Occupational exposures and male breast cancer: a nested case-control study in the Nordic countries

Talibov M, Hansen J, Heikkinen S, Martinsen JI, Sparen P, Tryggvadottir L, Weiderpass E, Pukkala E

ABSTRACT

Background. Male breast cancer (MBC) is a rare and understudied disease. There is limited evidence on association between environmental and occupational agents and MBC. Some similarities in risk factors may be shared with female breast cancer. We evaluated solvents, metals, exhaust gases and other agents in relation to MBC within the large Nordic Occupational Cancer Study (NOCCA).

Methods. The study included 1,469 MBC cases and 7,345 controls from Finland, Iceland and Sweden, matched for the date of birth, sex and country. Cases were identified through national cancer registries. Data on occupation and other demographic indicators were collected from census records and population registries. Overall, 24 occupational exposures were assessed. Exposure estimates were assigned by linking job titles to job-exposure matrices (NOCCA-JEM). Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by using conditional logistic regression models.

Results. Significantly decreased overall OR was observed for physical workload (OR=0.78, 95% CI 0.67-0.91). Protective effect of physical workload was stronger by increasing exposure level with significant dose-response relationship (p-trend<0.01). Non-significantly increased ORs were observed for trichloroethylene, iron, lead, chromium, welding fumes and wood dust, and decreased ORs for asbestos, silica dust and perchloroethylene. However, these results were not consistent across all analyses.

Conclusions. The current study showed 20-25% protective effect for physical workload at work, while no strong evidence for other agents was observed.

Keywords: case-control study; job-exposure matrix; male breast cancer; NOCCA; occupational exposure

BACKGROUND

Male breast cancer (MBC) is a rare and understudied disease, which accounts for about 1% of all breast cancers [1]. The incidence of MBC has slightly increased over the last decades in the Nordic countries with 159 new cases diagnosed in 2015 (Figure 1) [2].

Family history of breast cancer and genetic mutations, especially in the BRCA2 gene, and to a lesser extent in BRCA1, CHEK2 and PALB2 genes are risk factors for MBC [1]. Some hormone-related factors such as Klinefelter's syndrome, obesity, testicular abnormalities, and elevated estrogen levels have also been linked to an increased risk of MBC [3-6].

Environmental and occupational agents are also suspected risk factors of MBC. Some of these agents are highly lipophilic and may accumulate in adipose tissue of the breast initiating carcinogenesis through genotoxic mechanisms [7]. Associations for perchloroethylene, 1,2 dichloroethylene and vinyl chloride were also suggested in a study of Marine Corps Base Camp Lejeune, North Carolina [8]. Occupational exposure to trichloroethylene was significantly associated with MBC, and possible associations with benzene and ethylene glycol were reported in a European multi-centre case-control study [9]. A registry based study from Denmark observed an increased risk for MBC in jobs related to traffic exhaust exposures [10].

Radiation has been linked to MBC in studies of atomic bomb survivors [11, 12]. Occupational exposure to magnetic fields was associated with an increased risk of MBC among Canadian men [13]. Finally, it has been suggested that exposure to light-at-night through night work may increase the risk for MBC [14].

The aim of this large study was to evaluate occupational exposures in relation to MBC in selected Nordic countries.

METHODS

We conducted a case-control study nested within the Nordic Occupational Cancer Study (NOCCA) cohort [15]. The NOCCA cohort includes 14.9 million persons from Denmark, Finland, Iceland, Norway and Sweden, and it has been assembled by linking various population registries and census records with national cancer registries. Data from Denmark and Norway was not included in this study because we did not have an access to individual level data from these countries. The persons were included in the NOCCA cohort on 1 January of the year following the first available census where they participated, provided they were 30-64 years old. They were followed-up till the date of emigration, death or December 31 of 2005 in Finland and Sweden and 2004 in Iceland [15].

Study participants

The study included 1,469 incident MBC cases diagnosed between 1961 and 2005 in Finland, Iceland and Sweden.

Five controls for each case were randomly selected from the NOCCA cohort. Cases and controls were matched for country, sex and year of birth. Study participants had to be 20 years or older at the date of diagnosis of the case ("index date"), and had to have at least one census record before index date.

Data collection

Cancer cases were identified from national cancer registries [15]. The Finnish Cancer Registry was established in 1953, and cases were registered based on reports from clinical and pathological hospital departments, private clinics, general practitioners and death registry records. The Icelandic Cancer Registry started in 1955, and case reporting was based on records from pathology laboratories complemented by information from cytology and hematology laboratories, hospitals, health centers, and death certificates. In Sweden, reporting of cancer cases during 1958-1982 was based on reports from hospitals and pathologists. Private practitioners were required to report cancer cases since 1983. Unlike other Nordic countries, Sweden does not use death certificates information for cancer registration [15].

Information on occupation held during the follow-up was obtained from computerized census records. Computerized census records were available from 1960 and later censuses in Sweden and from 1970 and later censuses in Finland. The only computerized census record available in Iceland was from 1981 census. Census questionnaires were self-administered and included questions on economic activity, occupation and industry. In Finland and Sweden, they were filled in by the heads of households, while each member of household who was at least 17 years old, personally filled in the questionnaire in Iceland [15].

Data on date of birth and emigration were obtained from Central Population Registries of these countries. Data from various registries were linked by using unique personal identification numbers used in the Nordic countries. This ensured complete ascertainment of relevant events for each person included in the study, because the possibility of error in identifiers is extremely small [15].

Exposure assignment

Occupational exposure estimates were assigned by linking job titles of study participants to the NOCCA job-exposure matrix (NOCCA-JEM). The NOCCA-JEM was developed by expert panel consisting of industrial hygienists/exposure experts from each Nordic country [16]. It assigns exposure prevalence (P) and annual average exposure (L) for 29 occupational agents, which are confirmed or suspected carcinogens, in more than 300 occupational categories in four time periods: 1945-1959, 1960-1974, 1975-1984, 1985-1994 [16].

Extremely low-frequency magnetic field (ELF-MF) exposure was assigned by using ELF-MF JEM described by Talibov et al [17].

Statistical analysis

We assigned a product of P and L (P x L) to each year over the employment period of study participants. These estimates were then summed up to derive cumulative exposure index. This procedure was repeated for all exposure agents included in the current analysis.

Exact start and end dates of employment were not available for study participants. Therefore, we assumed that they started employment at the age of 20 and ended at the age of 65 (typical retirement age in the Nordic countries) or index date, whichever came first. If a person had different occupations in different censuses, we assumed that he/she changed occupation midway of known census years.

Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by conditional logistic regression models. Cumulative exposure indices of exposures were categorized to dichotomous and polytomous exposures. The latter was defined by using 50th and 90th percentiles of exposure distribution among exposed controls as cut-points. Unexposed persons were used as a reference category both for dichotomous and polytomous exposures. Ordinal exposure metrics were treated as continuous in regression models in order to obtain an estimate of the slope and associated p-values (p-trend).

We used single and multiple exposure models to obtain risk estimates. In single exposure models (Model 1), we included each exposure agent one at a time, while in a multiple exposure model (Model 2), all exposure agents were added in the model simultaneously. If exposure agents were highly correlated (Spearman correlation > 0.80), we included them in separate models. To evaluate robustness of the main results, we performed sensitivity analyses with 5- and 10-year lag-time, analysis with tertile categorization and adjustment for lifestyle related factors. The lag-time analyses were performed under the assumption that cancer may develop over a number of years, and recent exposures may not be related to the disease. Therefore, in lag-time analyses, we did not count exposures occurring 5 and 10 years before the index date, respectively. In order to adjust for multiple comparisons, we used Holm's method which was described elsewhere [18].

Adjustment for lifestyle factors could be made only for the Finnish part of the data, because lifestyle factors by occupation were available from the Finnish job-exposure matrix, FINJEM [19]. FINJEM provides data on proportions of daily smokers in each occupation, men drinking at least 8 and women at least 5 portions of alcohol weekly, those who fulfil fewer than 3 of 4 recommended dietary habits, those who have leisure time exercise less than twice a week, and those whose body mass index is 25 kg/m^2 or higher. Lifestyle related factors in FINJEM are based on data from annual surveys of adult population conducted from 1978 to 2014 by the Finnish National Institute for Health and Welfare [20]. Finally, we restricted analysis to the age group 30-70 years at index date, assuming that occupational exposures are unlikely to be related to MBC in younger or older persons.

All analyses were performed by using R version 3.5.1 (R Core Team. 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/) software.

RESULTS

About 77% of the cases and controls were from Sweden, 21% from Finland and only 2% from Iceland. About 60% were 60-80 years old at diagnosis (Table 1). Metals were highly correlated with welding fumes and benzo[a]pyrene (Spearman correlation > 0.80), toluene with benzene and methylene chloride, benzene with gasoline (Supplementary Table 1).

Solvents

We evaluated six organic solvents in this analysis (Table 2). Non-significantly increased OR was observed for trichloroethylene (1.15, 95% CI 0.79-1.68) and decreased OR for perchloroethylene (0.52, 95% CI 0.28-0.96), only in multiple exposure models (Table 2). These results did not change in analyses of polytomous exposure (Table 3).

Metals

Overall OR was non-significantly elevated for iron (1.39, 05% CI 0.70-2.75), chromium (1.19, 95% CI 0.89-1.60) and lead (1.23, 95% CI 0.91-1.64) only in a multiple exposure models (Table 2). ORs remained elevated for iron and lead also in analyses of polytomous exposures, while inverse association was observed for chromium (Table 3).

Exhaust gases

We evaluated diesel engine exhaust and gasoline exhaust in this group and these agents were not related to MBC risk (Tables 2 and 3).

Other agents

Significantly decreased ORs were observed for physical workload at work (0.76, 95% CI 0.67-0.85 from single exposure model and 0.78, 95% CI 0.67-0.91 from multiple exposure model), and for asbestos (0.83, 95% CI 0.73-0.95) and silica dust (0.79, 95% CI 0.65-0.96) only from single exposure models (Table 2). Protective effect of physical workload was stronger by increasing exposure level with statistically significant dose-response relationship (p-trend<0.01) (Table 3).

Non-significantly increased overall ORs were observed for welding fumes (1.39, 95% CI 0.70-2.75), and a positive trend (p=0.02) was observed by increasing exposure levels (Table 3) in the multiple exposure model.

Sensitivity analyses

In analyses with 5- and 10-year lag-time, overall ORs remained non-significantly elevated for trichloroethylene, iron, lead and welding fumes (data not shown). OR for chromium was statistically significantly elevated (1.37, 95% CI 1.02-1.84) in a 10-year lag-time analysis in a multiple exposure model. However, analysis of polytomous exposure showed inverse relationship for chromium (OR=1.46, 95% CI 1.05-2.06 for the category < 50th percentile; OR=1.21, 95% CI 0.70-2.09 for 50th-90th; and OR=0.69, 95% CI 0.24-2.02 for >90th percentile).

Protective effect of physical workload was observed in both lag-time analyses (OR=0.79, 95% CI 0.68-0.91 in 5-year lag-time and OR=0.78, 95% CI 0.67-0.91 in 10-year lag-time).

The main observations did not change in the analyses with tertile categorization or in the analyses restricted to age group 30-70 years. Adjusting for lifestyle factors in the Finnish data has not considerably changed OR estimates from the main analyses (Supplementary Table 2).

DISCUSSION

The current study showed positive associations for trichloroethylene, iron, chromium, lead, welding fumes and wood dust, and negative associations for physical workload, asbestos, silica dust and perchloroethylene. However, most of these associations were not consistent across sensitivity analyses. Overall OR for chromium was significant only in a 10-year lag-time analysis. Only associations for physical workload were statistically significant across all analyses with dose-response relationship.

Physical activity has been associated with reduced risk of breast cancer in women in previous studies [21, 22]. In a meta-analysis of 31 prospective studies, average breast cancer risk reduction was 12% for leisure time and occupational physical activity combined, and 10% for occupational physical activity alone [22]. In another study, 25% average risk reduction was observed among physically active women compared to the least active women [21]. Protective effect of physical activity is likely to happen through lowering the levels of hormones, such as insulin and estrogen and of certain growth factors that have been associated with breast cancer [23]. To our knowledge, there have been no studies assessing effect of physical activity on MBC risk. However, because hormones and growth factors are also risk factors of MBC [1], mechanism suggested for protective effect of physical activity among women is likely to be the same among men.

Our findings for perchloroethylene and ELF-MF is in contrast with findings from Ruckart et al (2015) [8] and Grundy et al (2016) [13] who reported non-significantly increased ORs for perchloroethylene (OR=1.20, 95% CI 0.16-5.89, based on 2 exposed cases and 8 controls) and for ELF-MF ≥ 0.6 µT (micro Tesla) (OR=1.80, 95% CI 0.82-3.95). In our study, MBC was

inversely associated with perchloroethylene and ELF-MF, although not consistently in all analyses. Our finding for trichloroethylene was consistent with findings from Ruckart et al [8] and Laouali et al [9]. Laouali et al observed significantly increased OR for cumulative trichloroethylene >23.9 ppm years (OR=2.1, 95% CI 1.2-4.0, p-trend < 0.01) compared to unexposed. In our study, OR for trichloroethylene >23.9 ppm years was 1.14 (95% CI 0.87-1.50) in a single exposure model and 1.62 (95% CI 0.97-2.71) in a multiple exposure model.

Night work was not associated with breast cancer in this study in contrast to previous studies showing increased risk of breast cancer in women [24]. Previous studies also showed that frequency of night shift work, particularly a number of consecutive shifts, may be an important predictor of its carcinogenicity [25, 26]. Such exposure details for night shift work is not captured by the NOCCA-JEM. This may explain the inconsistency between the results for night work exposure.

Accuracy and completeness of cancer incidence data is one of the strengths of the current study. Validation studies demonstrated high level of completeness, comparability, accuracy and timeliness of cancer registration in the Nordic countries [27]. Other advantages of the study are accuracy of job titles and quantitative exposure assignment by using JEMs. Previous validity studies demonstrated high accuracy of occupational classifications based on census records in the Nordic countries [28, 29]. By linking job histories to JEMs, we were able to control for the effect of many concomitant agents simultaneously.

The main limitation of the study is potential exposure misclassification which could happen because of the following reasons. First, we do not have lifetime occupational history, but rather assume that study subjects stay in same job as assessed by the censuses, which however, is unlikely to cause major misclassification because occupational mobility in the Nordic countries has been low [15, 28]. Second, the JEMs used in the current study assign average exposure to all members of the occupation, while exposure heterogeneity within the occupation might be substantial. In addition, imputations were made based on four computerized census records from Sweden (77% of study participants) and three census records from Finland (21%). In Iceland, the only available computerized census record was from 1981. However, Icelandic data contributed to less than 2% of all data included in this study (Table 1).

We used the same exposure estimation method for cases and controls in this study. Therefore, exposure estimation was independent of disease status of study participants, and exposure misclassification was likely to be non-differential. Bias from non-differential exposure is generally towards the null for dichotomous exposures [30]. When exposure has more than two categories, biases away from the null occur only for intermediate exposure categories, but misclassified odds ratio for the highest category will be towards the null [31]. Therefore, overall odds ratios from Table 2 and odds ratios for highest exposure levels from Table 3 are likely to be underestimated and true estimate were likely to be larger, if misclassification would occur.

Chance findings related to multiple comparisons was another issue to be considered in this study. In order to adjust for multiple comparisons, we applied Holm's method by comparing p-values to critical values smaller than conventional 0.05. Details of selection of new critical values are described elsewhere [18]. This procedure showed that associations observed for physical workload from single and multiple exposure models, and ultraviolet radiation only from single exposure model remained statistically significant after adjustment suggesting that these findings were unlikely to be chance findings due to multiple comparisons.

We could not control for smoking, alcohol, leisure time physical activity, and obesity in the main analyses because we did not have data on these factors. However, we do not think that lifestyle factors would be strong confounders in this study because there is limited evidence that they are strong risk factors of MBC. Obesity was moderately linked to increased MBC risk in previous studies [4, 6]. Further, alcohol and tobacco smoking were not associated with MBC in a recent pooling study [32]. Finally, additional adjustments for lifestyle factors in the Finnish part of the data did not change the main results in our study.

In conclusion, this study showed associations with MBC risk for iron, chromium, lead, welding fumes, wood dust, physical workload and perchloroethylene. While most of these results were inconsistent across sensitivity analyses, 20-25% protective effect of physical workload was significant in all analyses with exposure-response trend.

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ETHICAL APPROVAL

The Icelandic study was approved by the National Bioethics Committee of Iceland (VSN- 05-082) and the Data Protection Authority (PV 2006070395). In Sweden and Finland, neither ethical committee approval nor informed consent from study participants is required for registry based studies.

CONFLICT OF INTERESTS

The authors declare no conflict of interests in connection with this study.

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DISCLAIMER

Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

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Figure 1. Age-standardized 5-year floating averages of incidence rates of male breast cancer in 1960-2015 in the Nordic countries. World Standard Population was used as a standard population. Source: NORDCAN data [2].
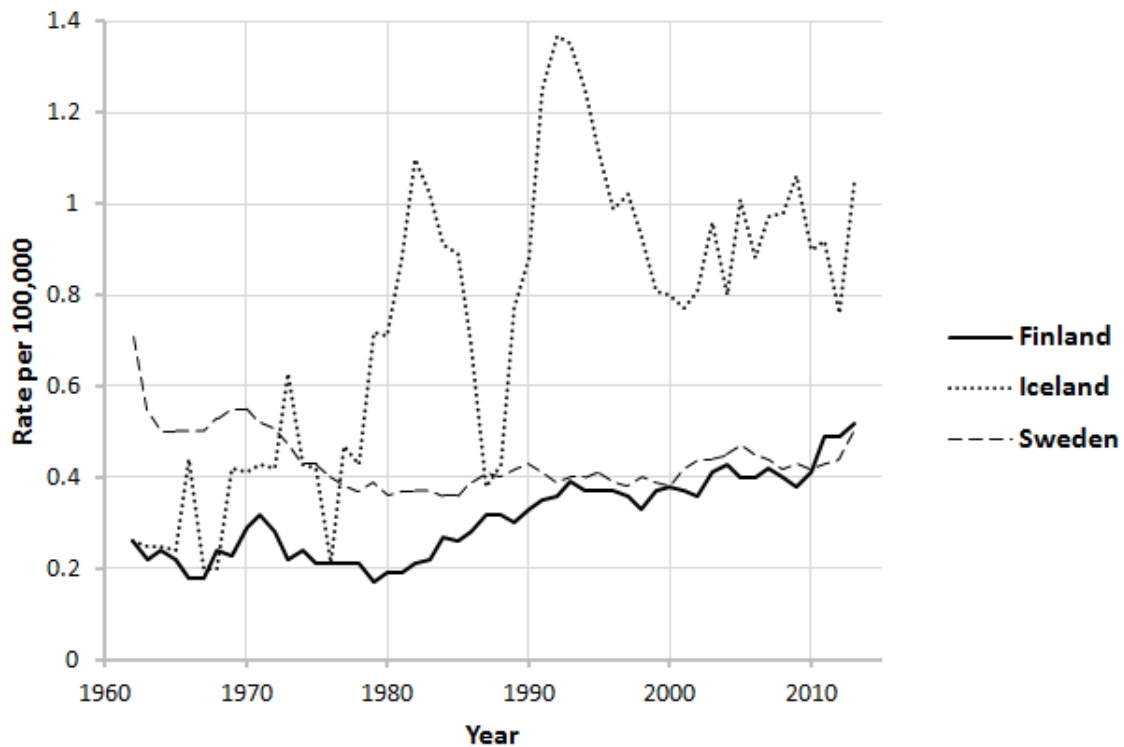
Table 1. Selected demographic characteristics of MBC study population.

Characteristics	Cases (n=1,469)		Controls (7,345)	
	n	%	N	%
Country				
Finland	308	21.0	1540	21.0
Iceland	28	1.9	140	1.9
Sweden	1133	77.1	5665	77.1
Age at diagnosis				
≤ 40	17	1.2	82	1.2
41-60	371	25.3	1849	25.3
61-80	868	59.1	4339	59.1
≥ 80	213	14.5	1075	14.5
Mean (Median)	67.6 (68.6)			
Year of birth				
≤ 1920	725	49.4	3625	49.4
1921-1930	346	23.6	1730	23.6
1931-1940	209	14.2	1045	14.2
1941-1950	142	9.7	710	9.7
1951-1960	46	3.2	235	3.2

Table 2. Odds ratios (OR) and 95% confidence intervals (95% CI) for binary exposure to selected occupational agents and breast cancer in men.

Agent	Case, N	Control, N	Model 1 [a]			Model 2 [b c]		
			OR	95% CI	p-value	OR	95% CI	p-value
Solvents								
Benzene								
never	1355	6756	1.00					
ever	114	589	0.96	0.78-1.19	0.71	0.99	0.72-1.37	0.98
1,1,1-trichloroethane								
never	1288	6441	1.00					
ever	181	904	1.01	0.84-1.20	0.95	1.02	0.67-1.57	0.92
Methylene chloride								
never	1356	6772	1.00					
ever	113	573	0.99	0.80-1.22	0.89	0.97	0.58-1.64	0.92
Perchloroethylene								
never	1455	7231	1.00					
ever	14	114	0.61	0.35-1.06	0.08	0.52	0.28-0.96	0.04
Toluene								
never	1351	6749	1.00					
ever	118	596	0.99	0.80-1.22	0.89	0.96	0.60-1.53	0.86
Trichloroethylene								
never	1349	6738	1.00					
ever	120	607	0.99	0.81-1.22	0.94	1.15	0.79-1.68	0.46
Metals								
Chromium								
never	1224	6100	1.00					
ever	245	1245	0.99	0.85-1.15	0.80	1.19	0.89-1.60	0.24
Iron								
never	1266	6286	1.00					
ever	203	1059	0.95	0.81-1.12	0.54	1.39	0.70-2.75	0.35
Nickel								
never	1268	6273	1.00					
ever	201	1072	0.93	0.79-1.09	0.39	0.71	0.35-1.41	0.32
Lead								
never	1183	5896	1.00					
ever	286	1449	0.98	0.85-1.14	0.83	1.23	0.91-1.64	0.17
Exhaust gas								
Diesel exhaust								
never	1192	5927	1.00					
ever	277	1418	0.96	0.83-1.11	0.58	0.95	0.71-2.36	0.57
Gasoline exhaust								
never	1398	6989	1.00					
ever	71	356	0.99	0.77-1.30	0.98	1.29	0.76-2.65	0.28

Other agents								
Formaldehyde								
never	1313	6472	1.00					
ever	156	873	0.89	0.75-1.08	0.25	0.97	0.77-1.22	0.79
Benzo[a]pyrene								
never	1310	6476	1.00					
ever	159	869	0.91	0.75-1.08	0.26	0.75	0.54-1.05	0.09
Bitumen fumes								
never	1452	7237	1.00					
ever	17	108	0.79	0.47-1.33	0.36	0.99	0.58-1.69	0.97
Asbestos								
never	1143	5456	1.00					
ever	326	1889	0.83	0.73-0.95	0.01	0.89	0.73-1.10	0.29
Silica dust								
never	1334	6490	1.00					
ever	135	855	0.79	0.65-0.96	0.02	0.97	0.74-1.27	0.81
Sulphur dioxide								
never	1437	7142	1.00					
ever	32	203	0.79	0.55-1.16	0.24	0.91	0.60-1.37	0.65
Night-shift work								
never	1136	5533	1.00					
ever	333	1812	0.89	0.78-1.02	0.09	0.92	0.78-1.07	0.27
ELF-MF								
never	844	4188	1.00					
ever	625	3157	0.98	0.87-1.10	0.73	0.98	0.85-1.13	0.81
Physical workload								
never	594	2430	1.00					
ever	875	4915	0.76	0.67-0.85	<0.01	0.78	0.67-0.91	<0.01
Wood dust								
never	1358	6770	1.00					
ever	111	575	0.98	0.79-1.21	0.84	1.14	0.88-1.48	0.32
Welding fumes								
never	1266	6286	1.00					
ever	203	1059	0.95	0.81-1.13	0.58	1.39	0.70-2.75	0.35
Ultraviolet radiation								
never	1010	4633	1.00					
ever	459	2712	0.80	0.71-0.91	<0.01	0.89	0.77-1.04	0.13

Abbreviations: ELF-MF, extremely low-frequency magnetic fields

[a] Single exposure model where each agent was added one at a time and adjusted for socioeconomic status (SES).

[b] Multiple exposure model where all agents were added simultaneously and adjusted for SES.

[c] The following agents were highly correlated (Spearman correlation > 0.80), and therefore, were not included in the same model: all metals with each other and with welding fumes and benzo[a]pyrene; toluene, benzene and methylene chloride; benzene and gasoline (Supplementary Table 1).

Table 3. Odds ratios (OR) and 95% confidence intervals (95% CI) for multilevel exposure to selected occupational agents and breast cancer in men.

Agent [a][b]	Case, N	Control, N	Model 1 [c]			Model 2 [d][e]		
			OR [f]	95% CI	p-trend	OR [f]	95% CI	p-trend
Solvents								
Benzene								
≤ 5.5	55	297	0.92	0.68-1.24		0.90	0.59-1.37	
5.6-15.1	47	234	1.00	0.73-1.38		0.82	0.49-1.38	
> 15.1	12	58	1.03	0.55-1.94	0.89	0.78	0.38-1.63	0.38
1,1,1-trichloroethane								
≤ 5.6	122	623	0.98	0.80-1.20		1.18	0.70-1.98	
5.7-13	41	190	1.10	0.77-1.55		1.36	0.74-2.50	
> 13	18	91	1.01	0.60-1.69	0.83	1.10	0.50-2.41	0.73
Methylene chloride								
≤ 12.5	51	294	0.87	0.64-1.18		0.81	0.42-1.56	
12.6-76.4	52	220	1.18	0.87-1.62		0.99	0.51-1.96	
> 76.4	10	59	0.85	0.43-1.67	0.88	0.65	0.25-1.70	0.69
Perchloroethylene								
≤ 9.0	8	56	0.70	0.33-1.46		0.59	0.25-1.41	
9.1-75.6	5	46	0.54	0.22-1.37		0.31	0.11-0.88	
> 75.6	1	12	0.41	0.05-3.16	0.07	0.37	0.04-3.51	0.02
Toluene								
≤ 62.9	53	304	0.87	0.64-1.17		0.68	0.33-1.38	
70-732	52	233	1.11	0.82-1.51		1.18	0.67-2.06	
> 732	13	59	1.10	0.60-2.03	0.76	1.13	0.45-2.85	0.48
Trichloroethylene								
≤ 27.2	56	308	0.90	0.67-1.21		1.19	0.75-1.90	
27.3-138	54	237	1.17	0.86-1.58		1.46	0.86-2.49	
> 138	10	62	0.80	0.41-1.57	0.94	1.55	0.64-3.76	0.29
Metals								
Chromium								
≤ 24.4	132	613	1.08	0.89-1.33		1.19	0.85-1.67	
24.5-152	93	503	0.93	0.74-1.17		1.03	0.62-1.72	
> 152	20	129	0.77	0.48-1.23	0.42	0.90	0.44-1.85	0.90
Iron								
≤ 5.1	103	528	0.97	0.77-1.21		1.72	0.78-3.81	
5.2-55	77	427	0.90	0.70-1.16		1.48	0.69-3.18	
> 55	23	104	1.11	0.70-1.75	0.66	2.04	0.72-5.78	0.44
Nickel								
≤ 12.8	97	540	0.89	0.71-1.12		0.58	0.27-1.22	
12.9-73	82	426	0.95	0.74-1.22		0.56	0.26-1.20	
> 73	22	106	1.03	0.65-1.63	0.59	0.92	0.36-2.34	0.93
Lead								
≤ 4.2	126	742	0.84	0.69-1.03		0.84	0.57-1.25	
4.3-12.1	125	568	1.10	0.90-1.35		1.15	0.76-1.74	
> 12.1	35	139	1.25	0.86-1.82	0.45	1.56	0.99-2.46	0.06

Exhaust gas								
Diesel exhaust								
≤ 0.7	133	715	0.91	0.75-1.11		0.91	0.73-1.13	
0.8-2.2	113	564	0.98	0.80-1.22		1.05	0.80-1.39	
> 2.2	31	139	1.10	0.74-1.64	0.90	1.09	0.62-1.91	0.95
Gasoline exhaust								
≤ 1.7	36	178	1.02	0.71-1.48		1.67	0.65-4.29	
1.8-4.3	30	140	1.08	0.72-1.61		1.13	0.42-2.99	
> 4.3	5	38	0.63	0.25-1.60	0.80	0.53	0.16-1.73	0.27
Other agents								
Formaldehyde								
≤ 0.2	71	444	0.82	0.63-1.06		0.94	0.68-1.31	
0.3-3.2	67	344	0.96	0.74-1.26		0.93	0.63-1.39	
> 3.2	18	85	1.04	0.62-1.73	0.51	0.80	0.34-1.89	0.68
Benzo[a]pyrene								
≤ 0.3	84	430	0.97	0.76-1.25		1.01	0.61-1.64	
0.4-2.1	63	348	0.89	0.68-1.18		0.80	0.48-1.34	
> 2.1	12	91	0.66	0.36-1.21	0.17	0.80	0.33-1.93	0.36
Bitumen fumes								
≤ 0.3	8	55	0.74	0.35-1.57		0.77	0.34-1.73	
0.4-3.1	8	41	0.95	0.44-2.03		1.02	0.41-2.51	
> 3.1	1	12	0.45	0.06-3.48	0.41	0.88	0.10-7.74	0.69
Asbestos								
≤ 2	167	943	0.85	0.71-1.02		0.89	0.70-1.14	
3-17.4	129	754	0.83	0.68-1.02		0.72	0.50-1.04	
> 17.4	30	192	0.76	0.52-1.13	0.01	0.74	0.39-1.38	0.17
Silica dust								
≤ 1.2	74	421	0.89	0.69-1.15		1.22	0.83-1.81	
1.3-6.6	48	348	0.69	0.50-0.93		1.07	0.69-1.68	
> 6.6	13	86	0.75	0.41-1.34	0.01	0.91	0.44-1.88	0.74
Sulphur dioxide								
≤ 9.4	16	102	0.79	0.47-1.34		0.87	0.49-1.52	
9.5-37	14	79	0.91	0.51-1.61		0.78	0.38-1.58	
> 37	2	22	0.45	0.11-1.92	0.23	0.44	0.09-2.14	0.68
Night-shift work								
≤ 5.1	168	905	0.90	0.75-1.08		0.90	0.74-1.11	
5.2-21.2	128	729	0.85	0.69-1.03		0.87	0.69-1.10	
> 21.2	37	178	1.00	0.70-1.44	0.14	1.27	0.82-1.97	0.23
ELF-MF								
≤ 38.4	321	1570	1.02	0.88-1.18		1.01	0.85-1.21	
38.5-139	259	1253	1.02	0.87-1.19		0.99	0.82-1.20	
> 139	45	334	0.68	0.49-0.93	0.27	0.67	0.45-0.98	0.25
Physical workload								
≤ 6.4	466	2429	0.81	0.71-0.93		0.84	0.71-0.99	
6.5-20	334	1982	0.72	0.62-0.84		0.82	0.65-1.02	
> 20	75	504	0.63	0.48-0.82	< 0.01	0.68	0.48-0.96	< 0.01

Wood dust								
≤ 10.8	58	291	1.02	0.77-1.37		1.12	0.80-1.58	
10.9-44.2	39	229	0.85	0.60-1.20		0.95	0.62-1.46	
> 44.2	14	55	1.29	0.71-2.32	0.88	1.26	0.60-2.64	0.19
Welding fumes								
≤ 3.0	92	539	0.86	0.68-1.08		1.19	0.55-2.59	
3.1-142	88	416	1.04	0.82-1.33		1.86	0.89-3.91	
> 142	23	104	1.11	0.70-1.75	0.96	2.25	0.80-6.34	0.02
Ultraviolet radiation								
≤ 5510	241	1345	0.85	0.73-0.99		0.95	0.78-1.17	
5511-9720	169	1108	0.72	0.60-0.86		0.84	0.66-1.08	
> 9720	49	259	0.88	0.63-1.21	< 0.01	1.07	0.69-1.68	0.58

Abbreviations: ELF-MF, extremely low-frequency magnetic fields;

[a] Exposure agents were categorized by using 50th and 90th percentiles of exposure distribution among exposed controls.

[b] Unit of exposure was parts per million years (ppm years) in the workroom air for solvents, gasoline, formaldehyde, sulphur dioxide; milligram of cubic meter years (mg/m^3 years) in the workroom air for iron, diesel, benzo[a]pyrene, bitumen fumes, silica dust, wood dust, welding fumes; microgram per cubic meter years ($\mu g/m^3$) in the workroom air for nickel, chromium; micromoles in litre of blood years ($\mu mol/litre$) for lead; fibres per cubic centimetre (f/cm^3) for asbestos; joule per square meters (J/m^2) for ultraviolet radiation; microTesla years (μT years) for ELF-MF; perceived physical workload years (ppwl years) for physical workload (27); probability of night-work years (nigw years) for night-shift work (28).

[c] Single exposure model where each agent was added one at a time and adjusted for socioeconomic status (SES).

[d] Multiple exposure model where all agents were added simultaneously and adjusted for SES.

[e] The following agents were highly correlated (Spearman correlation > 0.80) and therefore, were not included in the same model: all metals with each other and with welding fumes and benzo[a]pyrene; toluene, benzene and methylene chloride; benzene and gasoline (Supplementary Table 1).

[f] Reference category is unexposed group.

Highlights

- Male breast cancer (MBC) is a rare and understudied disease.
- We assessed associations between occupational agents and MBC in the current study.
- While no strong evidence was observed for other agents, physical activity at work was linked to 20-25% reduced MBC risk.

Supplementary Table 1. Spearman correlation coefficients for the agents included in the study.

Agent [a]	BENZ	ASB	BAP	CR	FORM	TCE	BITU	DEEX	FE	GASO	MCH	NI	PB	PER	QUAR	SO2	TOLU	TRI	WELD	WOOD	UV	NIGW	PPWL	ELFMF
BENZ	1.00																							
ASB	0.36	1.00																						
BAP	0.42	0.31	1.00																					
CR	0.47	0.40	0.73	1.00																				
FORM	0.19	0.19	0.11	0.28	1.00																			
TCE	0.62	0.28	0.64	0.73	0.20	1.00																		
BITU	0.06	0.04	0.06	-0.01	0.05	-0.01	1.00																	
DEEX	0.36	0.12	0.30	0.17	-0.09	0.25	0.21	1.00																
FE	0.34	0.37	0.82	0.88	0.10	0.63	-0.01	0.22	1.00															
GASO	0.77	0.34	0.56	0.42	-0.03	0.55	0.00	0.50	0.47	1.00														
MCH	0.85	0.39	0.43	0.51	0.29	0.72	0.06	0.32	0.35	0.70	1.00													
NI	0.35	0.38	0.80	0.87	0.11	0.64	0.00	0.22	0.96	0.49	0.37	1.00												
PB	0.48	0.41	0.67	0.81	0.25	0.71	0.02	0.20	0.78	0.44	0.55	0.78	1.00											
PER	0.04	0.03	0.01	0.03	0.08	0.20	0.01	0.00	0.03	0.00	0.10	0.04	0.14	1.00										
QUAR	-0.03	0.54	0.09	0.03	0.01	-0.03	0.06	-0.04	0.04	-0.03	-0.03	0.08	0.06	-0.02	1.00									
SO2	0.00	0.03	0.11	0.15	0.01	0.04	0.00	0.01	0.16	-0.01	0.00	0.19	0.12	0.03	0.16	1.00								
TOLU	0.92	0.37	0.41	0.49	0.23	0.64	0.06	0.35	0.33	0.74	0.87	0.34	0.50	0.08	-0.03	0.01	1.00							
TRI	0.14	0.12	0.49	0.59	0.02	0.62	-0.02	0.05	0.64	0.15	0.13	0.62	0.53	0.30	-0.01	0.05	0.12	1.00						
WELD	0.36	0.40	0.80	0.87	0.10	0.62	-0.01	0.23	1.00	0.50	0.37	0.96	0.78	0.03	0.03	0.15	0.35	0.61	1.00					
WOOD	-0.02	0.24	-0.05	0.02	0.25	-0.03	-0.02	-0.09	-0.07	-0.04	-0.01	-0.07	-0.09	-0.02	0.35	-0.02	-0.01	-0.05	-0.07	1.00				
UV	-0.05	0.25	-0.06	0.00	0.20	-0.08	-0.02	-0.18	-0.03	-0.10	-0.02	-0.03	-0.01	-0.04	0.26	-0.08	0.04	-0.05	-0.03	0.10	1.00			
NIGW	0.02	-0.06	0.06	0.03	0.03	-0.03	0.04	0.32	0.04	0.00	0.00	0.04	0.05	0.05	0.01	0.32	0.02	-0.03	0.03	-0.05	-0.14	1.00		
PPWL	0.07	0.35	0.17	0.25	0.19	0.16	0.00	-0.15	0.22	0.05	0.09	0.21	0.18	0.00	0.32	0.02	0.09	0.17	0.21	0.20	0.64	-0.16	1.00	
EMF	0.17	0.17	0.42	0.42	0.24	0.30	-0.02	0.16	0.48	0.23	0.17	0.47	0.43	0.11	-0.05	0.21	0.18	0.31	0.48	-0.09	0.09	0.19	-0.02	1.00

[a] BENZ-benzene; ASB-asbestos; BAP-benzo[a]pyrene; CR-chromium; FORM-formaldehyde; TCE-trichloroethylene; BITU-bitumen fumes; DEEX-diesel exhaust; FE-iron; GASO-gasoline; MCH-methylene chloride; NI-nickel; PB-lead; PER-perchloroethylene; QUAR-silica dust; SO2-sulphur dioxide; TOLU-toluene; TRI-1,1,1 trichloroethane; WELD-welding fumes; WOOD-wood dust; UV-ultraviolet radiation; NIGW-night-shift work; PPWL-physical workload; ELFMF-extremely low-frequency magnetic fields.

Supplementary Table 2. Odds ratios (OR) and 95% confidence intervals (95% CI) for exposure to selected occupational agents and breast cancer in men. Analysis with adjustment for the life-style related factors in the Finnish data.

Agent	Case, N	Control, N	Model 1 [a]			Model 2 [b c]		
			OR	95% CI	p-value	OR	95% CI	p-value
Solvents								
Benzene								
never	291	1454	1.00			1.00		
ever	17	86	0.98	0.56-1.69	0.93	1.00	0.23-4.39	0.99
1,1,1-trichloroethane								
never	275	1403	1.00			1.00		
ever	33	137	1.09	0.72-1.68	0.67	1.87	0.40-8.62	0.43
Methylene chloride								
never	292	1447	1.00			1.00		
ever	16	93	0.79	0.46-1.38	0.42	0.52	0.11-2.37	0.39
Perchloroethylene								
never	308	1525	1.00			1.00		
ever	0	15	-	-	-	-	-	-
Toluene								
never	289	1449	1.00			1.00		
ever	19	91	0.99	0.59-1.67	0.98	1.99	0.48-8.23	0.34
Trichloroethylene								
never	283	1436	1.00			1.00		
ever	25	104	1.11	0.68-1.79	0.68	1.12	0.22-5.71	0.89
Metals								
Chromium								
never	259	1326	1.00			1.00		
ever	49	214	1.12	0.78-1.61	0.54	1.01	0.53-1.91	0.98
Iron								
never	270	1383	1.00			1.00		
ever	38	157	1.14	0.76-1.71	0.53	1.83	0.21-16.36	0.58
Nickel								
never	269	1368	1.00			1.00		
ever	39	172	1.06	0.71-1.57	0.78	6.03	0.07-5.12	0.64
Lead								
never	261	1312	1.00			1.00		
ever	47	228	0.92	0.64-1.32	0.66	0.65	0.27-1.56	0.34
Exhaust gas								
Diesel exhaust								
never	265	1300	1.00			1.00		
ever	43	240	0.92	0.63-1.33	0.65	0.99	0.60-1.65	0.99
Gasoline exhaust								
never	298	1492	1.00			1.00		
ever	10	48	0.98	0.48-2.01	0.97	0.68	0.13-3.59	0.65
Other agents								
Formaldehyde								
never	282	1354	1.00			1.00		
ever	26	186	0.73	0.47-1.14	0.16	0.67	0.37-1.19	0.18

	Cases	Controls	OR[a]	95% CI	p	OR[b]	95% CI	p
Benzo[a]pyrene								
never	285	1414	1.00			1.00		
ever	23	126	0.85	0.52-1.36	0.49	0.63	0.28-1.39	0.25
Bitumen fumes								
never	303	1509	1.00			1.00		
ever	5	31	0.89	0.34-2.30	0.81	1.28	0.43-3.79	0.65
Asbestos								
never	238	1154	1.00			1.00		
ever	70	386	0.79	0.57-1.12	0.18	1.06	0.65-1.73	0.82
Silica dust								
never	282	1346	1.00			1.00		
ever	26	194	0.58	0.36-0.92	0.02	0.39	0.19-0.83	0.01
Sulphur dioxide								
never	303	1502	1.00			1.00		
ever	5	38	0.64	0.25-1.65	0.35	0.73	0.26-2.07	0.56
Night-shift work								
never	253	1212	1.00			1.00		
ever	55	328	0.77	0.55-1.09	0.14	0.76	0.49-1.16	0.20
ELF-MF								
never	192	985	1.00			1.00		
ever	116	555	1.01	0.77-1.32	0.92	1.02	0.49-1.16	0.92
Physical workload								
never	137	560	1.00			1.00		
ever	171	980	0.69	0.49-0.97	0.03	0.60	0.39-0.94	0.02
Wood dust								
never	286	1415	1.00			1.00		
ever	22	125	0.97	0.59-1.59	0.90	1.46	0.77-2.79	0.25
Welding fumes								
never	270	1383	1.00			1.00		
ever	38	157	1.14	0.76-1.71	0.53	1.84	0.21-16.36	0.59
Ultraviolet radiation								
never	205	892	1.00			1.00		
ever	103	648	0.96	0.69-1.33	0.82	1.22	0.82-1.80	0.33

Abbreviations: ELF-MF, extremely low-frequency magnetic fields

[a] Single exposure model where each agent was added one at a time and adjusted for socioeconomic status SES).

[b] Multiple exposure model where all agents were added simultaneously and adjusted for SES.

[c] The following agents were highly correlated (Spearman correlation > 0.80), and therefore, were not included in the same model: all metals with each other and with welding fumes and benzo[a]pyrene; toluene, benzene and methylene chloride; benzene and gasoline (Supplementary Table 1).