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MORTALITY FROM LYMPHOHEMATOPOIETIC NEOPLASMS AND OTHER CAUSES IN A COHORT OF LAMINATED PLASTIC WORKERS EXPOSED TO FORMALDEHYDE

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Abstract
Purpose A possible relationship between exposure to formaldehyde and leukaemia particularly myeloid leukaemia as well as of lymphoid neoplasms has been debated and is still controversial. We thus examined the issue using data from a cohort of workers of a laminated plastic factory sited in Piedmont, northern Italy.
Methods The study cohort included 2,750 subjects (2,227 men and 523 women) who worked in the factory between 1947 and 2011, for at least 180 days. Follow-up ended in May 2011, for a total of 70,933 person-years of observation. We computed standardized mortality ratios (SMR) and 95% confidence intervals (CI) using national and (whenever available) Piedmont Region death rates.
Results Overall, there were 417 deaths versus 493.4 expected ones (SMR = 84.5, 95% CI 76.6–93.0). The SMRs were 79.8 (95% CI 67.5–93.6) for total cancer mortality, 148.5 (95% CI 68.0–282.2) for oral cavity and pharynx (three deaths were registered, but not confirmed, as nasopharyngeal cancer), 48.3 (95% CI 13.1–123.7) for pancreas, 66.1 (95% CI 13.6–193.0) for larynx, and 96.7 (95% CI 72.0–127.2) for lung cancer. The SMR of all lymphohematopoietic malignancies was 68.6 (95% CI 31.4–130.3; nine observed deaths). This tended to increase with duration of exposure and to decrease with period at first exposure, always remaining below 100. There were four deaths from lymphoma (SMR = 74.1, 95% CI 20.1–189.6) and five deaths from leukemia (SMR = 92.4, 95% CI 29.9–215.3).
Conclusions We found no meaningful excess mortality from any lymphohematopoietic nor other neoplasms, except possibly for nasopharyngeal cancer.

Keywords: Cohort studies • Formaldehyde • Hematologic neoplasms • Leukemia • Occupational exposure

Introduction

In the European Union alone, about 1 million workers were occupationally exposed to variable doses of formaldehyde in the early 1990s [1]. Formaldehyde exposure occurs in various industrial settings, including manufacture of furniture and fixtures, wood products, wearing apparel and textiles, chemicals, and plastic products, as well as in several services such as medical, dental, and veterinary ones [2,3].
A causal relationship between formaldehyde exposure and leukaemia particularly of the myeloid type and other lymphoid neoplasms is controversial [3-10]. Two large US studies published during 2009, one of workers of ten formaldehyde-using or formaldehyde-producing plants [5] and one of professionals of the funeral industry [8], provided evidence for a role of formaldehyde on myeloid leukemia. Besides confirming the overall evaluation of formaldehyde as ‘‘carcinogenic to humans (Group 1),’’ a recent International Agency for Research on Cancer (IARC) Monograph concluded

that there is adequate evidence for a causal role of formaldehyde on leukemia, though not all the members of the Working Group agreed [3]. On the other hand, a systematic review published during 2012 concluded for a lack of consistent or strong evidence for any lymphohematopoietic cancer [7]. The issue has been widely debated [5, 8, 11-14] and is still open to discussion.
In 2006, a IARC Working Group evaluated that enough epidemiological evidence was available that formaldehyde causes cancer of the nasopharynx in humans [15]. This conclusion was confirmed in the subsequent Monograph 100F [3]. The association with other cancers, including oral cavity, pancreas, larynx, lung, and brain, is inconsistent [6]. Therefore, we examined the data from a cohort of workers of a laminated plastic factory sited in Piedmont, northern Italy, in order to provide further information on the effect of occupational exposure to formaldehyde on mortality from cancer, with particular focus on lymphohematopoietic neoplasms.

Methods

The study cohort included 3,126 subjects (2,558 men and 568 women) who worked in an Italian laminated plastic factory between 1947 and 2011, i.e., present in 1947 or hired thereafter. Subjects who worked for <180 days (i.e., 6 months) at the factory (n = 362, 11.6%), those with missing information on the date of first employment (n = 10, 0.3%), and those lost to follow-up with available information on the date of first employment only (n = 4, 0.1%) were excluded from the cohort, leaving 2,750 subjects (2,227, 81.0% men and 523, 19.0% women) under investigation. These were followed-up until 31 May 2011 or until reaching 85 years of age, if this occurred earlier. A total of 2,208 (80.3%) subjects survived to the end of the follow-up period, 457 (16.6%) died, and 85 (3.1%) emigrated or were lost to follow-up for other causes, these being included in the study up to the latest date of available information. Overall, 70,933 person-years of observation (57,036 man-years and 13,897 woman-years) were included in the present analysis.
We obtained the employment data from personnel records at the factory, and ascertained vital status and causes of death through population registers and copies of death certificates from municipal registration offices. Information was available on sex, dates of birth, employment(s), migration(s), and death, on cause of death and contributory causes and, for over 85 % of subjects, on job category (i.e., blue-or white-collar worker). Cause of death could not be retrieved for 26 out of 457 (5.7 %) deceased subjects. For 53 (1.9 %) subjects, information on the date at last cessation of employment was missing. The latter subjects were kept into all analyses, except those on duration and time since last exposure. Most subjects (n = 2,579, 93.8% of the cohort) had only one period of employment in the factory. Therefore, we calculated the duration of exposure for all subjects using only the date of first hiring and last termination of employment. Anyway, we conducted a sensitivity analysis on the duration of exposure by excluding the 171 subjects that had more than one period of employment.
The factory was founded in 1946. Its main product is high-pressure plastic laminate (HPPL) used in the furniture industry, hospital equipment, floors, and walls. The raw materials used in the production of HPPL laminates are phenolic resin, melamine resin, decorative papers, and kraft papers. None of these products can be classified according to the material safety data sheets as a highly toxic substance.
Figure 1 shows the scheme blocks of the production process. Technical measures that were adopted to reduce the risks from substances in the workplace include (1) segregated operations for impregnation of papers; (2) aspiration of volatile organic compounds at the point of release; (3) utilization of locked machinery and automatic procedures, when possible; and (4) use of personal protective equipment. A further improvement of the working environment was obtained by replacing the phenolic resin in solvent with the phenolic resin in water in 1991. The major chemical risk, mainly in the past, is due to formaldehyde exposure. Formaldehyde is a by-product from resins in the phase of machining.

Data analysis

We computed expected number of deaths from lymphohematopoietic and other neoplasms, as well as total mortality, using the Piedmont Region deaths rates [16, 17] from 1981 onwards, and the national death rates before 1980 [18], by sex, 5-year calendar period, and age group. As Piedmont Region (and Italian) death rates were not available for 2004–2005 and after 2010, we applied those of 2001–2003 to the period 2000–2004 and those of 2006–2010 to the period 2005–2011 (i.e., the central years of the two periods). We computed the standardized mortality ratios (SMR) of various cancers and total mortality separately by sex and overall, as the ratio of observed and expected numbers of deaths, multiplied by 100. For lymphohematopoietic neoplasms, we also computed the SMRs according to several factors related to employment. The Poisson distribution was used to compute the confidence intervals (CI) for up to 10 observed deaths, and the normal approximation for >10 observed deaths [19]. The causes of death were coded according to the Ninth Revision of the International Classification of Diseases (ICD-IX).

Results

Table 1 shows the number of observed and expected deaths from various lymphohematopoietic cancers, separately for men and women, and the corresponding SMR and 95% CI. SMRs are presented for men and women combined, too. Seven male deaths from all lymphohematopoietic malignancies combined were reported, as compared to 11.6 expected on the basis of population mortality rates (SMR = 60.2, 95% CI 24.1–124.0). The corresponding observed and expected deaths in women were 2 and 1.5, respectively (SMR = 134.1, 95% CI 16.2–484.2). The overall SMR of lymphohematopoietic malignancies was thus 68.6 (95% CI 31.4–130.3). With reference to the type of lymphohematopoietic malignancy, there were four deaths from lymphoma (all non-Hodgkin) versus 5.4 expected ones (SMR = 74.1, 95% CI 20.1–189.6) and five deaths from leukemia (three myeloid and two of unspecified cell type) versus 5.4 expected ones (SMR = 92.4, 95% CI 29.9–215.3). No death from multiple myeloma was reported, as compared to 2.3 expected ones.

Table 2 reports the observed deaths from lymphohematopoietic malignancies (excluding multiple myeloma), and the corresponding SMRs and 95% CIs, according to several, mainly time-related, characteristics of employment. The SMR of all lymphohematopoietic cancers tended to increase with duration of exposure (from 54.6 for <10 years to 90.1 for ≥20 years) and to decrease with period at first exposure (from 90.6 for first exposure before 1970 to 0.0 from 1980 onwards), being in any case lower than 100. All lymphoma deaths occurred 10 or more years after exposure ceased (SMR = 147.1) and in subjects first employed before 1970 (SMR = 128.6). For leukemia, the SMRs tended to increase with age at first exposure (from SMR = 0.0 for first exposure before age 25 years to SMR = 149.8 at 35 years or more) and to decrease with time since last exposure (from SMR = 152.7 for current exposure to SMR = 68.3 for 10 or more years since stopping exposure). Almost 90% of total person-years and eight out of nine deaths from lymphohematopoietic cancers occurred in blue-collar workers [i.e., 2,133 out of 2,389 (89.3%) subjects for which the information on job category was available].

Table 3 shows the observed and expected numbers of deaths from several cancers and all causes, and the corresponding SMR and 95% CI. A total of 417 deaths occurred before age 85 years. On the basis of mortality rates, 493.4 deaths were expected; thus, the corresponding SMR was 84.5 (95% CI 76.6–93.0). The SMR for total cancer mortality was 79.8 (95% CI 67.5–93.6; 149 observed deaths). With reference to the main cancer sites of interest, the SMRs were 148.5 (95% CI 68.0–282.2; nine observed deaths, of which three were from nasopharyngeal cancer) for oral cavity and pharynx, 70.6 (95% CI 32.3–134.1; nine observed deaths) for stomach, 88.6 (95% CI 51.7–141.8; 17 observed deaths) for colorectum, 48.3 (95% CI 13.1–123.7; four observed deaths) for pancreas,

66.1 (95% CI 13.6–193.0; three observed deaths) for larynx, 96.7 (95 % CI 72.0–127.2; 51 observed deaths) for lung, 150.6 (95% CI 72.3–277.1; 10 observed deaths) for bladder, 96.4 (95% CI 26.2–246.7; four observed deaths) for kidney, and 41.1 (95% CI 5.0–148.3; two observed deaths) for brain cancer. No deaths were reported from nasal cavity and paranasal sinus cancer.

Discussion

In this cohort of workers exposed to formaldehyde, no excess in mortality from leukemia and lymphoid neoplasms was reported. In fact, the SMR for all lymphohematopoietic neoplasms was lower than 100. When we restricted the analyses to blue-collar workers only, i.e., those subjects more likely of having experienced formaldehyde exposure, the results were materially unchanged. Further, no clear pattern of risk emerged when we examined time-related factors of exposure and mortality from lymphohematopoietic cancers. The latter analyses were, however, limited by the relatively small numbers in each subgroup. With reference to leukemia subtypes, there were three deaths from the myeloid type. In the absence of specific mortality rates, the proportion of the myeloid leukemia subtype in Italy was about 40 % both in the late 1980s [20] (mortality data) and in 2003–2005 [21] (incidence data). Assuming that the proportion has remained stable over the whole follow-up period, and that the age distribution in adults resembles that of total leukemia, about 2–2.5 deaths were expected from myeloid leukemia, as compared to three observed deaths. The corresponding SMR would thus range between 120 and 150. It is, however, difficult to disentangle leukemia subtypes using mortality data, since 15–30 % of deaths from leukemia in most European countries, including Italy, are of undefined subtype [22]. We do not have information on the dose of formaldehyde exposure in this cohort, and thus, our data cannot rule out an effect at doses higher than those occurring in these workers.

The IARC classified formaldehyde as carcinogenic to humans [3, 15]. In the evaluation of the epidemiological evidence, the Working Group concluded that sufficient data were available for a causal relation with nasopharyngeal neoplasm [15]. Other reviews and meta-analyses of the available evidence on formaldehyde and cancer risk suggested a modest excess risk of nasopharyngeal cancer, due to a cluster of deaths in one US plant of the NCI Cohort study [6, 23, 24]. It was hypothesized that the excess mortality in that cohort was due to prior exposure to metal working rather than to formaldehyde exposure [25]. This notwithstanding, a recent update of the NCI Cohort investigation confirmed an excess of nasopharyngeal cancer for peak, average intensity, and cumulative exposure [23]. In our study, 3 deaths from nasopharyngeal cancer were reported. Population mortality rates were available for most of the follow-up period only for oral and pharyngeal cancer as a whole (ICD-IX: 140–149). Thus, we could not calculate the expected deaths and SMR for nasopharyngeal cancer. However, about 5–10% of all Italian deaths from oral and pharyngeal cancer were of the nasopharynx in the 1980s and 1990s [20, 26, 27]. In Piedmont, in the periods 2001–2003 and 2006–2010, the corresponding proportion was 5–6% [17]. Therefore, approximately 0.3–0.6 deaths were expected from nasopharyngeal cancer, with the corresponding SMR ranging between 500 and 1,000. All the 3 deaths occurred in males first employed before 1970, when exposure levels were likely to be higher [15]. Therefore, this study is in line with a possible excess in mortality from nasopharyngeal cancer in workers exposed to formaldehyde. Given the rough calculation method used, caution is however needed in the interpretation of these results. Furthermore, nasopharyngeal cancers were not histologically confirmed in this study. This cohort was set in a rural setting, and potential higher exposure of subjects to Epstein–Barr virus (e.g., contact with farm animals) may be a confounding factor [28].

With reference to other cancer sites, some studies indicated a possible increase in risk of nasal [29, 30], lung [31, 32], and brain cancer [33–35] in formaldehyde-exposed professionals or industry workers, but results were generally inconsistent [6, 23, 36]. Our data do not support any of these associations.

Among the limits of this study there are the unavailability of exposure measurements or other indices of formaldehyde exposure, apart from the duration of employment and type of occupation (i.e., blue- or white-collar worker), the lack of specific SMR estimates for myeloid leukemia and nasopharyngeal cancer, and the limited power for subgroup analyses on lymphohematopoietic neoplasms. Cause of death was missing for about 6% of deceased subjects, mainly because death occurred outside Italy or death certificate could not be found by competent authorities. The Piedmont Region, and particularly the Tanaro River area where the factory is sited, was affected by a ruinous flood in 1994 that, in fact, damaged a number of registration archives. Main strengths of this study are its relatively large size, the long follow-up period covering about 65 years (i.e., from 1947 to 2011, median 23.6 years), and the completeness of follow-up information that was available for over 95% of subjects in the cohort.

In conclusion, this cohort study of workers of an Italian laminated plastic factory reported no excess mortality from lymphohematopoietic neoplasms overall nor, when considered separately, from lymphoma, myeloma, and leukemia. Overall mortality in the cohort was about 15% lower than in the general population, possibly explained by the healthy worker effect [37]. However, total cancer mortality, which is not affected by the healthy worker effect, was decreased by about 20% among workers of the factory. No meaningful excess mortality from any type of neoplasm emerged, except possibly for cancer of the nasopharynx (three observed deaths), in the absence however of precise estimates of the SMR.

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Fig. 1
Scheme blocks of the production process

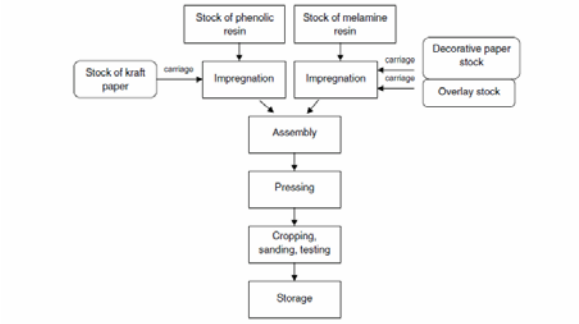

Table 1
Observed and expected deaths from lymphohematopoietic malignancies, and corresponding standardized mortality ratios (SMR) and 95 % confidence intervals (CI), in a cohort of laminated plastic workers (Italy, 1947–2011)

Cause of death	ICD-IX	Men			Women			All subjects
		Observed deaths	Expected deaths	SMR (95 % CI)	Observed deaths	Expected deaths	SMR (95 % CI)	SMR (95 % CI)
Lymphoma	200–202	3	4.8	62.6 (12.9–182.8)	1	0.6	164.7 (4.2-917.5)	74.1 (20.1–189.6)
Myeloma	203	0	2.0	0.0	0	0.3	0.0	0.0
Leukemia	204–208	4	4.8	83.2 (22.6–212.9)	1	0.6	167.9 (4.2–935.5)	92.4 (29.9–215.3)
All lymphatic and hematopoietic tissue neoplasms	200–208	7	11.6	60.2 (24.1–124.0)	2	1.5	134.1 (16.2–484.2)	68.6 (31.4–130.3)
Person-years (no. of subjects)				57,036 (2,227)			13,897 (523)	70,933 (2,750)

Deaths and person-years occurring at age C85 years are excluded. Cause of death was unknown for 24 out of 417 subjects (5.8 %) who died before age 85 (all 24 were males)

Table 2
Observed deaths (O) from lymphohematopoietic malignancies, and corresponding standardized mortality ratios (SMR), according to various characteristics of exposure in a cohort of laminated plastic workers (Italy, 1947–2011)

	Lymphoma		Leukemia		All L/H		Person-years
	O	SMR	O	SMR	O	SMR	
Duration of exposure[a]							
<10	1	42.9	2	86.2	3	54.6	40,388
10–19	2	129.0	1	63.7	3	78.9	17,773
≥20	1	75.8	2	150.4	3	90.1	10,709
Age at first exposure							
<25	1	87.7	0	0.0	1	38.8	29,461
25–34	0	0.0	1	60.2	1	24.2	23,955
≥35	3	119.5	4	149.8	7	109.0	17,517
Time since first exposure							
<20	0	0.0	2	120.5	2	52.1	46,219
20–29	1	76.9	0	0.0	1	31.7	13,261
≥30	3	130.4	β	121.5	6	98.0	11,454
Time since last exposure[a]							
During exposure	0	0.0	2	152.7	2	65.1	38,562
1–<10	0	0.0	1	104.2	1	41.5	12,996
≥10	4	147.1	2	68.3	6	84.0	17,312
Period at first exposure							
Before 1970	4	128.6	3	93.5	7	90.6	26,765
1970–1979	0	0.0	2	129.0	2	51.9	19,824
1980 or after	0	0.0	0	0.0	0	0.0	24,344
Type of occupation[b]							
Blue-collar worker	4	82.3	4	81.8	8	50.6	57,024
White-collar worker	0	0.0	1	357.1	1	151.5	7,671

Deaths and person-years occurring at age C85 years are excluded L/H lymphatic and hematopoietic tissue neoplasms
a 53 out of 2,750 subjects (1.9 %) were excluded from these analyses because information on the date at last exposure was missing
b 361 out of 2,750 subjects (13.1 %) were excluded from this analysis because information on the type of occupation was missing

Table 3

Observed and expected deaths from other (non-lymphohematopoietic) cancers, and corresponding standardized mortality ratios (SMR) and 95 % confidence intervals (CI), in a cohort of laminated plastic workers (Italy, 1947–2011)

Cause of death	ICD-IX	Men			Women			All subjects
		Observed deaths	Expected deaths	SMR (95 % CI)	Observed deaths	Expected deaths	SMR (95 % CI)	SMR (95 % CI)
Cancers								
Oral cavity and pharynx[a]	140–149	8	5.8	137.7 (59.3–271.3)	1	0.3	398.2 (10.1–2,217.8)	148.5 (68.0–282.2)
Esophagus	150	1	4.1	24.5 (0.6–136.3)	0	0.1	0.0	23.8 (0.6–132.3)
Stomach	151	9	11.9	75.7 (34.6–143.7)	0	0.9	0.0	70.6 (32.3–134.1)
Colorectum	152–154, 159.0	17	17.2	98.6 (57.4–157.9)	0	1.9	0.0	88.6 (51.7–141.8)
Liver	155	4	10.0	40.0 (10.9–102.4)	0	0.9	0.0	**36.8 (10.0–94.3)**
Pancreas	157	3	7.4	40.7 (8.4–118.9)	1	0.9	110.3 (2.8–614.2)	48.3 (13.1–123.7)
Larynx	161	3	4.5	66.9 (13.8–195.3)	0	0.0	0.0	66.1 (13.6–193.0)
Lung	162	46	51.0	90.3 (66.1–120.4)	5	1.8	281.8 (91.3–656.5)	96.7 (72.0–127.2)
Breast	174	–	–	–	0	4.3	0.0	0.0
Prostate	185	7	8.4	83.4 (33.4–171.8)	–	–	–	83.4 (33.4–171.8)
Bladder	188	10	6.5	154.7 (74.0–284.5)	0	0.2	0.0	150.6 (72.3–277.1)
Kidney	189	3	3.9	77.0 (15.9–224.9)	1	0.3	390.8 (9.9–2,176.7)	96.4 (26.2–246.7)
Brain and CNS	191–192	1	4.3	23.2 (0.6–129.2)	1	0.6	178.0 (4.5–991.6)	41.1 (5.0–148.3)
All cancers	140–239	135	168.4	**80.1 (67.2–94.9)**	14	18.4	76.2 (41.6–127.9)	**79.8 (67.5–93.6)**
All causes of death	1–999	384	453.6	**84.7 (76.4–93.6)**	33	39.9	82.8 (57.0–116.3)	**84.5 (76.6–93.0)**
Person-years (no. of subjects)				57,036 (2,227)			13,897 (523)	70,933 (2,750)

In bold, statistically significant results (95 % CI)

Deaths and person-years occurring at age C85 years are excluded. Cause of death was unknown for 24 out of 417 subjects (5.8 %) who died before age 85 (all 24 were male deaths)

a There were 3 deaths from nasopharyngeal cancer (all males