Original article

Scand J Work Environ Health. 2018:44(3):312–322. doi:10.5271/sjweh.3717

Occupational exposure to organic solvents and risk of male breast cancer: a European multicenter case–control study

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Laouali N, Pilorget C, Cyr D, Neri M, Kaerlev L, Sabroe S, Gorini G, Richiardi L, Morales-Suárez-Varela M, Llopis-Gonzalez A, Ahrens W, Jöckel K-H, Afonso N, Eriksson M, Merletti F, Olsen J, Lynge E, Guénel P. Occupational exposure to organic solvents and risk of male breast cancer: a European multicenter case–control study. *Scand J Work Environ Health*. 2018:44(3):312–322. doi:10.5271/sjweh.3717

Objectives The etiology of male breast cancer (MBC) is largely unknown but a causal role of exposure to organic solvents has been suggested. Previous studies on occupational risk factors of breast cancer were often restricted to women who are frequently exposed to lower levels and at a lower frequency than men. We investigated the association between MBC and occupational exposure to petroleum and oxygenated and chlorinated solvents in a multicenter case–control study of rare cancers in Europe.

Methods The study included 104 MBC cases and 1901 controls. Detailed lifetime work history was obtained during interviews, together with sociodemographic characteristics, medical history and lifestyle factors. Occupational exposures to solvents were estimated from a job-exposure matrix. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated using unconditional logistic regression models.

Results Lifetime cumulative exposure to trichloroethylene >23.9 ppm years was associated with an increased MBC risk, compared to non-exposure [OR (95% CI): 2.1 (1.2–4.0); P trend <0.01). This increase in risk persisted when only exposures that occurred ≥10 years before diagnosis were considered. In addition, a possible role for benzene and ethylene glycol in MBC risk was suggested, but no exposure–response trend was observed.

Conclusions These findings add to the evidence of an increased risk of breast cancer among men professionally exposed to trichloroethylene and possibly to benzene or ethylene glycol. Further studies should be conducted in populations with high level of exposure to confirm our results.

Key terms alcoholic solvent; benzene; chlorinated solvent; ethylene glycol; JEM; job-exposure matrix; petroleum solvent; trichloroethylene.

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Breast cancer is the most frequent cancer among women, with over 1.6 million new cases in 2012 across the world (1), but it is a rare disease among men, accounting for <1% of all breast cancers (2). Risk factors related to hormones and reproduction are well-established causes of female breast cancer, but the etiology of male breast cancer (MBC) is largely unknown (3). However, the clinical features of MBC are often similar to those of the late-onset type of female breast tumors (4), suggesting that these two conditions may share some risk factors. The risk factors for MBC that have been investigated so far include genetics (family history of breast cancer, mutations in *BRCA2* or *CHEK2*), conditions associated with an abnormal estrogen-to-androgen ratio (Klinefelter's syndrome, obesity, orchitis, infertility, exogenous estrogen or testosterone use), and lifestyle (lack of physical activity, alcohol consumption) (3, 5, 6).

Environmental and occupational factors are also suspected to play a role in the etiology of breast cancer in both sexes (7, 8). Solvents are ubiquitous chemicals in occupational settings. They have retained particular attention because they are highly lipophilic compounds that can accumulate in the adipose tissue of the breast and initiate or promote carcinogenesis through genotoxic mechanisms (9). Because of the high proliferative activity of epithelial cells of the mammary gland and susceptibility to chemical carcinogens, mammary terminal duct lobular units are likely target tissues for tumorigenesis (10). Animal studies have provided strong evidence for an association between organic solvents and breast cancer (11), and the International Agency for Research on Cancer (IARC) has recognized solvents such as benzene and trichloroethylene (TCE) as known human carcinogens. However, there are limited data on solvents as human breast carcinogens (12, 13).

The major families of solvents used in the work places include petroleum, chlorinated and oxygenated solvents. Petroleum solvents consist of fuel and organic solvents produced by oil refining. The main petroleum solvent, benzene, was initially used as industrial solvent, eg, to degrease metals, besides being a constituent of gasoline. The toxicity of benzene has largely been proven in leukemia risk (14). Its use has now been restricted as an intermediate for the synthesis of other chemicals. Chlorinated solvents including TCE, perchloroethylene or methylene chloride, are usually used as solvents in paints, paint removers or resines, chemical intermediates for pesticide synthesis, in dry-cleaning and in the steel industry. Most of them have been used as solvents in place of benzene. Oxygenated solvents include alcohols, ketones, esters, ethylene glycol, or tetrahydrofurans and are widely used in the paint, ink, pharmaceutical, fragrance, adhesive, cosmetic, detergent, or food industries. Ethylene glycol, in particular, is used as a sterilizing agent for medical equipment and supplies.

A limited number of epidemiological studies have investigated the role of organic solvents in female breast cancer, and the increases were either small or inconsistent (15–22). Only two studies have considered MBC in relation to occupational exposure to solvents (23, 24). Because occupational exposures to many chemicals, including solvents, are usually present in jobs mostly held by men (eg, mechanics or painters), studies among men with higher prevalence of exposure than women and less competing risk factors (eg, hormonal and reproductive factors) may facilitate the detection of an association between exposure to solvents and breast cancer, despite the rarity of the disease in men.

In a previous paper based on data from a European case–control study on rare cancers including 104 cases of MBC (25), we reported that motor vehicle mechanics and painters with probable exposure to organic solvents had a two- to threefold increased risk of MBC. To further evaluate the hypothesis that organic solvents increases the incidence of MBC, we specifically assessed lifetime occupational exposure to organic solvents by solvent subtype using a detailed job exposure matrix (JEM) (26).

Methods

We conducted a European multi-center retrospective case–control study on occupational risk factors of seven rare cancer sites (gallbladder and extra-hepatic bile ducts, small intestine, bone, eye melanoma, mycosis fungoides, and male breast). Cases and controls were recruited from selected areas of eight European countries (Denmark, France, Germany, Italy, Latvia, Portugal, Spain and Sweden) representing a source population of 37 million people. The study design and the procedures of data collection have been described in detail earlier (25, 27) and are summarized below. The local ethics committees in each participating country approved the study.

Recruitment of cases and controls

Men living in the study areas who were diagnosed with a breast cancer between 1995 and 1997, aged 35–70 years at diagnosis were eligible for inclusion in the study. This age range was based on the assumption that occupational exposures are not likely to be the cause of the disease in younger patients.

Case ascertainment was based on regular contacts with clinical and pathology departments and/or cancer registers in each study area. For each case, an expert pathologist reviewed the pathology report and, if possible, a representative histological slide of the tumor. In total, 122 MBC patients were eligible for the study from all the countries. Eighteen cases could not be included

because the doctor did not give permission to contact the patient or the patient refused to participate. Thus, 104 cases (85%) were interviewed and available for analysis.

The controls were selected randomly from population registers in Denmark, Italy, and Sweden, from electoral rolls in France and from municipality registers in Germany during the case recruitment period and were frequency-matched to the cases by gender, year of birth (5-year strata), and residence area. In countries where population controls were difficult to identify, colon and stomach cancer patients were regarded as appropriate alternatives to population controls, as no occupational exposure to organic solvents is suspected to play an important role in these cancers. Hospital-based cancer controls were selected randomly among incident colon cancer patients in Latvia and Spain, and among colon or stomach cancer patients in Portugal. The controls served as a common pool of controls for each of the seven groups of rare cancer cases included in the European study. The participation rate among male population controls was high in France (81%) and Italy (74%) but relatively low in Denmark, Germany, and Sweden (<60%). In countries using a hospital-based design, the participation rate among cancer controls was >95%. The overall participation rate among controls was 67%. For the present study, we selected only male controls sampled in study areas from which ≥1 MBC patient was included. Finally, 1901 male controls (1395 population controls and 506 cancer controls) were available for the analyses.

Data collection

A structured questionnaire was first developed in English, and then translated into the language of each participating country. Back-translation to English was performed for quality control, and no major departure from the original version was observed. A trained interviewer administered this questionnaire face to face or by telephone and collected information on sociodemographic characteristics, previous medical conditions, lifestyle factors, anthropometric characteristics, alcohol and tobacco consumption, and detailed occupational activities in each job held for >6 months. For each occupational period, we recorded data on products and production processes, the year the job started and ended, job title, and working hours per week. The materials handled, chemical exposures, and occupations held by nearby workers were also recorded. The specific nature of the work was also addressed, such as work tasks, machines or products used, and duration of their use (hours per week). Specific questionnaires were also developed for 27 definite jobs or tasks, such as welding or painting.

Exposure assessment

As previously described, trained coders coded the jobs (28). Briefly, occupation was coded according to the International Standard Classification of Occupations of the International Labor Office (ISCO), 1968 revision, while industry was coded according to the Classification of Activities in the European Community (NACE), 1996 revision.

Occupational exposures to organic solvents were assessed using JEM developed at the Occupational Health Department of the French National Agency for Public Health (Santé Publique France) by experts in occupational hygiene (29, 30). Jobs were defined according to both the ISCO code and the Nomenclature d'Activité Française (NAF: Institut National de la Statistique et des Etudes Economiques, revision 1, 2003), subsequently converted to the European NACE code for the purpose of this study. Exposures to occupational hazards were assessed by job and calendar period to account for changes in exposures over time.

In the JEM, exposure to chlorinated solvents [TCE, perchloroethylene (tetrachloroethylene), methylene chloride (dichloromethane), chloroform (trichloromethane) and carbon tetrachloride], petroleum solvents [benzene, special boiling point spirits and other aliphatic petroleum-based solvents (SBP), gasoline, white spirits, and kerosene/diesel oil/fuel oils (KDF)] and to oxygenated solvents (alcohol, ketones/esters, diethyl ether, ethylene glycol and tetrahydrofuran) was determined for each job using semi-quantitative indicators for exposure probability (ie, proportion of exposed workers 0, 0–10, 10–20, … ≥90%), exposure frequency (eg, for petroleum solvents 1=<30%, 2=30–70%, 3=>70% of working hours) and exposure intensity [semi-quantitative exposure scores on the basis of literature review of occupational measurement data, for example, for benzene: 1=0.1–1 ppm, 2>1–5 ppm, 3=>5–15 ppm, and 4=>15 ppm].

Each job held by a case or a control included in the European study was assigned the exposure indices reported in the JEM. In order to improve specificity, exposure to a given solvent was assigned only to jobs whose probability of exposure according to the JEM was >10%, while the jobs below this cut-off were considered as non-exposed. A job-specific exposure score was then calculated as the result of the product of exposure probability, frequency and intensity, and duration of the job in years. An individual Cumulative Exposure Score (CES) was then calculated for each study subject as the sum of the job-specific exposure scores over his entire work history.

Statistical analysis

The distributions of baseline characteristics of study population according to cases and controls status were expressed as means and standard deviation (SD) for con-

tinuous variables or number (percentage) for dichotomous variables. The CES was categorized into "not exposed" plus two classes of exposed workers, according to the median among the exposed controls. Regarding ethylene glycol and tetrahydrofuran, subjects were simply defined as "never or ever exposed" because of the small number of exposed workers. We could not estimate associations between MBC and exposure to perchloroethylene, carbon tetrachloride, chloroform and diethyl ether because no case of breast cancer was exposed to these solvents.

We conducted unconditional logistic regressions to estimate odds ratios (OR) and their 95% confidence intervals (95% CI) adjusting for age, country, alcohol intake in three categories (0–≥30; >30–≤60; >60 g/day), education in three categories (left school at age ≤18; professional training; university) and body mass index (BMI) in four categories (≤18.5, >18.5–≤25, >25–≤30 and >30 kg/m²) as these variables are potentially associated with both breast cancer and solvent exposure. We used three different models: model A where each solvent was included separately; model B where all solvents where included simultaneously to control for potential confounding between exposures; model C using a stepwise multiple logistic regression method that allowed dropping and adding solvents at each step to identify independent predictors of MBC. F probabilities were used as stepping criteria: 0.05 was the entry cut-off and 0.10 was the removal cut-off (31).

All analyses were performed using Statistical Analysis Systems (SAS) software, version 9.3 (SAS Institute, Inc, Cary, NC, USA).

Table 1. Comparison of cases and controls by selected characteristics (European study on male breast cancer) [BMI=body mass index; CI=confidence interval; SD=standard deviation]

	Cases (N=104)		Controls (N=1901)		OR [a]	95% CI
	N	%	N	%		
Country						
Denmark	8	7.7	195	10.3		
Sweden	7	6.7	140	7.4		
Latvia	3	2.9	69	3.6		
France	29	27.9	308	16.2		
Germany	10	9.6	542	28.5		
Italy	20	19.2	210	11		
Spain	19	18.3	365	19.2		
Portugal	8	7.7	72	3.8		
Age (years)						
<40	6	5.8	218	11.5		
40–44	6	5.8	193	10.1		
45–49	10	9.6	190	10		
50–54	14	13.4	202	10.6		
55–59	16	15.4	264	13.9		
60–64	20	19.2	329	17.3		
≥65	32	30.8	505	26.6		
Alcohol intake (g/day)						
0–30	43	41.4	1130	59.4	1.0	reference
30–60	31	29.8	503	26.5	1.3	0.8–2.2
>60	30	28.8	268	14.1	2.6	1.5–4.4
Education [b]						
Left school at ≤18	63	60.6	866	45.6	1.5	0.8–2.8
Professional training	25	24.0	515	27.1	1.5	0.8–2.9
University	16	14.4	516	27.1	1.0	reference
BMI (kg/m²)						
<18.5	8	7.7	83	4.4	2.0	0.9–4.7
18.5–25	40	38.5	733	38.6	1.0	reference
25–30	40	38.5	883	46.4	0.8	0.5–1.3
>30	16	15.4	202	10.6	1.5	0.8–2.7

[a] Adjusted for age and country.
[b] Four missing values.

Results

The main characteristics of cases (N=104) and controls (N=1901) are presented in table 1. Compared to controls, cases tended to be older and have a lower education level. The BMI and the mean number of jobs did not differ significantly. An elevated consumption of alcohol >60 g/day was associated with a 2.6 increased risk of MBC, as reported in a previous paper (5).

The proportion of men ever exposed to organic solvent of any kind was higher among cases than among controls (table 2). As regards the most common exposures, 44% of the cases and 32% of the controls had been exposed to TCE, 30% and 20% respectively to white spirits, 21% and 17% to KDF, 21% and 9% to benzene. Each of the other exposures accounted for ≤10% of cases and controls. Each subject was typically exposed to more than one substance. For example, 144 subjects had been exposed to both benzene and TCE, a number that repre-

Table 2. Prevalence of occupational exposure to organic solvents for cases and controls (European study on male breast cancer) [KDF=kerosene/diesel oil/fuels oil; SBP=special-boiling-point spirits]

Solvents	Cases (N=104) ever exposed		Controls (N=1901) ever exposed	
	N	%	N	%
Petroleum solvents				
Benzene	22	21.1	178	9.3
SBP	6	5.7	83	4.3
Gasoline	9	8.6	112	5.8
White spirits	31	29.8	376	19.7
KDF	22	21.1	317	16.6
Chlorinated solvents				
Trichloroethylene	46	44.2	613	32.2
Perchloroethylene	0	0.0	16	0.8
Methylene chloride	8	7.6	96	5.0
Chloroform	0	0.0	6	0.3
Carbon tetrachloride	0	0.0	1	0.0
Oxygenated solvents				
Alcohol	10	9.6	171	8.9
Ketones/esters	11	10.5	137	7.2
Diethyl ether	0	0.0	11	0.5
Ethylene glycol	5	4.8	25	1.3
Tetrahydrofuran	2	1.9	8	0.4

sented 72% of all those exposed to benzene (N=200) and 21% of all those exposed to TCE (N=659).

Table 3 shows the adjusted OR for MBC associated with cumulative exposure scores of organic solvents obtained with three different models.

Among the petroleum solvents, significant two- to threefold increased OR were observed in all the models for the low benzene exposure levels compared to non-exposure. The narrower CI were observed in model C, which reports a 2.2 increase in risk. However the OR were smaller and did not reach statistical significance in the high exposure group.

High exposures to gasoline, white spirits and KDF were associated with similarly increased OR of 1.9, 1.8, and 1.7, respectively, using model A where each solvent was included separately. However no evidence of association was found in model B including all the solvents at a time. Exposure to SBP was not associated with MBC.

For chlorinated solvents, high exposure to TCE was associated with OR≈2 in all models, with a dose–response trend (P<0.01). The three models gave very similar estimates, including the one with stepwise variable selection.

Low level exposure to methylene chloride was associated with an OR of 2.4 in model A, but this decreased to 1.9 and was non-significant after adjustment for other solvents

Table 3. Odds ratios (OR) for male breast cancer for exposure to organic solvents. [CES=cumulative exposure score; CI=confidence interval; KDF=kerosene/diesel oil/fuel oils; SBP=special-boiling-point spirits]

Solvent CES (ppm.years)	Cases (N=104)	Controls (N=1901)	Model A [a]		Model B [b]		Model C [c]	
			OR	95% CI	OR	95% CI	OR	95% CI
Benzene								
Not exposed	82	1723	1.0	reference	1.0	reference	1.0	reference
>0–<0.87	13	89	2.6	1.3–5.1	3.1	1.1–8.9	2.2	1.1–4.3
≥0.87	9	89	1.9	0.9–4.1	2.6	0.7–9.4	1.5	0.7–3.4
Gasoline								
Not exposed	95	1789	1.0	reference	1.0	reference	Not selected	
>0–<0.16	4	56	1.3	0.4–3.8	1.2	0.4–3.6		
≥ 0.16	5	56	1.9	0.7–5.0	0.7	0.2–3.0		
SBP								
Not exposed	98	1818	1.0	reference	1.0	reference	Not selected	
>0–<1.10	3	42	1.1	0.3–3.8	0.5	0.1–1.8		
≥1.10	3	41	1.2	0.4–4.2	0.6	0.1–2.6		
White spirits								
Not exposed	73	1525	1.0	reference	1.0	reference	Not selected	
>0–<0.13	14	188	1.5	0.8–2.8	0.9	0.4–2.0		
≥0.13	17	188	1.8	1.0–3.1	0.8	0.3–2.1		
KDF								
Not exposed	82	1584	1.0	reference	1.0	reference	Not selected	
>0–<0.08	9	158	1.1	0.6–2.4	0.8	0.4–1.8		
≥0.08	13	159	1.7	0.9–3.3	0.9	0.4–2.1		
Trichloroethylene								
Not exposed	58	1288	1.0	reference	1.0	reference	1.0	reference
>0–<23.90	17	306	1.5	0.8–2.8	1.3	0.7–2.6	1.4	0.7–2.5
≥23.90	29	307	2.2	1.3–3.7	2.1	1.2–4.0	1.9	1.1–3.3
Methylene chloride								
Not exposed	96	1805	1.0	reference	1.0	reference	Not selected	
>0–<17.71	6	49	2.4	1.0–6.0	1.9	0.7–5.1		
≥17.71	2	47	0.7	0.2–2.9	0.5	0.1–2.6		
Alcohol								
Not exposed	94	1730	1.0	reference	1.0	reference	Not selected	
>0–<10.25	7	84	1.9	0.8–4.3	1.3	0.5–3.4		
≥10.25	3	87	0.6	0.2–2.1	0.6	0.2–2.7		
Ketones/esters								
Not exposed	93	1764	1.0	reference	1.0	reference	Not selected	
>0–<20.25	7	70	2.0	0.9–4.6	1.4	0.5–3.7		
≥20.25	4	67	1.0	0.3–2.8	1.1	0.3–4.5		
Ethylene glycol								
Not exposed	99	1876	1.0	reference	1.0	reference	Not selected	
Exposed	5	25	2.4	1.1–4.9	1.1	0.4–3.1		
Tetrahydrofuran								
Not exposed	102	1893	1.0	reference	1.0	reference	Not selected	
Exposed	2	8	0.7	0.2–3.0	0.4	0.1–2.6		

[a] Adjusted for age, country, education, body mass index, and alcohol consumption.

[b] Adjusted for variables in model A and all solvents.

[c] Adjusted for variables in model B and regression model performed respectively with stepwise backward and stepwise forward variable selection.

Table 4. Odds ratios (OR) for male breast cancer according to occupational exposures to organic solvents with 10-year lag time period. [CES=cumulative exposure score; CI=confidence interval; KDF=kerosene/diesel oil/fuels oil; SBP=special-boiling-point spirits]

Solvent CES (ppm.years)	Cases (N=104)	Controls (N=1901)	Model A [a]		Model B [b]		Model C [c]	
			OR	95% CI	OR	95% CI	OR	95% CI
Benzene								
Not exposed	91	1762	1.0	reference	1.0	reference	Not selected	
>0–<0.51	8	70	1.8	0.7–4.6	1.8	0.7–4.7		
≥0.51	5	69	1.7	0.6–5.0	1.6	0.5–4.9		
Gasoline								
Not exposed	96	1805	1.0	reference	1.0	reference	Not selected	
>0–<0.09	4	49	1.0	0.4–2.7	1.0	0.4–2.8		
≥ 0.09	4	47	1.1	0.3–3.2	0.8	0.2–2.8		
SBP								
Not exposed	98	1823	1.0	reference	1.0	reference	Not selected	
0–1.10	3	39	1.2	0.4–4.1	0.9	0.2–2.1		
≥1.10	3	39	1.2	0.3–4.2	0.7	0.1–2.4		
White spirits								
Not exposed	80	1559	1.0	reference	1.0	reference	Not selected	
0–0.05	11	172	1.2	0.6–2.3	1.1	0.6–2.2		
≥0.05	13	170	1.2	0.6–2.6	1.1	0.5–2.5		
KDF								
Not exposed	86	1648	1.0	reference	1.0	reference	Not selected	
0–0.05	8	126	1.6	0.8–3.0	1.4	0.7–2.8		
≥0.05	10	127	1.3	0.6–2.8	1.0	0.5–2.4		
Trichloroethylene								
Not exposed	64	1363	1.0	reference	1.0	reference	1.0	reference
0–15.30	15	269	1.2	0.6–2.2	1.0	0.5–1.9	1.2	0.6–2.1
≥15.30	25	269	2.2	1.3–3.6	1.6	0.8–2.9	1.9	1.2–3.2
Methylene chloride								
Not exposed	99	1826	1.0	reference	1.0	reference	Not selected	
0–9.37	3	37	0.9	0.3–3.0	1.0	0.3–3.5		
≥9.37	2	38	1.0	0.4–2.5	1.1	0.4–3.2		
Alcohol								
Not exposed	97	1763	1.0	reference	1.0	reference	Not selected	
0–3.48	4	69	0.5	0.2–1.4	0.5	0.2–1.5		
≥3.48	3	69	0.7	0.3–1.9	0.7	0.2–1.9		
Ketones/esters								
Not exposed	95	1790	1.0	reference	1.0	reference	Not selected	
0–7.00	5	56	2.1	0.8–5.5	1.7	0.6–5.1		
≥7.00	4	55	1.9	0.7–5.4	1.4	0.4–4.8		
Ethylene glycol								
Not exposed	101	1878	1.0	reference	1.0	reference	1.0	reference
Exposed	3	23	2.3	0.9–5.6	2.1	0.7–6.3	1.8	0.8–3.9
Tetra-hydrofuran								
Not exposed	102	1895	1.0	reference	1.0	reference	Not selected	
Exposed	2	6	0.5	0.1–2.4	0.6	0.1–3.0		

[a] Adjusted for age, country, education, body mass index and alcohol consumption.
[b] Adjusted for variables in model A and all solvents.
[c] Adjusted for variables in model A and stepwise selection of solvents.

exposure in model B indicating no strong association.

Occupational exposure to oxygenated solvents was not associated with MBC except for ethylene glycol in the least-adjusted model based on five ever-exposed cases.

In order to estimate the stability of the results, we repeated the analyses using 10-year lagtime between exposure and diagnosis or interview (table 4). Overall, we observed a shift towards null results. OR for benzene were lower and not statistically significant anymore, while the association between exposure to TCE and MBC was more stable. OR≈2 (not significant) were found in association with ethylene glycol exposure. The stepwise analysis selected TCE (statistically significant) and ethylene glycol, but not benzene.

Results were not substantially modified in sensitivity analyses performed by excluding the hospital-based cancer controls in all countries (supplemental table S1, www.sjweh.fi/show_abstract.php?abstract_id=3717).

Discussion

In this European case–control study on MBC, one of the largest ever conducted, occupational exposure to organic solvents was assessed using a detailed JEM. High exposure to TCE was significantly associated with a doubling of the risk of MBC, a finding that remained

stable in different models and after accounting for a 10-year lag time period. A dose–response trend was also indicated. In addition, a possible role for benzene and ethylene glycol in the etiology of MBC was suggested.

Petroleum solvents

The toxicity of benzene has been largely proven towards leukemia risk, and the IARC has classified benzene as a carcinogen (group 1) (12). It is generally recognized that aromatic hydrocarbons, such as benzene or methylene chloride, are mammary carcinogens in animals (7, 8, 32, 33). Benzene induces oxidative stress, is genotoxic and immunosuppressive. It causes genomic instability and induces apoptosis (12). In a study on female mice, benzene-induced mammary tumors exhibited a distinct pattern in the p53 and H-ras mutations compared to spontaneous tumors, suggesting that benzene induces specific genetic alterations (34). In addition, benzene and other aromatic hydrocarbons have exhibited endocrine-disrupting properties (35, 36) making the mammary gland more prone to tumor cell proliferation through hormonal mechanisms (37, 38).

In our study, exposure to benzene was associated with MBC, although the highest OR was found in the low-exposure group. Overall, this is consistent with the two-fold increased OR of MBC among motor vehicle mechanics and painters with known exposure to benzene previously reported in the same study population (25). According to the JEM, in addition to motor vehicle mechanics and painters, the most frequent occupations involving exposure to benzene included machinery fitters, shoe makers, printers, precision-instrument makers, tire makers and vulcanizers. To explain the non-monotonic dose–response curve between benzene exposure and MBC in our study, it is possible that the participation rate of the most highly exposed cases was reduced, eg, because of survival bias, thus leading to a smaller OR in the high exposure group. It is also possible that the risk of health outcome induced at low doses of benzene exposure does not increase linearly at higher doses, as is frequently observed in studies on health effects of endocrine disrupting chemicals (39). Several epidemiological studies have examined breast cancer in men or women in relation to benzene exposure. One study has evaluated the risk of MBC associated with exposure to benzene among US marines exposed to drinking water contaminated with solvents (40), but no association was found. However, the context and route of exposure were not the same as in our study and exposure levels were very low. As regards female breast cancer, population-based or occupational cohort studies reported positive associations with occupational exposure to benzene (17, 18, 41), but other did not (19, 42). However, most studies did not assess benzene exposure levels quantitatively. One study among shoe factory workers in Italy reported a two-fold increased standardized incidence ratio among women exposed to benzene >40 ppm years, but this results was based on only one case (41). In total, our study provides some support for the hypothesis that benzene may increase breast cancer risk, but this should be scrutinized in further studies.

Apart from benzene, petroleum solvents in our analysis were complex mixtures of polycyclic aromatic hydrocarbons (PAH). We found elevated OR for white spirits, but the association disappeared when benzene was included in the model, suggesting that benzene content in white spirits explains this association. Previous studies on MBC reported no association between MBC mortality and PAH exposure (23) or a doubling of MBC incidence in workers exposed to PAH or gasoline (24). Occupational exposures to aromatic, aliphatic and alicyclic hydrocarbon solvents were positively associated with female breast cancer in some studies (16, 20). However, other studies gave inconsistent or null results (19, 42, 43). In another study, PAH DNA adducts, considered as a body-burden measure of exposure to PAH of any source, were more frequent in female breast cancer patients than controls (44). In total, these studies are very sparse, are based on weak exposure characterization, and do not allow to conclude about breast cancer risk in relation to petroleum derivatives in general.

Exposure to chlorinated solvents

TCE is one of the most important chlorinated solvents, and the IARC recently upgraded it from group 2A (probably carcinogenic to humans) to group 1 (carcinogenic to humans) based on epidemiological and animal evidence of a role in the risk of kidney cancer (13). TCE is metabolized to multiple mutagenic and carcinogenic metabolites that contribute to the carcinogenicity of the parent compound via genotoxic or non-genotoxic mechanisms (45). However, the biological mechanisms that could explain an excess breast cancer risk associated with TCE exposure are not known.

We found that TCE exposure was associated with an increased risk of MBC. This association was stable in different models, robust in the analysis accounting for a 10-year lagtime and reinforced by a dose–response trend. The most frequent occupations exposed to TCE in our data were motor mechanics, machine fitters, plumbers and painters. Conversely, no consistent association with methylene chloride was detected in our study after adjustment for exposure to other solvents based on eight exposed cases, whereas no cases were exposed to the three remaining chlorinated solvents (perchloroethylene, chloroform and carbon tetrachloride).

In the study of US marines exposed to contaminated drinking water, exposure to TCE did not increase the risk of MBC (40). However exposure to TCE in this

study (median cumulative exposure 159 ppb months) was several orders of magnitude lower than in our data. Previous studies on female breast cancer, including a large population-based cohort in Finland (20) and a cohort of military women in the US (15) occupationally exposed to TCE, reported no evidence of an association with exposure to chlorinated solvents. No association of breast cancer with urinary biomarkers of exposure to TCE was found in a Scandinavian study, which included 260 female and 2 male cases (46). However, in an electronics workers cohort study in Taiwan, an increased risk of female breast cancer in association with a long duration of exposure to chlorinated solvents was reported (47). Overall, results of epidemiological studies do not allow for the drawing of firm conclusions, but our data add to the evidence that TCE may play a role in breast cancer.

Oxygenated solvents

Oxygenated solvents include a large variety of chemicals. Among alcoholic solvents, ethanol has well-known carcinogenic effects on many organs including the breast. These effects have been investigated intensively among alcohol drinkers in numerous studies. However exposure to alcoholic solvents from occupational origin through inhalation or cutaneous absorption may have different effects on health. Exposure to oxygenated solvents in general has been known to cause reprotoxic or neurologic effects, but their carcinogenic properties are not documented. It has been shown for example, that female workers exposed to ethylene glycol ethers had prolonged menstrual cycles and time-to-pregnancy compared to those who were not exposed (48, 49). Experimental studies have also demonstrated an increased production of progesterone in ovarian luteal cells exposed to ethylene glycol ethers (50, 51). It can be hypothesized that modifications of hormone synthesis in exposed women has an impact on breast cancer risk.

Our findings suggest a possible role of occupational exposure to ethylene glycol in MBC. OR were ≈2 in the model without adjustment for other solvents and in the analyses (five exposed cases) and in the models accounting for a 10-year lag time (three exposed cases). Conversely, we did not observe any association with occupational exposure to alcohol (seven exposed cases), tetrahydrofuran (two exposed cases), and ketones/esters (nine exposed cases) in our study. The small number of cases in our data and the lack of known mechanistic pathway does not allow us to draw conclusions.

To the best of our knowledge, no study has evaluated the risk of MBC specifically associated with exposure to oxygenated solvents to date. One case–control study in Australia evaluated occupational exposure to alcohol solvents in women and found no association with female breast cancer (43). Of note, cohort studies of workers exposed to ethylene oxide, an intermediate chemical used in the production of ethylene glycol that is also used as a sterilizing agent for medical equipment, found that breast cancer incidence was increased in exposed women (52, 53). However, the data on breast cancer in relation to oxygenated solvents are sparse and require further investigations in groups of workers with well-characterized exposure.

Study strengths and limitations

As reported earlier (27), the number of eligible cases identified during the study period was close to the expected number, based on incidence data from cancer registries in the participating areas. The case participation rate was 85%. The overall participation rate among controls was 67%, but there were large disparities across countries. Among countries that used population controls, the response rate was low in Northern Europe (Denmark, Germany, and Sweden). A differential participation of cases and controls, eg, according to social class, is thus possible, but its effects on our results were attenuated by adjustment on education level. Selection bias could occur in countries using hospital-based controls, mainly colon cancer patients. However, the results were not different when the analyses were conducted separately for subjects recruited with a population- and hospital-based design.

Regarding the quality of exposure assessment, we used a detailed JEM elaborated for assessing occupational exposures in France as far back as the 1950s and based on the expertise of experienced industrial hygienists, extensive literature review and relevant exposure monitoring data at the work places. Using a JEM is considered to be a less accurate method than expert judgment based on the review of individual job histories (54). Moreover, the same JEM were used for all countries, while the jobs and the job tasks could differ to some extent between European countries. This could have led to errors in exposure estimates, however misclassification errors are expected to be non-differential.

Although this is the largest case–control study ever conducted to evaluate the association of MBC and occupational exposure to organic solvents, an important limitation is the relatively small number of cancer cases for certain exposures evaluated due to the rarity of the disease. This may lead to low statistical power for detecting significant associations or concluding on the lack thereof, particularly for the less-frequent exposures. However, our study permitted the detection of some associations between occupational factors and breast cancer that could have been difficult to observe in studies on women.

Concluding remarks

In conclusion, this study suggests that men occupation-

ally exposed to TCE, and possibly benzene or ethylene glycol, are at increased risk of breast cancer, a finding that conceivably can be extrapolated to female breast cancer. Mechanisms that can explain these associations are still to be elucidated. Further epidemiological studies should be conducted in populations with well-characterized exposure to organic solvents in order to confirm these findings.

Acknowledgements

Rare Cancer Study Group members. Project management group: Wolfgang Ahrens, Mikael Eriksson, Pascal Guenel, Henrik Kolstad, Linda Kaerlev, Jean-Michel Lutz, Elsebeth Lynge, Franco Merletti, Maria M. Morales Suarez-Varela, Jorn Olsen, and Svend Sabroe. Other members: Denmark: Herman Autrup, Lisbeth Norum Pedersen, Preben Johansen, Stein Poulsen, Peter Stubbe Teglbjaerg, and Mogens Vyberg. France: Antoine Buemi, Paule-Marie Carli, Gilles Chaplain, Jean-Pierre Daures, Jean Faivre, Joelle Fevotte, Pascale Grosclaude, Anne-Valérie Guizard, Michel Henry-Amar, Guy Launoy, Francois Menegoz, Nicole Raverdy, and Paul Schaffer. Germany: Cornelia Baumgardt-Elms, Sibylle Gotthardt, Ingeborg Jahn, Karl-Heinz Jockel, Hiltrud Merzenick, Andreas Stang, Christa Stegmaier, Antje Timmer, and Hartwig Ziegler. Italy Terri Ballard, Franco Bertoni, Giuseppe Gorini, Sandra Gostinicchi, Giovanna Masala, Enzo Merler, Lorenzo Richiardi, Lorenzo Simonato, and Paola Zambon. Latvia: Irena Rogovska, Galina Sharkova, and Aivars Stengrevics. Lithuania: Jolita Gibaviciene, Laimonas Jazukevicius, Juozas Kurtinaitis, and Roma Pociute. Portugal: Noemia Afonso, Altamiro Costa-Pereira, Sonia Doria, Carlos Lopes, Jose Manuel Lopes, Ana Miranda, and Cristina Santos. Spain: Daniel Almenar, Ines Aguinaga, Juan J. Aurrekoetxea, Concepcion Brun, Alicia Cordoba, Francisco Guillen, Rosa Guarch, Agustin Llopis, Rosa Llorente, Blanca Marın, Amparo Marquina, Miguel Angel Martınez, JM Martınez Penuela, Ana Puras, Ma Adela Sanz, Francisco Vega, and Ma Aurora Villanueva. Sweden: Lennart Hardell, Irene Larsson, Hakan Olson, Monica Sandstrom, and Gun Wingren. The United Kingdom: Janine Bell, Ian Cree, Tony Fletcher, and Alex JE Foss.

We acknowledge collaboration from the patients, controls, participating hospitals and data providers. The contribution of the individual cancer registries is gratefully acknowledged. The study was financially supported by the European Commission, DGXII, Grants No. BMH1 CT 931630 and ERB CIPD CT 940285, and national funding agencies. Denmark: The Strategic Environment Programme and the Danish Science Foundation. France: Ligue Nationale contre le Cancer, Fondation de France (Grant No. 955368), Institut National de la Santé et de la Recherche Médicale, Programme Environnement-Santé, Ministère de l'Environnement. Germany: Federal Ministry for Education, Science, Reseach and Technology (BMBF), Grant No. 01-HP-684/8. Italy: MURST, Italian Association for Cancer Research, Compagnia San Paolo/FIRMS. Portugal: Junta Nacional de Investigacao Cientifica e Tecnologica, Praxis XXI, No. 2/2.1/SAU/1178/95. Spain: Fondo de Investigacion de la Sanitarie, Ministerio de Sanidad y Consumo, Unidad de Investigacion Clinico Epidemiologica, Hospital Dr. Peset. Generalitet Valenciana; Departmento de Sanidad y Consumo, Gobierno Vasco; Fondo de Investigacion de la Sanitaria (FIS), Ministerio de Sanidad y Consumo, Ayuda a la Investigacion del Departamento de Salud del Gobierno de Navarra. Sweden: Swedish Council for Work Life Research, Research Foundation of the Department of Oncology in Umea, Swedish Society of Medicine, Lund University Hospital Research Foundation, Gunnar, Arvid and Elsebeth Nilsson Cancer Foundation.

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Received for publication: 27 September 2017