Occupational exposure to chlorinated and petroleum solvents and mycosis fungoides.

UNIVERSITÀ DEGLI STUDI DI TORINO

OCCUPATIONAL EXPOSURE TO CHLORINATED AND PETROLEUM SOLVENTS AND MYCOSIS FUNGOIDES

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INTRODUCTION

Mycosis Fungoides (MF) is the most common form of chronic T-cell cutaneous lymphoma (CTCL)[4], a heterogeneous group of non-Hodgkin´s lymphomas of skin-homing T cells[5]. It is a cancer with a male predominance that has an age profile and a rare occurrence that vary across countries.[1] The incidence of MF is estimated at 1/ 100,000 person per year in Europe[2] and 4.1 /100,000 in USA[3]. As a result of its rarity and inability to study large number of patients, relatively little is known regarding its etiology.
MF may vary from limited patchy skin disease to extensive cutaneous plaque and tumour involvement to extracutaneous compartments of blood, lymph nodes, and viscera.[6] MF often starts with contact dermatitis.[7]
The rising incidence rates suggest that environmental, occupational and lifestyle factors play a role in the etiology of the disease.[8] It is thought that continuous activation of skin T helper lymphocytes leads to malignant transformation of a specific clone. Possible risk factors include occupational chemical exposure, radiation, drugs and infection. The carcinogenic process is probably multifactorial and multistep, combining the genetic predisposition of the individual and its immune status with various

exogenous factors.

To date no occupational exposure has been clearly established as risk factor of MF, although associations with some occupations have been observed.[1,7] Machinists and machine operators[10] exposed to a variety of agents such as metals and plastics have been reported to be at increased risk. Irritants and sensitizers in this occupational environment are recognized carcinogens. Employment in manufacturing industries, especially petrochemical, textile, and metal machinery was found in 29% of the patients with MF in a descriptive study from the USA.[11] Studies in Scotland,[12] California and Washington State[13] reported elevated risks in the paper and wood industry. An elevated risk of MF was also observed among Swedish women employed in hotel, restaurant work and garment industry.[14]

Long-term exposure to solvents may also trigger MF and hasten its progression from the patch stage to the plaque and tumour stage.[15] However, no association between occupational or chemical exposures and MF has been reported.[9]

Some of the industries associated with an elevated risk of MF have in common exposure to organic solvents such as fuels and petroleum solvents. Cocco et al. have found an association between occupational exposure to solvents and lymphomas type B but did not find associations with T-cell lymphoma.[16] Reports of increased risks of T-cell lymphoma in relation with occupational exposure to solvents as benzene are also found in the literature.[17]

Further assessment of occupational and environmental exposure may suggest preventive and surveillance measures along with adjustment of existing health policies. The present study aims to evaluate the association between MF and occupational exposure to organic solvents including chlorinated and petroleum solvents.

MATERIAL AND METHODS

We conducted a European multi-centre case-control study on 7 sites of rare cancers including MF (gallbladder and extrahepatic bile ducts, small intestine, bone, eye melanoma, thymus and breast cancer) using a common control group and a common protocol. Cases and controls were recruited in selected areas of 6 European countries between January 1st, 1995 and June 30th, 1997. As part of this study 100 MF cases were recruited in Denmark (the whole country), Sweden (Umea, Orebro/Uppsala, Linköping, Lund), France (Calvados, Côte d'Or, Doubs, Hérault, Isère, Manche, Bas-Rhin, Haut-Rhin, Somme, Tarn), Germany (Hamburg, Bremen, Essen, Saarland), Italy (Torino, Firenze, Padova) and Spain (Valencia, Navarre and the Basque Country). The study design and the procedures of data collection have been described in detail earlier and are summarized below.[18]

Recruitment of cases and controls

Incident cases of MF were identified according to their ICD diagnostic codes or according to codes from the International Classification of Diseases for Oncology (ICD-O 1976: codes for morphology 9700/3-97001/3 and topography 173.0-173.9). Case ascertainment (with clinical and pathological diagnosis of MF) was based upon repeated requests to hospital departments, pathology departments and/or by frequent screening of regional or national cancer and pathology registers. For all centres, geographical borders defined the study base except in Spain where the participating hospitals' catchment areas defined the study base.

Patients between 35 to 69 years of age diagnosed with MF (n=140), were recruited. Diagnoses were checked by a reference pathologist who confirmed diagnosis in 118 cases and did not confirm diagnosis in 22 other patients, according to morphological and topographical criteria of MF. Among the 118 confirmed cases, 100 cases were interviewed and were available for the analysis. Only those 100 cases who took part in the interview are presented in the tables of this paper. The overall participation rate among cases was 84.75%.

Population controls were randomly selected from the regions of case ascertainment. They were frequency matched on age and sex with the combined set of cases from all seven cancer sites included in the study. The aim was to obtain at least 4 controls in each 5-year age and sex stratum for the most frequent case group in each region. Population registries or electoral rolls were used for sampling in Denmark, Sweden, France, Germany and Italy. Since no population registry was available in Spain, colon cancer controls from the hospitals that provided the cases were selected by a procedure identical to that used for the cases, as no occupational exposure to chemical is known to play a role in colon cancer. The controls served as a common pool of controls for each of the seven groups of rare cancer cases included in the European study. For the present study we selected only controls in the study areas where at least one case of MF patients was included. 4574 controls were accepted for the study of which 4561 were interviewed. The overall participation rate in controls was 99.72%. All together 2846 fulfilling the criteria for MF.

Data collection

A set of common questionnaires on occupational exposures and life style factors were developed and tested in cooperation with all participating centers. The original version was written in English and translated into Danish, Swedish, German, French, Italian, Spanish, and Portuguese. Back-translation to English was performed to limit ambiguity in the phrasing of the questions.

The questionnaire included questions on socio-demographic characteristics, smoking habits, alcohol

consumption and lifelong occupational history. A complete lifetime job history was collected for each person by an interviewer using a structured questionnaire. For each job, we asked about the type of occupation and industry. For each occupational period, data concerning the products and production processes, the year of starting and ending of the job were recorded, as well as work tasks, job title and working hours per week. We also recorded materials handled, chemical exposures and occupations held by nearby workers. The specific nature of the work was also addressed such as work tasks, machines or products used, duration of their use (hours per week) and dates of job tenure.

Exposure assessment

Each job held for more than 6 months was coded by trained coders. Occupation was coded according to the International Standard Classification of Occupation (ISCO) of the International Labor Office, 1968 revision.[14] Industry was coded according to the Classification of Activities in the European Community (NACE), 1996 revision.[19]

Occupational exposures to solvents were assessed using a job-exposure matrix (JEM), developed at the Occupational Health Department of the French Institute of Health Surveillance (*Institut de Veille Sanitaire* InVS) by occupational hygienists. Exposures to occupational hazards were evaluated for all jobs in the general population, and for different calendar periods to account for exposure changes over time. Jobs were defined according to both the International Standard Classification of Occupations (ISCO 1968 revision) and a French classification of industrial activities (NAF) which was easily converted to the European classification code NACE, rev 1996 [20], as both classification systems are almost equivalent. Exposure to chlorinated solvents (trichloroethylene, perchloroethylene, carbone tetrachloride, chloroform and methylene chloride) and to petroleum solvents (benzene, paraffinic and aliphatic hydrocarbons, gasoline, mineral spirit, and kerosene/fuel/gasoil) was determined for each job using semi-quantitative indicators for exposure probability (0: not exposed; 1: possibly exposed; 2: probably exposed; 3: certainly exposed), exposure frequency (e.g. for petroleum solvents 1: < 30% of working hours; 2: 30-70%; 3: > 70%) and exposure intensity.

Each job held by a case or a control included in the European study was assigned the corresponding exposure indices as reported in the JEM. A job-specific exposure score was then calculated as the product of exposure probability, frequency and intensity and the duration of the job in years. An individual cumulative exposure score was calculated for each study subject as the sum of the job-specific exposure scores over his or her entire work history.

For the presentation of the exposure intensity, the maximum intensity reached during a worker´s entire workfile was used.

Statistical analysis

For benzene, mineral spirit and kerosene/fuel/gasoil, exposed workers were categorized according to exposure tertiles among exposed controls, and unexposed subjects served as the reference group. For chlorinated solvents, paraffinic/alicyclic hydrocarbons and gasoline, exposed workers were categorized according to exposure median among exposed controls, with unexposed subjects as the reference group. For carbone tetrachloride and chloroform, workers were divided into exposed and not exposed as the number of exposed workers was very low. The analysis was conducted using unconditional logistic regressions using the software SPSS v17.

Odds ratios (OR) and their 95% confidence intervals (95%CI) were calculated for each exposure agent as the measure of the association between the specific exposure and MF. The following confounders were considered in the adjusted analysis: age, gender, country, smoking habit, alcohol intake, BMI, educational level and exposure to other solvents.

We also conducted several rounds of analyses calculating cumulative exposure scores with a lag time of 5, 10, or 15 years before diagnosis or interview for the controls and excluding jobs with low exposure probability from the cumulative exposure scores. These sensitivity analyses did not modify our findings and are not shown.

The study was conducted in accordance with the requirements of the Ethical Committees and data inspectorates in each of the participating countries or regions.

RESULTS

Table 1 shows the characteristics of cases (n=100) and controls (n=2846). Controls had slightly higher educational level than cases and were less likely to be smokers. Cases and controls were comparable with respect to their BMI, and did not differ with respect to alcohol consumption. Male controls presented slightly higher educational level, were less likely to be smokers and had lower alcohol consumption than male cases. Otherwise, male cases and controls were comparable with respect to their BMI. Female cases and controls were comparable with respect to educational level, smoking habit, BMI and alcohol consumption.

Table 2 summarizes ORs describing the associations between exposure to different chlorinated solvents and MF. Cases and controls did not differ with respect to the exposure of any of the chlorinated solvents studied (trichloroethylene, perchloroethylene, carbone tetrachloride, chloroform and methylene chloride), with the exception of an elevated odds ratio in women exposed to perchloroethylene above median.

Table 3 shows ORs describing the associations between exposure to different petroleum solvents and MF. In the total sample, cases and controls did not differ with respect to exposure to any of the petroleum solvents (benzene, paraffinic/alicyclic hydrocarbons, gasoline, mineral spirit, and kerosene/fuel/gasoil). No association between MF and exposure to petroleum solvents was observed among men or among women, with the exception of kerosene/fuel/gasoil among women. However, only the odds ratio for exposure below median was statistically significantly elevated for this solvent (OR = 8.59; 95%CI: 1.14-64.49), and was based on only 2 exposed cases.

All analyses were repeated after excluding each country one after the other in the analyses. In another set of analyses, only population controls were used. The results were quite similar to those presented.

DISCUSSION

Chlorinated solvents

Our results indicate no association with MF and chlorinated solvent, with the exception of a high risk for MF for women who had a history of high exposure to perchloroethylene. This result needs to be interpreted with caution, because the association was based on 2 exposed cases only in the highest level and was not found in men, but it is in line with the most recent evaluation of the International Agency for Research on Cancer (IARC), which found consistently positive associations in studies of perchloroethylene-exposed cohorts for non-Hodgkin's lymphoma.[21]

Trichloroethylene is the chlorinated solvent that has been studied most extensively. It has been widely used as an industrial solvent and degreasing agent and was classified by IARC as a probable carcinogen (group 2A) with limited evidence of carcinogenicity in humans.[21] Some studies have reported an association between trichloroethylene and non Hodgkin's lymphoma [25,26] but others did not[22]. In a review based on more than 80 studies, Wartenberg et al. provided some support for an association with non-Hodgkin lymphoma,[23] but this analysis was later questioned. Many of the comments focused on how the studies were grouped and how the results were combined.[24]

Several issues may affect interpretation of results in these studies and the comparison of findings: 1. Different subtypes of non-Hodgkin's lymphoma have been studied and different classifications used. The studies carried by Hansen et al.[25] and Raaschou-Nielsen[26] classified non Hodgkin's lymphoma according to the seventh revision of the ICD (ICD-7; World Health Organization (WHO) 1957), but we

used the tenth revision (ICD-10; World Health Organization (WHO) 1976). 2. The methods used for assessing exposure to trichloroethylene varied widely, ranging from use of broad job or industry categories to analysis of biomonitoring data.[27] Divergent observations may be due to exposure misclassification bias reflecting incorrect assignment of study subjects to exposure groups. Hansen et al. identified study subjects using the trichloroethylene biological marker of urinary trichloroacetic acid, which provides some evidence of past trichloroethylene exposure, although usually not a full exposure history. In our study, exposure has been assigned to subjects using a JEM. 3. Animal studies have reported elevated risk of some haematopoietic cancers with thichloroethylene exposure.[28,29]

Petroleum solvents

Our results do not show any clear association between MF and petroleum solvent, with the exception of a high risk for MF for women who had a history of high exposure to kerosene/fuel/gasoil. However, this finding needs to be interpreted with caution, as the association found in women was based on 2 exposed cases only in the highest level and was not found in men.

Occupational exposure to kerosene/fuel/gasoil occurs in oil refineries, petrochemical plants, petroleum distribution terminals, marine petroleum tankers, among car mechanics and filling station attendants.[30] In a review carried by Kane et al., the authors found no epidemiological evidence that occupational exposure to gasoil increased the risk of incidence non-Hodgkin lymphoma.[31-34] No study examined risk by subtype.

There has been no consensus on whether benzene is associated with non-Hodgkin lymphoma, but in a review among workers in industries, the authors concluded that there was no association.[35]

Interpretation of the results needs to take into account a number of issues. First, we included only 100 MF cases, although we recruited patients from several European countries to increase the number of cases of this rare cancer. The study was also larger than other published case-control studies on MF. However, the small number of cases may have lead to low statistical power to detect an association.

MF is difficult to diagnose and to separate from other types of dermatosis.[36,37] We used only cases with a diagnosis based on strict criteria applied by one reference pathologist. MF is nonspecific to exposure to organic solvents, which partly contributes to the inconsistent observations. Other factors have been identified or suggested as associated with MF, limiting the statistical power. Additionally, mean occupational exposure concentrations are relatively low in Europe, with an impact of further limiting statistical power.[24]

Data were collected from many centres and it is difficult to compare occupations across geographical borders despite the fact that a similar coding system was used. The specific work tasks within a given occupation may differ from country to country.

Occupational exposures to chlorinated and petroleum solvents were assessed using a JEM. This exposure assessment method is considered as less efficient than expert judgment made from reviewing individual job history, since the exposure is evaluated for groups of workers with the same job and not on an individual basis. It was seen that for fixed sample size the interview and expert evaluation design was estimated to provides greater statistical power for detecting risks.[38] Non-differential exposure misclassification arises from the use of a JEM when assessing occupational exposure, and is likely to bias odds ratio toward unity.

CONCLUSION

Perchloroethylene and kerosene/fuel/gasoil may be occupational risk factors for MF in women, but these results need to be interpreted with caution, as they were not seen in men.

Table 1: Distribution of for Mycosis Fungoides cases and Odds ratios (OR) according to certain characteristics.

		All (n=100)		Men (n=59)		Women (n=41)	
		n	%	n	%	n	%
Centre	Spain	40	6.9	20	5.2	20	10.1
	Denmark	6	1.0	2	0.6	4	1.7
	Sweden	3	1.3	1	0.7	2	2.2
	France	26	5.1	17	5.0	9	5.3
	Germany	6	0.8	5	0.9	1	0.7
	Italy	19	6.2	14	6.5	5	5.5
Age	30 - 50	27	4.6	15	3.5	12	8.5
	51 - 60	28	7.6	15	6.5	13	9.4
	> 60	44	9.8	29	8.3	15	14.9
		n	OR (CI95%)	n	OR (CI95%)	n	OR (CI95%)
Educational level	Medium (Professional training) and High (University)	38	1 Ref	24	1 Ref	14	1 Ref
	Low (Left school at age before 18)	58	1.99 (1.31-3.02)	32	2.40 (1.39-4.14)	26	1.40 (0.69-271)
Alcohol consumption (g/day)	0-30.00	67	1 Ref	28	1 Ref	39	1 Ref
	30.01-60.00	22	1.07 (0.66-1.75)	20	1.91 (1.06-3.46)	2	0.61 (0.14-2.68)
	> 60	11	1.21 (0.63-2.32)	11	1.48 (0.72-3.03)	0	-
Smoking habit (cigarettes/day)	0	44	1 Ref	15	1 Ref	29	1 Ref
	1-25	44	0.91 (0.59-1.39)	32	1.19 (0.63-2.23)	12	0.91 (0.44-1.84)
	>25	12	0.97 (0.51-1.87)	12	1.12 (0.52-2.46)	0	-
Body Mass Index (Kg/m2)	<18.50	15	1 Ref	4	1 Ref	11	1 Ref
	18.51 - 25.00	61	0.74 (0.42-1.31)	37	1.14 (0.40-3.27)	24	0.99 (0.47-2.11)
	25.01 -30.00	24	1.11 (0.58-2.15)	18	1.66 (0.55-5.06)	6	1.09 (0.38-3.14)

CI95%, 95% Confidence Interval.

Include a column with number of controls for all, for men and for women

Table 2. Odds ratios (OR) for Mycosis Fungoides according to chlorinated solvents exposure.

		All				Men				Women			
Solvent (ppm)	**Exposure score**	**Cases**	**Controls**	**OR**	**CI 95%**	**Cases**	**Controls**	**OR**	**CI 95%**	**Cases**	**Controls**	**OR**	**CI 95%**
Trichloroethylene	Not exposed	73	1947	1 Ref.	-	38	584	1 Ref.	-	35	303	1 Ref.	-
	<median*	16	449	1.53	0.64-3.66	11	182	0.91	0.25-3.29	5	26	3.08	0.81-11.82
	>=median	11	449	1.15	0.48-2.77	10	195	1.08	0.41-2.83	1	11	1.13	0.13-9.84
Perchloroethylene	Not exposed	94	2634	1 Ref.	-	55	889	1 Ref.	-	39	329	1 Ref.	-
	<median*	2	106	0.92	0.12-7.28	2	37	1.80	0.22-14.80	0	7	-	-
	>=median	4	106	2.48	0.52-11.90	2	35	-	-	2	4	11.38	1.04-124.85
Carbone Tetrachloride	Not exposed	98	2822	1 Ref.	-	59	958	1 Ref.	-	39	336	1 Ref.	-
	Exposed	2	24	2.75	0.27-27.84	0	3	-	-	2	4	3.70	0.20-70.07
Chloroform	Not exposed	99	2835	1 Ref.	-	59	958	1 Ref.	-	40	338	1 Ref.	-
	Exposed	1	11	-	-	0	3	-	-	1	2	-	-
Methylene Chloride	Not exposed	91	2571	1 Ref.	-	53	855	1 Ref.	-	38	326	1 Ref.	-
	<median*	5	137	1.10	0.25-4.86	2	52	-	-	3	11	2.90	0.54-15.72
	>=median	4	138	0.63	0.08-4.87	4	54	0.73	0.09-5.62	0	3	-	-
All chlorinated solvents	Not exposed	73	1940	1 Ref.	-	38	584	1 Ref.	-	35	300	1 Ref.	-
	Exposed	27	906	1.30	0.67-2.55	21	377	1.02	0.44-2.35	6	40	2.21	0.69-7.03

ORs adjusted for age, country, smoking habit, alcohol intake, BMI and educational level (as well as sex for all sample).
95% CI, 95% Confidence Interval.
*Median calculated among exposed controls.

Table 3: Odds ratios (OR) for Mycosis Fungoides according to petroleum solvents exposure.

		All				Men				Women			
Solvent (ppm)	**Exposure score**	**Cases**	**Controls**	**OR**	**95% CI**	**Cases**	**Controls**	**OR**	**95% CI**	**Cases**	**Controls**	**OR**	**95% CI**
Benzene	Not exposed	87	2408	1 Ref.	-	50	807	1 Ref.	-	37	316	1 Ref.	-
	<median*	4	219	1.43	0.41-4.94	1	69	-	-	3	10	4.63	0.99-21.79
	>=median	9	219	1.57	0.59-4.22	8	85	1.70	0.55-5.22	1	14	1.33	0.15-11.58
Paraffinic/alicyclic hydrocarbons	Not exposed	92	2648	1 Ref.	-	54	897	1 Ref.	-	38	325	1 Ref.	-
	<median*	4	99	3.24	0.68-15.38	3	29	1.73	0.20-14.68	1	6	6.67	0.52-86.48
	>=median	4	99	1.03	0.23-4.54	2	35	-	-	2	9	3.45	0.62-19.22
Gasoline	Not exposed	91	2466	1 Ref.	-	50	801	1 Ref.	-	41	336	1 Ref.	-
	<median*	5	184	0.99	0.22-4.38	5	77	1.06	0.24-4.80	0	1	-	-
	>=median	4	196	0.90	0.20-4.07	4	83	0.93	0.21-4.24	0	3	-	-
Mineral Spirit	Not exposed	69	1792	1 Ref.	-	36	544	1 Ref.	-	33	257	1 Ref.	-
	<median*	13	526	0.50	0.19-1.32	8	197	0.41	0.09-1.82	5	63	0.63	0.17-2.37
	>=median	18	528	1.36	0.64-2.88	15	220	1.16	0.47-2.90	3	20	2.28	0.56-9.35
Kerosene, fuel or gasoil	Not exposed	86	2125	1 Ref.	-	49	651	1 Ref.	-	37	326	1 Ref.	-
	<median*	6	351	0.85	0.28-2.54	4	145	0.42	0.10-1.85	2	7	8.53	1.11-65.62
	>=median	8	370	0.72	0.24-2.18	6	165	0.51	0.14-1.77	2	7	1.96	0.13-30.31
All petroleum solvents	Not exposed	65	1488	1 Ref.	-	36	444	1 Ref.	-	29	241	1 Ref.	-
	Exposed	35	1358	0.74	0.40-1.36	23	517	0.56	0.25-1.27	12	99	1.14	0.44-2.98

ORs adjusted for age, country, smoking habit, alcohol intake, BMI and educational level (as well as sex for all sample).
95% CI, 95% Confidence Interval.
*Median calculated among exposed controls.

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APPENDIX

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