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SHORT COMMUNICATION

Occupational exposure to chemicals and risk of thyroid cancer in Sweden

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Abstract
Purpose To explore thyroid cancer (TC) risk in the Swedish population, associated with occupational exposure to certain chemicals.
Methods National cancer and death registries were used to follow-up (1971–1989) all Swedish workers employed in the 1970 census. Each combination of occupation and industry was linked to a Swedish job-exposure matrix (JEM), with exposure to 13 chemicals classified as "possible exposure", "probable exposure" or "unexposed". Relative risks were obtained using Poisson models adjusted for age, period and geographical area. A second analysis was performed, in which adjustment was additionally made for simultaneous exposure to other matrix chemicals and ionising radiations.
Results Probable exposure to solvents among women displayed an increased risk (RR = 1.91; 95%CI:1.05–3.45), mainly due to a higher risk observed among shoe-cutters, lasters and sewers engaged in shoe-making.
Conclusions Exposure to solvents, used mainly in the shoe and leather industry, seems to be associated with excess TC among women.

Keywords Thyroid neoplasm · Occupation · Industry · Chemical exposure · Risk

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Introduction

Despite being a relatively infrequent tumour, thyroid cancer is the most common malignancy of the endocrine system and ranks as the eighth leading cancer among women. The only reliably known risk factor is exposure to ionising radiation, essentially in cases where such exposure has occurred during childhood. This tumour has however also been associated with other factors, such as history of benign thyroid diseases or hormonal, reproductive, dietary and genetic factors (Ron and Schneider 2006).

While there is no chemical substance that is currently recognised as a thyroid carcinogen in humans (International Programme on Chemical Safety (IPCS) 2002), accidental or occupational exposures to high levels of some chemicals may indeed cause moderate alterations in this organ (Brucker-Davis 1998). Hence, a number of studies have described thyroid gland anomalies in humans (mostly benign) associated with exposure to chemicals and solvents in general (Baccarelli 1999; Wingren et al. 1993; Wingren and Axelson 1997), certain organochlorinated pesticides

(Brucker-Davis 1998; Ejaz et al. 2004; International Agency for Research on Cancer (IARC) 2001; Langer et al. 2005; Langer 2005; National Institute of Environmental Health Sciences (NIEHS) 1992) and other industrial chemicals, such as polychlorinated biphenyls, polybrominated biphenyls (Bahn et al. 1980; Brucker-Davis 1998; Langer et al. 2005; Mallin et al. 2004), dioxins (International Agency for Research on Cancer (IARC) 1997; Brucker-Davis 1998; Saracci et al. 1991; Zober et al. 1994), hexachlorobenzene (Brucker-Davis 1998; Grimalt et al. 1994; Sala et al. 2001), polyhydroxyphenols/phenol derivatives (Brucker-Davis 1998) and phthalates (Brucker-Davis 1998).

Occupational studies, based mainly on retrospective cohorts, are a particularly useful tool for identifying substances that are harmful in the long term, since occupational exposures are more intense, more prolonged and more easily identifiable than exposures in other settings. The availability of a huge historical Swedish cohort, comprising almost 3 million people and followed up over a period of 19 years, thanks to a link between the Swedish cancer register and the population register, enabled our group to analyse the risk of TC by occupation and industry in a previous study (Lope et al. 2005). The availability of a matrix, which was purpose-made for this specific cohort and reflected job exposure to a series of chemical substances, rendered it possible for the effect of such substances in the workplace to be explored. The aim of this study was thus to investigate the possible association between TC and occupational exposure to the chemical compounds among the gainfully employed Swedish population.

Materials and methods

The base population for this historical cohort study comprised all Swedish men and women who were gainfully employed at the time of the 1970 census, and were still alive and over the age of 24 years as of 1 January 1971. This encompassed 1,890,497 men and 1,101,669 women followed up for 19 years until year-end 1989, yielding a total of 33,359,168 and 20,695,264 person/years for men and women, respectively.

Information was drawn from two linked datasets. The first of these was the Swedish cancer environment register, which links the National Cancer Registry to the 1970 census and thus provides information on incident cancer cases, occupation, industrial branch, residence and various demographic variables from the 1970 census (Barlow and Eklund 1995; Centre for Epidemiology 1994). This register was used to compute specific rate numerators. TC is classified as code 194 under the International Classification of Diseases (7th revision). The second data source links the National Death Registry to the 1970 census and served to compute the contribution in terms of person per years for each member of the cohort. A detailed description of the record-linkage between these two registers will be found elsewhere (Centre for Epidemiology 1994).

In the 1970 census, occupations were coded according to the Nordic Classification of Occupations (Systematisk förteckning över yrken, Folk och bostadsräkningen 1975). Each occupation is represented by a three-digit number. The first digit refers to one of ten major occupational sectors (0–9), with higher numbers indicating manual occupations and lower numbers non-manual occupations, which often require longer education associated with a higher socio-economic status. Industrial branch was coded on a four-digit basis, in accordance with the Nordic Registry of Industries (Swedish Standard Industrial Classification of all Economic Activities (SNI) 1977).

The overall person per time that each person contributed to the study was allocated to the corresponding cells of the variables of stratification. These variables were: occupation; industrial branch; sex; 5-year age group (from 25–29 to 80–84 years); calendar time period (1971–1975, 1976–1980, 1981–1985 and 1986–1989); and county of residence in 1970.

To assess exposure to chemical substances, a matrix of job exposure to chemicals was used. This job exposure matrix was originally developed for a study on bladder cancer and occupational exposures (Plato and Steineck 1993). It was subsequently updated for the study of exposure to potential carcinogens in the gainfully employed Swedish population (Jaruholm 1996) and used in a study on childhood cancer and paternal occupational exposures (Feychting et al. 2001). It was based on a crossclassification of occupation and industrial branch, was drawn up by two senior occupational hygienists with over 30 years of experience. The JEM evaluates exposure of each job-industry combination to 13 chemical substances indirectly, based on the likelihood of all workers in a specific cell being exposed to the respective substances in Sweden around 1970; in many situations exposure assessment was confirmed by old measurements, contact with industries, trade unions, industry reports, scientific papers and handbooks in concern industry. Hence, the matrix classifies: combinations where under 10% of workers were exposed to levels that exceed 1/10 of the threshold limit value (TLV) of a given substance as "unexposed"; combinations where 10–66% of workers were exposed to such levels, as "possible exposure"; and combinations where over 66% workers were exposed to such levels, as "probable exposure". It covered 73.2% of the male and 75.2% of the female cohorts used in this study, as certain combinations of job and industry were not assessed, owing to the low number of subjects. The chemicals included in the matrix were arsenic, asbestos, chromium/nickel, lead, mercury, metal compounds, oil mist, polycyclic aromatic hydrocarbons, pesticides or herbicides, pesticides or herbicides at peak exposure (mainly sprayers), petroleum products, quartz, solvents and textile dust. Arsenic and pesticides or herbicides at peak exposure were solely classified as "possible exposure" and quartz was solely classified as "probable exposure".

Analysis of chemical-related risk was restricted to persons with exposure levels ascertained in the matrix. Assuming that the observed number of cases was distributed in each stratum as a Poisson variable, log-linear Poisson models were fitted in order to obtain relative risks (RRs) for possible and probable exposure versus non-exposure to a specific chemical factor, adjusted for geographical risk area. This last variable grouped counties of residence into three levels in terms of their standardised incidence ratios (SIRs), i.e., <90, 90–110 and >110. In these models, the number of expected cases was introduced as an offset (Breslow and Day 1987). As the expected number of cases was computed by taking the age- and period-specific rates of the study cohort as reference, the RR was likewise age- and period-adjusted. Possible and probable exposures were pooled when the number of expected cases was <5 in some of these categories. Due to the fact that the same job title entails different activities and exposures between the sexes, separate analyses were performed for men and women.

Since some combinations of occupation and industrial branches can be exposed to several chemical agents, additional analyses were undertaken, adjusting for simultaneous exposure to other compounds present in the matrix. Furthermore, in view of the fact that ionising radiation is the best-established TC risk factor, the possible confounding effect of occupational exposure to this radiation was also assessed for all subjects in the cohort, using a common JEM for both sexes which had been used to evaluate risk of TC in a previous study (Lope et al. 2006).

Results

During follow-up, 1,103 cases of TC were diagnosed among men and 1,496 among women across the entire cohort. Of these, 809 and 1,122 cases respectively belonged to occupations for which occupational exposure to matrix chemicals were evaluated. Tables 1 and 2 show the RRs of TC for men and women, associated with occupational exposure to various chemical substances and adjusted for age, period and geographical area. Only chemicals for which there were five or more (possible and probable together) exposed cases are shown. These tables also display the estimators obtained after exposure to ionising radiations and simultaneous exposure to other matrix chemicals had been incorporated into the models; in general, no major changes in risk were observed following adjustment for these agents.

Among men, non-statistically significant risk excesses over 35% were observed among workers with possible exposure to textile dust and probable exposure to asbestos, although this last result was observed only in the adjusted analysis. In the case of women, the number of subjects exposed to these substances was usually low, and so the probable and possible categories often had to be pooled. We observed a moderate though non-statistically significant excess risk for women with possible exposure to solvents (RR = 1.16; 95%CI: 0.81–1.66), and a clear significant excess risk for probable exposure to same (RR = 1.91; 95%CI: 1.05–3.45).

Table 3 shows the number of observed and expected cases for the different occupation-industry combinations linked to possible and probable exposure to solvents. For comparison purposes, male and female workers are include in this table. In general, women were far less exposed than men. The higher risk observed among women classified as probably exposed to solvents was mainly due to the occupation of shoe cutters, lasters and sewers engaged in the manufacture of shoes (six observed versus 2.43 expected cases). Even among men, this occupation registered twice more cases than the number expected, but figures were too small to be statistically significant (Table 3).

Discussion

This study sought to investigate risk of TC associated with occupational exposure to a number of chemicals in a cohort of 2,992,166 Swedish workers followed up across 19 years. Although in general no association was found with most of the substances studied, the results nevertheless indicate an excess risk linked to probable exposure to solvents among women.

Among this study's principal strengths are: its considerable size; stratification of the analysis into men and women; use of a purpose-built matrix for the cohort; and the increased statistical power attributable to the JEM, the result of pooling subjects from different occupations for which a similar range of exposure was estimated. Our risk estimators were adjusted for age, period and geographical area, since TC incidence varies among the different Swedish counties, being highest in certain regions lying in the centre and south of the country (Jensen et al. 1988) but evincing no great differences between rural and urban areas (Pettersson et al. 1996). The only fully established risk factor, however, is exposure to ionising radiation, and, while the effect of this physical agent was confirmed in this same cohort by using an ionising-radiation-specific JEM (Lope

Table 1 Thyroid cancer risk associated with occupational exposure to chemicals among men, adjusted for age, period and geographical area

Occupational exposure factors[a]	OC[b]	EC[c]	Unadjusted for other chemicals			Adjusted for other chemicals and radiation		
			RR[d]	95%CI[e]	p[f]	RR[d]	95%CI[e]	p[f]
Arsenic								
No exposure	792	789.5	1.00			1.00		
Possible	7	7.0	0.97	0.46–2.04	0.936	1.01	0.46–2.18	0.985
Asbestos								
No exposure	722	720.2	1.00					
Possible	70	71.5	0.98	0.77–1.26	0.891	1.13	0.79–1.61	0.492
Probable	17	15.4	1.11	0.69–1.80	0.663	1.39	0.76–2.53	0.280
Chromium/nickel								
No exposure	786	782.9	1.00					
Possible/Probable	23	24.2	0.94	0.62–1.43	0.786	0.96	0.55–1.66	0.872
Metal compounds								
No exposure	777	776.5	1.00					
Possible	4	8.4	0.48	0.18–1.28	0.144	0.51	0.18–1.42	0.196
Probable	28	22.2	1.26	0.87–1.84	0.224	1.30	0.79–2.15	0.301
Oil								
No exposure	761	750.1	1.00					
Possible/Probable	48	56.9	0.82	0.61–1.10	0.186	0.87	0.63–1.19	0.385
PAHs (combustion products)								
No exposure	701	709.5	1.00					
Possible	33	31.4	1.07	0.76–1.52	0.694	1.10	0.77–1.57	0.608
Probable	75	66.2	1.16	0.91–1.47	0.224	1.14	0.89–1.45	0.304
Pest/herb peak exposures								
No exposure	725	720.6	1.00					
Possible	84	86.0	0.96	0.77–1.20	0.719	0.97	0.77–1.23	0.805
Petroleum products								
No exposure	788	788.3	1.00					
Possible/Probable	21	2.2	1.12	0.72–1.72	0.618	1.15	0.74–1.79	0.521
Solvents								
No exposure	689	671.8	1.00					
Possible	89	102.6	0.84	0.67–1.05	0.124	0.88	0.63–1.23	0.456
Probable	31	32.6	0.93	0.65–1.33	0.680	0.96	0.67–1.38	0.820
Textile dust								
No exposure	756	764.7	1.00					
Possible	11	8.3	1.38	0.76–2.50	0.293	1.39	0.75–2.58	0.289
Probable	4	5.1	0.84	0.31–2.24	0.722	0.82	0.31–2.20	0.693

[a] Occupational exposure factors with at least five observed cases
[b] Observed cases
[c] Expected cases
[d] Relative risk adjusted for age and geographical area
[e] Confidence intervals for the RR
[f] *p* value

et al. 2006), adjustment for such exposure nonetheless resulted in no change to the estimators obtained for the chemicals studied in this paper.

Our study also displays some limitations. On the one hand, we were unable to distinguish between the different histological types of TC. The risk factors described for this tumour appear to play a different role for each histological type, and thus the relationship between TC and the agents studied might not be homogeneous for all types of tumour. On the other hand, occupation and industry were allocated on the basis of the information furnished by the subjects at the beginning of the study, in the 1970 census, so that this might be a one-off exposure measure not exempt from a possible risk of misclassification. Another aspect to consider is the follow-up time: our 19 years follow up might be a short time in the carcinogenic process, as TC—like all solid tumours—has a long latency period. Finally, the use of job exposure matrices constitutes an imperfect measure of estimating exposure, and generally implies a non-differential classification bias (Blair and Stewart 1992). The importance of this problem depends on the variability of exposure within and among the occupational groups

Table 2 Thyroid cancer risk associated with occupational exposure to chemicals among women, adjusted for age, period and geographical area

Occupational exposure factors[a]	OC[b]	EC[c]	Unadjusted for other chemicals			Adjusted for other chemicals and radiation		
			RR[d]	95%CI[e]	p[f]	RR[d]	95%CI[e]	p[f]
Arsenic								
No exposure	1109	1109.9	1.00			1.00		
Possible	7	7.0	1.01	0.48–2.13	0.970	1.20	0.38–3.80	0.750
Mercury								
No exposure	1112	1116.4	1.00			1.00		
Possible/Probable	10	9.1	1.11	0.60–2.07	0.738	0.81	0.10–6.37	0.844
Oil								
No exposure	1083	1089.3	1.00			1.00		
Possible/Probable	39	36.1	1.08	0.79–1.49	0.633	1.05	0.75–1.46	0.778
PAH (combustion products)								
No exposure	1108	1109.2	1.00			1.00		
Possible/Probable	14	16.3	0.86	0.51–1.46	0.580	0.87	0.51–1.47	0.597
Pest/herb peak exposures								
No exposure	1110	1112.4	1.00			1.00		
Possible	12	13.0	0.93	0.53–1.65	0.814	0.84	0.35–2.03	0.706
Solvents								
No exposure	1080	1092.8	1.00			1.00		
Possible	31	26.7	1.16	0.81–1.66	0.406	0.81	0.48–1.38	0.446
Probable	11	5.9	1.91	1.05–3.45	0.033	1.92	1.05–3.52	0.035
Textile dust								
No exposure	1066	1071.6	1.00			1.00		
Possible	37	36.3	1.03	0.74–1.43	0.859	1.14	0.82–1.59	0.446
Probable	19	17.6	1.11	0.71–1.76	0.640	1.13	0.71–1.77	0.611

[a] Occupational exposure factors with at least five observed cases
[b] Observed cases
[c] Expected cases
[d] Relative risk adjusted for age and geographical area
[e] Confidence intervals for the RR
[f] p value

considered, as well as possible changes in exposure across time.

According to our study, women with probable exposure to solvents in their workplace registered a risk that was almost double that of their unexposed counterparts. Organic solvents are widely used in the occupational context. Although their use and number have grown with time, exposure levels may nevertheless have fallen thanks to labour safety regulations. Furthermore, this is a very heterogeneous exposure category. Risk patterns among exposed workers seem to show a wide variation, which could be due to differences in the nature of the solvents used and/or the procedures for using them. The only solvent recognised by the IARC as having sufficient evidence of carcinogenicity in humans is benzene, though experimental animal studies point to the existence of some more carcinogenic compounds (Lynge et al. 1997). With respect to TC, Wingren et al. (1993) detected an excess of papillary tumours associated with occupational contact with solvents among males. Another subsequent study also described possible alterations in the pituitary hormones after occupational exposure to certain solvents (Baccarelli 1999). Insofar as exposure to specific solvents is concerned, Wingren et al. associated occupational exposure to trichloroethylene with benign thyroid diseases (Wingren and Axelson 1997), yet other studies have failed to find any relationship between this solvent and TC (Axelson et al. 1994; Lynge et al. 1997; Wartenberg et al. 2000). Lastly Wong et al. (2005) detected excess risk of TC in female workers who had been exposed to benzene and formaldehyde for at least 10 years.

In our cohort, the female workers most closely linked to excess risk associated with probable exposure to solvents were shoe cutters, lasters and sewers engaged in the manufacture of shoes. Work in the footwear industry entails exposures that are carcinogenic in humans (primarily nose and nasal sinuses) (International Agency for Research on Cancer (IARC) 1987). These workers are exposed to solvents present in glues and adhesives, such as acetone, ethylacetate, dichloromethane, methyl ethyl ketone, cyclohexane and toluene, among others (Perbellini et al. 1992). In connection with the last-mentioned solvent, there are two studies that describe alterations in the hypothalamic-pituitary axis after exposure to toluene (Chen et al. 2003; Svensson et al. 1992). In the analysis of the categories of probable and possible exposure to solvents, men, despite being more exposed than women, displayed no association. This result

Table 3 Calculation of observed and expected cases in occupations and industries linked to exposure to solvents

Occupation[a]		Industry[a]		Men		Women	
				OC[b]	EC[c]	OC[b]	EC[c]
Possible exposure							
11	Chemists	9320	Research and development	2	0.24	0	0.20
14	Laboratory technicians and assistants	9313	Post-secondary education	0	0.10	3	1.17
32	Dentists	9331	Medical, dental and other health services	0	2.21	4	1.96
45	Medical technicians	9331	Medical, dental and other health services	0	1.52	11	5.89
83	Display artists	8325	Advertising services	0	0.11	1	0.05
204	Cashiers in retail stores and restaurants	6242	Fuel retailing	1	0.01	0	0.50
302	Working proprietor, retail trade	6222	Retailing of paints and cosmetics	1	0.44	0	0.44
332	Shop managers	6222	Retailing of paints and cosmetics	0	0.43	1	0.33
333	Shop assistants	6222	Retailing of paints and cosmetics	1	0.36	2	2.91
714	Upholsterers	5029	Building crafts work not elsewhere classified	1	0.49	0	0.01
741	Precision toolmakers	3851	Manufacture of mechanical instruments	0	0.55	1	0.35
750	Toolmakers, machine-tool setters and operators	3811	Manufacture of tools and mechanical equipment	1	2.28	1	0.64
		3813	Manufacture of structural metal products	1	0.91	0	0.07
		3819	Manufacture of fabricated metal products	6	5.39	1	2.24
		3822	Manufacture of agricultural machinery	1	0.56	0	0.07
		3824	Manufacture of special industrial machinery	5	1.81	0	0.20
		3829	Machinery and equipment except electrical	5	6.59	1	1.18
		3839	Manufacture of electrical apparatus	1	0.50	0	0.24
		3841	Ship- and boat-building and repairing	1	1.46	0	0.04
		3843	Manufacture of motor vehicles and parts	2	2.12	0	0.34
		3845	Manufacture and repair of aircraft	1	0.58	0	0.05
771	Construction carpenters and joiners	5012	Building and engineering	38	28.03	0	0.01
793	Concrete and construction workers	5012	Building and engineering	15	27.59	0	0.01
831	Chemical process workers	3529	Manufacture of chemical products not elsewhere classified	1	0.33	1	0.26
852	Plastic products workers	3560	Manufacture of plastic products	4	1.98	3	3.52
883	Store and warehouse workers	3843	Manufacture of motor vehicles and parts	0	0.74	1	0.18
		9513	Repair of motor vehicles	1	0.62	0	0.06
	TOTAL			89	87.95	31	22.92
Probable exposure							
4	Chemical engineers and technicians	3540	Manufacture of lubricants, asphalt or coal products	1	0.03	-	-
14	Laboratory technicians and assistants	3511	Manufacture of basic industrial chemical	1	0.05	0	0.07
		9320	Research and development	0	0.08	1	0.53
722	Shoe cutters, lasters and sewers	3240	Manufacture of shoes	2	0.85	6	2.43
772	Bench carpenters and cabinet makers	3314	Manufacture of prefabricated wooden buildings	7	6.96	1	0.72
		3319	Manufacture of wood products not elsewhere classified	1	1.36	0	0.34
		3320	Manufacture of furniture and fixtures	4	4.60	2	0.75
		3841	Ship-and boat-building and repairing	1	1.13	0	0.02
781	Painters	5012	Building and engineering	5	1.64	0	0.01
		5025	Building-painting and paper hanging	6	11.30	0	0.09
		8310	Real estate	1	0.37	0	0.00
		8325	Advertising services	1	0.03	0	0.00
831	Chemical process workers	3540	Manufacture of lubricants, asphalt or coal products	1	0.03	0	0.00
852	Plastic products workers	3513	Manufacture of synthetic resins, plastic	0	0.38	1	0.49
	TOTAL			31	28.81	11	5.45

[a] Combinations of occupation and industry with at least one observed case in men or women

[b] Observed cases

[c] Expected cases

underscores the difficulty of drawing joint conclusions for the two sexes. Different effects in men and women might reflect hormonal differences, which would in turn entail greater susceptibility to TC among women, induced by exposure to these compounds, or could reflect exposure to solvents of a different nature.

In conclusion, our study suggests a rise in risk of TC linked to occupational exposure to solvents in women. Although this is a heterogeneous category of exposure, excess risk is concentrated among shoe cutters, lasters and sewers in the footwear industry, namely, workers exposed to different mixtures of solvents. This result calls for future studies in this occupational sector.

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