast tumour cases was found.[17] However, no other individual solvents or organic solvents, as a category, were analysed in this study. Organic solvents have some similarities with organochlorines with respect to their lipophilicity and potential role in breast cancer aetiology. 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 oestrogen receptor breast cancers, even though these substances are dioxin-like and potentially antioestrogenic.[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 in abstinent drinkers, but not in drinkers. Similarly, breast cancer and some organic solvent metrics were associated with cancer type and tumour 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 >1 mg/m^3. This may be due to the fact that work in an environment entailing exposure to benzene exceeding the Maximal Allowable Concentration has been banned for women since 1951 (the Maximal Allowable Concentration in Poland for benzene was 100 mg/m^3 since 1956 and 30 mg/m^3 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 were 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 tumour 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 conducted in epidemiological 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 vapour 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, that is, unknown solvents with different vapour 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 recognise that these data might have been 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 a 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 oestrogen- and progesterone-negative breast cancer.

Author footnote

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