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Female Breast Cancer and Electrical Manufacturing: Results of a Nested Case-control Study

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Abstract: Female Breast Cancer and Electrical Manufacturing: Results of a Nested Case-control Study: Enrico Oddone, *et al*. Department of Public Health, Experimental and Forensic Medicine, Occupational Medicine Unit, University of Pavia, Italy—Background: A previous explorative record-linkage study suggested a putative role of employment in electrical manufacturing in increasing female breast cancer risk in the Province of Milan (Italy). We deepened the understanding of this possible association in a single large electrical manufacturing plant located in Lombardy in the Province of Milan. **Methods:** We carried out a nested case-control study within a cohort of women employed in a large electrical manufacturing plant. All incident cases during 2002 to 2009 of female breast cancer in individuals who worked at least a 1 year in the factory and resided in Lombardy, Italy, were selected. Controls were randomly sampled from all women who worked in the same plant and resided in Lombardy as of December 31, 2005. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated using multiple logistic regression models, taking into consideration only female workers as ever/never exposed to physical/chemical agents and their longest occupational period. ORs were adjusted for several potential confounders, namely, other known risk factors. **Results:** The ORs for female breast cancer were significantly increased for exposure to chlorinated solvents (OR 1.65, 95% CI 1.04−2.62), and there was a twofold increase (OR 2.10, 95% CI 1.21−3.66) among women exposed for at least 10 years. We found no other significantly increased OR by exposure or job title. **Conclusions:** Our results suggest an increased risk of breast cancer after exposure to chlorinated solvents among women employed in the electrical manufacturing industry.
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Key words: Breast cancer, Electrical manufacturing, OCCAM project, Occupational exposures, Solvents

Breast cancer is the most common cancer in women worldwide; however, established risk factors account for a relatively small proportion of cases, and causative factors remain ambiguous and poorly defined.

Alongside risk factors known from some time, such as ionizing radiations[1, 2], smoking[3], alcohol consumption[4, 5], menopause after the age of 55[6], low parity[7, 8], late first pregnancy[9] and a positive family history of breast cancer[10], increasing evidence shows that occupational and environmental exposures can play a role in female breast cancer development[11, 12]. Among others, some emerging evidence suggest a possible relationship between exposures in the electrical or electronic manufacturing industry and the risk of female breast cancer[13, 14]. In the framework of the Occupational Cancer Monitoring (OCCAM) project[15], an Italian cancer surveillance program, we previously carried out an explorative record-linkage study suggesting a putative role of employment in the electrical manufacturing, paper, rubber and textile industries in the development of female breast cancer[16]. These preliminary results, which suggested the aim of this study, prompted further analyses of the possible relationship between employment in manufacture of electric and electronic appliances and female breast cancer.

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Material and Methods

Overview of the study

Through the collaboration between the former Italian National Institute for Occupational Health (ex-ISPESL) and the National Cancer Institute of Milan (INT), the OCCAM project monitors cancers potentially caused by occupational exposures. Its aim is to detect potential occupational cancer cases by identifying a possible relationship between employment by industry and cancer occurrence. The OCCAM workflow allows for carrying out population-based case-control studies by record linkage between the regional databases of hospital discharge records, through which cancer cases are identified, and the archives of pension funds at the National Institute for Social Security (INPS), which records the occupational history of every person who has worked in private enterprises (that is about 50–60% of the total regional workforce) since 1974. The hospital discharge records database covers all the population of Lombardy region. This approach has previously been used, both for cancers[17–19] and other chronic diseases[20], and could lead to analyses of virtually every association between trades and cancer sites[15].

An explorative study based on OCCAM methods was recently carried out suggesting a possible role of employment in the electrical manufacturing, paper, rubber and textile industries in development of female breast cancer[16]. To extend the analysis, we selected cases and controls identified within this preliminary study from among individuals who worked in a single large electrical manufacturing plant located near Milan (Italy). This study design should be considered as a nested case-control study within an occupational cohort. The cohort included women working as of January 1, 1974 or who were subsequently hired to work at the plant until December 31, 2005, as directly defined by record linkage with the INPS database. Analysis was carried out on women for whom personal and occupational data were available and stored in the factory plant near Milan (Italy) where they worked. Details are presented below.

Enrollment of cases and controls

Incident cases were women employed for at least one year in the electrical manufacturing plant during the period of 1974 to 2005 and who were diagnosed with breast cancer (International Classification Of Diseases (ICD), IX rev.: 174) in the period of 2002 to 2009, resided in Lombardy and had no previous diagnosis of breast cancer in the period 1999 to 2001, as identified according to the Lombardy hospital discharge records.

In Italy, all public/private hospitals are obliged to provide individual, codified discharge records. For each patient, hospital discharge records provide Italian social security number, place of residence, up to six diagnostic ICD codes, and date of discharge. These hospital discharge records are stored in databases according to patients' region of residence, irrespective of hospital location.

Female breast cancer diagnosis were checked according to medical documents provided by the hospital of discharge; therefore only incident, histologically confirmed breast cancers were included. Women younger than 35 years of age were excluded because of the small number of expected cases. Women older than 69 years were not included in the analysis. Since information on employment history was available only from 1974, older subjects would potentially end up with too short employment histories for a meaningful analysis. Controls were extracted from the regional list of citizens registered with the National Health Service as of December 31, 2005, who worked in the plant for at least one year between 1974 and 2005. Thus, the cases and the controls belonged to the same base population.

In other words, we selected a subset of cases and controls previously enrolled for a regional-level study[16] that shared the characteristic of having been employed at the same plant for at least a year in order to deepen the putative relationship between exposures in the electrical manufacturing industry and female breast cancer. We reclassified cases and controls as "exposed" or "not exposed" to phyisical/chemical agents on the basis of the qualitative exposure data provided by the company, as reported above. The cases and controls of the regional-level study were frequency matched (2 controls for each case), taking into consideration province of residence and 5-year age categories.

Data collection

For each subject, a hard copy file was present in the company archives. It stored personal information, including date of hiring and discharge, job titles and their start and stop dates, exposures and occupational medical checks, smoking and alcohol intake habits, age at menarche, number of children and age at first child, body mass index (BMI) and educational level. Results of medical checks, exposures and number of children were updated during the employment period. On the other hand, no updates were available for BMI, smoking and alcohol intake habits; thus, they were considered in the analyses as of the date of hire. No information on menopausal status, hormonal therapies, breastfeeding and family history of breast cancer was available. Smoking habits were recorded in the form of smoking status (never or former/current smok-

er). Alcohol drinking was registered as never drinker or low/medium consumer. No further classification of the type of alcohol (wine, beer, spirits, etc.) was available. No woman was classified as a high alcohol consumer in the company files. Smoking and alcohol habits, BMI and educational level were assessed at hiring.

Job titles were provided by the company itself. For each subject, only the job title with the longest duration was considered in the analysis. Women included in this study had not been exposed to night work or shift work.

All data were abstracted from the available occupational medical records. These documents were stored in company's archives in compliance with the Italian law on occupational safety according to which employers assess occupational risks and provide for workers a regular medical examination. For each woman, exposures to single physical/chemical agents were assessed by the company, referring to their specific tasks, and subjects were classified as ever/never exposed. For the present study, no further assessment was carried out, as the assessment measurements were not provided by the company.

Given that the company produced, in the recent past, electric circuits and other components for telephones, computers and calculators, female workers would have been exposed to lead and lead alloys, solvents such as ethyl alcohol (CAS no. 64-17-5) or trichlorethylene (CAS no. 79-01-6), lubricant mineral oils, epoxy resins containing bisphenol A (CAS no. 25068-38-6) and F (CAS no. 9003-36-5) and 1,4-butanediol diglycidyl ether (CAS no. 2425-79-8), aluminum oxide (CAS no. 1344-28-1) and nonionizing radiation. The correspondences between job titles and exposures are reported in Table 3. It is of particular concern that almost all women employed as assembly and gluing operators or products testers were exposed to chlorinated solvents.

No further exposure assessment (namely, quantitative assessment) was present in the available company documents.

Data abstraction was carried out by occupational physicians (TV, EB) unaware of cases and controls statuses.

Statistical analysis

Odds ratios (ORs) of breast cancer and corresponding 95% confidence intervals (CIs) were estimated using unconditional logistic regression models. Adjustment variables were age at enrollment, age at hiring, age at menarche, smoking habits (two classes: never, former/current), alcohol consumption (two classes: never, low/medium consumer), number of children, age at first child (two classes: <30 or ≥30 years of age), BMI (two classes: <25, ≥25), educational level (three classes: <5, 5–8, >8 years of education), calendar year of hiring and duration of specific job title, when appropriate.

Exposures of interest were the job title with the longest duration (minimum duration of 1 year) and exposures to possible physical or chemical risk factors, as reported in Table 3 (minimum duration of 1 year). In addition, we conducted analyses restricted to women who held a job title or were exposed to possible chemical or physical risk factors for at least 10 years, 20 years or 30 years.

Exposures to physical or chemical agents were entered into the regression models alone (single-exposure model), while job titles were entered simultaneously (composite model).

Administrative clerks and managers were chosen as the reference category for the analysis by job title. For each analysis by exposure, the reference category consisted of all the other nonexposed blue collar women (i.e., women who were not administrative clerks or a managers and not exposed to the considered physical/chemical agents).

Calculations were carried out using the Stata/SE 11 (Statacorp, College Station, TX, USA) and SAS software (version 9; SAS Institute Inc., Cary, NC, USA).

Institutional review board (IRB) approval and written informed consent

Studies based on the OCCAM project use administrative data routinely collected by institutional subjects authorized by the Italian law on occupational safety (D. Lgs 81/08, art. 244). Therefore, such studies do not require approval from an institutional review board. No direct contact was established with the women included in the analyses, and therefore, no written informed consent was obtained.

Results

The total number of eligible cases and controls was of 108 and 216, respectively. Data on 32 (29.6%) cases and 64 (35.2%) controls were not available, as they worked in other production plants and/or offices of the same company, although they were registered with the company in Lombardy and were resident in the same Italian region.

Thus, we carried out our analysis on 76 (70.4%) women designated as cases and 140 (64.8%) women designated as controls for whom personal and occupational data were available and stored in the plant near Milan (Italy) where they worked.

Table 1 shows the distribution of cases and controls by personal habits, physical features, parity and reproductive factors. The median age at inclusion was 61 years for cases (range 35–69 years) and 60 years (range

Table 1. Distribution of cases and controls by personal habits, physical features, parity and reproductive factors

		Cases (%)	Controls (%)	Median (Cases)	Median (Controls)	*p* value[#]
Age at inclusion						
	35–54	16 (21.05)	29 (20.71)			
	55–69	60 (78.95)	111 (79.29)			
	All	76 (100)	140 (100)	61	60	0.953
Smoking status*						
	Never	56 (73.68)	96 (68.57)	—	—	
	Current	20 (26.32)	44 (31.43)	—	—	
	All	76 (100)	140 (100)	—	—	0.432
Alcohol drinking *						
	Never	26 (34.21)	32 (22.86)	—	—	
	Current	50 (65.79)	108 (77.14)	—	—	
	All	76 (100)	140 (100)	—	—	0.072
Age at menarche						
	<12	19 (25.00)	22 (15.71)			
	≥12	57 (75.00)	118 (84.29)			
	All	76 (100)	140 (100)	12	12.5	0.097
Number of children						
	0	29 (38.16)	35 (25.00)			
	1	29 (38.16)	58 (41.43)			
	2+	18 (23.68)	47 (33.57)			
	All	76 (100)	140 (100)	0.9	1.2	0.100
Age at first child						
	<30	40 (85.11)	90 (85.71)			
	≥30	7 (14.89)	15 (14.29)			
	All	47 (100)	105 (100)	26.7	25.9	0.922
Body mass index *						
	<18	- (-)	5 (3.57)			
	18–24.99	57 (75.00)	100 (71.43)			
	25–29.99	19 (25.00)	28 (20.00)			
	≥30	- (-)	7 (5.00)			
	All	76 (100)	140 (100)	23	22	0.067
Years of education						
	<5	36 (47.37)	80 (57.14)			
	5–8	30 (39.47)	48 (34.29)			
	>8	10 (13.16)	12 (8.57)			
	All	76 (100)	140 (100)	1	<1	0.323

* At hiring. [#] χ^2 test of independence.

35–69 years) for controls (p=0.953). Specifically, the inclusion date was the date of diagnosis for cases and the date at sampling for controls. The majority of cases and controls were nonsmokers, none reported high alcohol consumption, and about 25% of them had a BMI ≥25. The majority of women (75.0% of cases, 84.3% of controls) had menarche after the age of 12, about 38.2% of the cases and 25.0% of the controls were nulliparous, and among those who had at least one child, about 85% (85.1% of cases, 85.7% of controls) had their first child before age 30. The median of number of children was not statistically different between cases and controls (p=0.100). Educational level was low or very low (<8 years of education) for the large majority of cases (86.8%) and controls (91.4%).

Table 2 shows occupational data, job titles and exposures of cases and controls.

Most cases and controls were hired before age 30 and before 1980, although cases were somewhat

Table 2. Distribution of cases and controls by employment features, job task and exposures

		Cases (%)	Controls (%)	Median (Cases)	Median (Controls)	*p* value[#]
Age at hiring						
	≤19	12 (15.79)	48 (34.28)			
	20–29	43 (56.58)	74 (52.86)			
	≥30	21 (27.63)	18 (12.86)			
	All	76 (100)	140 (100)	24	21	0.002
Period of hiring						
	1960–1969	32 (42.10)	79 (56.43)			
	1970–1979	38 (50.00)	54 (38.57)			
	1980 +	6 (7.90)	7 (5.00)			
	All	76 (100)	140 (100)	1970	1969	0.125
Duration of employment (years)						
	1–9	6 (7.90)	8 (5.72)			
	10–19	29 (38.16)	47 (33.57)			
	20–29	30 (39.47)	45 (32.14)			
	≥30	11 (14.47)	40 (28.57)			
	All	76 (100)	140 (100)	20	23	0.135
Duration of job title (years)*						
	1–9	10 (13.16)	18 (12.86)			
	10–19	39 (51.32)	64 (45.71)			
	20–29	24 (31.57)	42 (30.00)			
	≥30	3 (3.95)	16 (11.43)			
	All	76 (100)	140 (100)	16	17.5	0.321
Job title*						
	Administrative clerk/managers	25 (32.89)	37 (26.42)	—	—	—
	Welder	18 (23.68)	58 (41.43)	—	—	—
	Assembly and glueing operator	7 (9.22)	11 (7.86)	—	—	—
	Cable production operator	3 (3.94)	4 (2.86)	—	—	—
	Products tester	5 (6.59)	9 (6.43)	—	—	—
	Cutting operator	3 (3.94)	6 (4.29)	—	—	—
	Warehouse operator	3 (3.94)	3 (2.14)	—	—	—
	Controlling operator	1 (1.32)	2 (1.43)	—	—	—
	Molding operator	4 (5.27)	3 (2.14)	—	—	—
	Cleaning and catering services	4 (5.27)	4 (2.86)	—	—	—
	All	76 (100)	140 (100)	—	—	0.547
Exposure**						
	None	38	51	—	—	—
	Lead and lead alloys	30	78	—	—	0.031
	Chlorinated solvents[$]	16	23	—	—	0.225
	Lubricant oils	3	6	—	—	0.989
	Nonionizing radiations	4	3	—	—	0.167
	Alumina (aluminum oxide)	1	2		—	0.994
	Epoxy resins	6	11			0.840

* Job title held longest. ** A single job title can entail more than one exposure. [$] Trichloroethylene. [#] χ^2 test of independence.

older than controls at hiring (p=0.002). The cumulative employment duration in the plant was at least 10 years for 92.1% of cases and 94.3% of controls, while the longest duration in the same job title was at least 10 years for 86.8% of cases and 87.1% of controls. The women in this study held up to four different job titles during their periods of employment in the plant. However, only 6 (2.7%) women changed their job title three times, while 29 (13.4%) did it twice. Administrative clerks and managers represented about 30% of the study group, while "blue collar" women were assigned to several tasks, frequently resulting in strata with small numbers of cases and controls. "Welder" was the most common job title among blue collar controls (41.4%). The most frequent exposures were those to lead and lead alloys and to chlorinated solvents (Table 3).

Table 4 shows the adjusted ORs and corresponding 95% CIs by job title of longest duration and exposure. The OR for female breast cancer was significantly

Table 3. Exposures assessed by the company in the electrical manufacturing plant (Milan, Italy, 1974–2005) by job title

	Cases/Controls	Exposure	Chemicals
Job title			
Administrative clerk/managers	25/37	None	—
Welder	18/58	Lead	Lead
Assembly and glueing operator	6/11	Lead	Lead
		Solvents	Trichlorethylene
		Epoxy resins	Bisphenol A
			Bisphenol F
			1,4-Butanediol diglycidyl ether
Cable production operator	3/4	None	—
Products tester	5/9	Lead	Lead
		Solvents	Trichlorethylene
Cutting operator	3/6	Lubricant oils	—
Warehouse operator	3/3	None	—
Controlling operator	1/2	Alumina	Aluminum oxide
		Solvents	Ethyl alcohol
Molding operator	4/3	Solvents	Trichlorethylene
		Nonionizing radiation	—
Cleaning and catering services	4/4	None	—
Other blue collar	3/3	None	—

increased for women exposed to solvents, in particular trichloroethylene (OR 1.65, 95% CI 1.04–2.62). This rose to a twofold increase (OR 2.10, 95% CI 1.21–3.66) when the analysis was restricted to women exposed for at least 10 years. Further analyses on those women working in the plant for more than 20 or 30 years showed a trend for an increased risk of female breast cancer in women exposed to chlorinated solvents, although the limited number of cases and controls did not allow us to determine any statistically significant result.

Further restricting the analyses to cases diagnosed after age 54, who reasonably were post-menopausal women, an increased in OR was observed both in the overall result (OR 1.45, 95% CI 0.91–2.30) and in the results of the subset exposed for at least 10 years (OR 1.74, 95% CI 1.00–3.03), although the differences were not statistically significant.

Exposure to lead and lead alloys was not significantly associated with breast cancer risk, even when only 10 or more years of exposure was considered, while exposures to mineral lubricant oils, nonionizing radiation, alumina and epoxy resins were inconclusive, mostly due to the small numbers of cases and controls.

Results from the analysis by job title were also affected by wide confidence intervals, except in the case of women employed as welders for 10 years or more, among whom a significantly decreased risk was observed.

Discussion

The present study identified a significantly increased OR of breast cancer among women exposed to chlorinated solvents, especially trichloroethylene, in an electrical manufacturing plant. This estimate amounted to a twofold increased in OR in women exposed for at least 10 years.

This result is consistent with previous findings from ecological[21] and cohort studies[22], with particular regard to female workers in the electronics industry[13, 14, 23]. In particular, Sung *et al*. showed an increased Standardized Incidence Ratio (SIR 1.38, 95% CI 1.11–1.70) among women first employed prior to 1974, which is when the Taiwan government promulgated a regulation on solvent use, and Peplonska *et al*. found a significantly increased risk of breast cancer (OR 1.7, 95% CI 1.1–2.7) among electronic and electric equipment manufacturers. Nevertheless, it is noteworthy that Peplonska *et al*. reported exposures to polychlorinated biphenyls (PCBs) and acetone.

Sparse available evidence suggests a role of chlorinated solvents as causal agents of tumors in the mammary gland of animals. In particular, 6 different chlorinated compounds were investigated and found to be associated with increases in mammary gland tumors in at least one study[24]. Moreover, chronic

Table 4. Adjusted[#] odds ratios (ORs) and 95% confidence intervals (95% CIs) by exposure, job title and duration of job title

	All		Duration of longest employment of 10+ years	
	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)
Exposure**				
Lead and lead alloys				
Unexposed°°	21/25	1 (reference)	17/18	1 (reference)
Exposed°°	30/78	0.46 (0.19–1.21)	28/69	0.51 (0.19–1.38)
Chlorinated solvents[$]				
Unexposed°°	35/80	1 (reference)	31/70	1 (reference)
Exposed°°	16/23	1.65 (1.04–2.62)	14/17	2.10 (1.21–3.66)
Lubricant oils				
Unexposed°°	48/97	1 (reference)	43/83	1 (reference)
Exposed°°	3/6	0.96 (0.56–1.66)	2/4	0.96 (0.48–1.92)
Non-ionizing radiations				
Unexposed°°	47/100	1 (reference)	42/86	1 (reference)
Exposed°°	4/3	1.40 (0.87–2.72)	3/1	1.83 (0.90–3.71)
Epoxy resins				
Unexposed°°	45/92	1 (reference)	40/79	1 (reference)
Exposed°°	6/11	1.11 (0.90–1.37)	5/8	1.12 (0.88–1.43)
Job title*				
Administrative clerk/managers	25/37	1 (reference)	21/35	1 (reference)
Welder	18/58	0.40 (0.13–1.29)	17/53	0.23 (0.06–0.88)
Assembly and glueing operator	7/11	1.17 (0.29–4.74)	6/8	0.93 (0.19–4.69)
Cable production operator	3/4	1.38 (0.21–9.23)	2/4	0.59 (0.07–5.29)
Products tester	5/9	1.17 (0.29–4.91)	5/8	1.02 (0.22–4.68)
Cutting operator	3/6	0.58 (0.09–3.96)	2/4	0.29 (0.03–3.18)
Warehouse operator	3/3	0.84 (0.10–6.76)	2/2	0.51 (0.04–6.15)
Controlling operator	1/2	1.90 (0.12–29.95)	1/1	1.93 (0.09–44.19)
Molding operator	4/3	1.97 (0.25–15.52)	3/1	3.96 (0.25–63.03)
Cleaning and catering services	4/4	1.93 (0.26–14.38)	4/3	0.60 (0.07–5.50)
Other blue collar	3/3	0.76 (0.10–5.81)	3/3	0.67 (0.08–5.52)

[#]Adjusted for age at diagnosis, age at hiring, age at menarche, smoking status, alcohol consumption, number of children, age at first child, body mass index, years of education, duration of job title and calendar year of hiring. * Job title held longest. **: A subject holding a job title could be exposed to more than one factor. Results for alumina are not reported due to small numbers of subjects (1 case and 2 controls). [$]Trichloroethylene. °° Only blue collar workers.

exposure to chlorinated alkanes and alkines, including trichloroethylene, seemed to be related to an increase in mammary cancers in female mice[25], and *in vitro* and *in vivo* studies failed to demonstrate that trichloroethylene had genotoxic activity, while dichlorovinylcysteine (a trichloroethylene metabolite) was observed to induce DNA damage in mammalian cells *in vitro* and *in vivo*[26]. These results, along with the carcinogenic activity of trichloroethylene in other sites (i.e, the kidney and probably liver and non-Hodgkin lymphomas)[27, 28], seem to suggest a similar situation for female breast cancer too.

Recently, exposure to metals and metal compounds have been evaluated as risk factors or possible therapeutic treatments for breast cancer[29]. Among them, lead was of particular concern in the discussion of this study. The results of studies on animals and humans are still divergent[29]. Lead seems to promote the development of mammary tumors in virus-infected female C3H mice. Moreover, high levels of this metal were found in blood and head hair samples of newly diagnosed patients with breast cancer, and some evidence[30] indicates that lead and other metals can also interact with iodine, a trace element that probably protects against breast cancer development. On the other hand, in the recent years, some metal-organic lead structures have been developed that actually exhibit cytostatic properties[30]. Our findings on this

topic are negative, though a decreased risk was found for female welders (Table 4), who were exposed for 10 or more years to lead and lead alloys.

Analyses by job title and in general of exposures to lubricant oils, nonionizing radiations and synthetic resins were strongly limited by the small numbers of women in the corresponding categories. Given that almost all women employed as assembly and gluing operators or products testers were exposed to chlorinated solvents, it is important to note that the ORs in these tasks were slightly above unity, decreasing after exposures of 10 years or more (Table 4), although with very wide CIs.

Company records did not allow for control of other potential confounders or other known risk factors, including exposure to ionizing radiation, positive family history of breast cancer, breastfeeding, hormone replacement therapy and menopausal status. Despite this issue, analyses restricted to women older than 55 (considered as a proxy of menopausal status) showed an OR consistent with other results.

Furthermore, adjustments for several other possible confounders (smoking status, alcohol consumption, age at menarche, age at first child, number of children and BMI), though assessed only at hiring, could improve the significance of our results. Nevertheless, residual uncontrolled or unmeasured potential bias cannot be excluded.

Moreover, the study base was not created for scientific or research purposes, and the classification of diagnostic codes and occupational exposures may be insufficiently detailed. In addition, this study suffers from a lack of a quantitative assessment of exposures. We are aware that the study of occupational exposures using job titles as a proxy is a limitation of this paper. Nevertheless, we needed this approximation to conduct the study, and we believe that it was not arbitrary. In Italy, industrial companies are obliged to carry out a chemical exposure assessment in order to classify workers as "not exposed" or "exposed". It follows that specific medical surveys and monitoring over time had to be planned and performed. In this case, the company actually carried out a quantitative chemical assessment in order to classify their workers, but these data were not provided (and possibly they are no longer available). We had access only to data from medical surveys and to the classification of each worker as "exposed" or "not exposed" to single compounds, that is, the final product of the quantitative assessment. Thus, job titles reflect real exposures, although no quantitative assessment is available in this study and no dose-response relationship was explored. Nonetheless, when we restricted the analyses to those women who worked at least 10 years, we observed a stronger effect.

Our results are strongly limited by the small simple size, which was due to the number of cases and controls available in this single plant. It follows that further studies are needed to assess the putative relationship between occupational exposures (in particular, to chlorinated solvents) and female breast cancer. Despite this, our study, although limited, could provide a useful incentive to deepen this field research in occupational medicine. It is reasonable to admit that the study design could appear not optimal for investigation of the hypothesized relationship, but it has the undeniable advantage of being rapid and inexpensive. Furthermore, we picked a nested case-control design to further test the capacity of the OCCAM method to explore a putative risk relationship at the single industrial plant level. In fact, we used the individuals designated as cases and controls who worked in this specific industrial plant and in the time period of interest from among all the cases and controls selected for a previous study at the regional level[16], in which an increased risk of breast cancer in the electrical manufacturing industry was observed. This procedure allowed us to assess that the putative risk observed in application of OCCAM monitoring at a given industrial sector level reflects the risk observed in one specific industrial plant included in that industrial sector.

Administrative clerks and managers were chosen as the reference category in the analysis by job title. As such jobs have been associated with a higher risks for breast cancer[31, 32], probably due to confounding from social and reproductive factors[32], some underestimation of the ORs associated with blue collar workers' job titles may have ensued. We had, however, no other reasonable choice, as there were just a few warehouse operators, a potentially preferable reference group.

Conclusions

The results of this study support the hypothesis of an increased risk of breast cancer among women exposed to chlorinated solvents, especially trichloroethylene. Our findings for exposure to lead and lead alloys are negative. Limited statistical power prevents drawing conclusions regarding other exposures and jobs. Further investigations are needed to deepen the analysis of these preliminary findings by extending our study to other similar industries and/or increasing the sample of involved subjects.

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