Mortality From Lymphohematopoietic Malignancies and Brain Cancer Among Embalmers Exposed to Formaldehyde

Michael Hauptmann, Patricia A. Stewart, Jay H. Lubin, Laura E. Beane Freeman, Richard W. Hornung, Robert F. Herrick, Robert N. Hoover, Joseph F. Fraumeni Jr, Aaron Blair, Richard B. Hayes

Background Excess mortality from lymphohematopoietic malignancies, in particular myeloid leukemia, and brain cancer has been found in surveys of anatomists, pathologists, and funeral industry workers, all of whom may have worked with formaldehyde. We investigated the relation of mortality to work practices and formaldehyde exposure levels among these professionals to address cancer risk in the funeral industry.

Methods Professionals employed in the funeral industry who died between January 1, 1960, and January 1, 1986, from lymphohematopoietic malignancies (n = 168) or brain tumors (n = 48) (ie, case subjects) were compared with deceased matched control subjects (n = 265) with regard to lifetime work practices and exposures in the funeral industry, which were obtained by interviews with next of kin and coworkers, and to estimated levels of formaldehyde exposure. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by use of logistic regression. All statistical tests were two-sided.

Results Mortality from myeloid leukemia increased statistically significantly with increasing number of years of embalming (P for trend = .020) and with increasing peak formaldehyde exposure (P for trend = .036). Compared with subjects who performed fewer than 500 lifetime embalmings, mortality from myeloid leukemia was elevated among those who performed embalmings for more than 34 years (OR = 3.9, 95% CI = 1.2 to 12.5, P = .024), who performed more than 3068 embalmings (OR = 3.0, 95% CI = 1.0 to 9.2, P = .057), and those whose estimated cumulative formaldehyde exposure exceeded 9253 parts per million–hours (OR = 3.1; 95% CI = 1.0 to 9.6, P = .047). These exposures were not related to other lymphohematopoietic malignancies or to brain cancer.

Conclusion Duration of embalming practice and related formaldehyde exposures in the funeral industry were associated with statistically significantly increased risk for mortality from myeloid leukemia.

J Natl Cancer Inst 2009;101:1696–1708

In recent decades, more than 2 million US workers are exposed to formaldehyde (1), including anatomists, pathologists, and professionals who are employed in the funeral industry and who handle bodies or biological specimens preserved with formaldehyde. Surveys of causes of death in these professions have shown excess numbers of lymphohematopoietic malignancies (2–11), in particular nonlymphocytic leukemia (3–6), and brain cancer (2–6,9–12) among these groups. However, specific work practices and exposures were not characterized in these studies (2–12)—three of which (4–6) used length of licensure to approximate duration of employment and obtained inconsistent results. Recently, some studies (2,13–15) of industrial workers exposed to formaldehyde noted excess numbers of deaths from lymphohematopoietic malignancies. One of these studies (15) used quantitative exposure estimates and observed an association for peak formaldehyde exposure, which is consistent with formaldehyde being a causative agent for lymphohematopoietic malignancies.

A recent review by the International Agency for Research on Cancer classified formaldehyde as a human carcinogen (group I) because of its genotoxic characteristics, because of experimental observations of nasal cancer in rodents, and because of epidemiological

Affiliations of authors: Department of Bioinformatics and Statistics, Netherlands Cancer Institute, Amsterdam, the Netherlands (MH); Formerly of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD (MH, PAS, RBH); Stewart Exposure Assessments, Arlington, VA, LLC (PAS); Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD (JHL, LEBF, RNH, JFF, AB); Cincinnati Children's Hospital Medical Center, Cincinnati, OH (RWH); Department of Environmental Health, Harvard School of Public Health, Boston, MA (RFH); Department of Environmental Medicine, New York University Medical Center, New York, NY (RBH).

Correspondence to: Laura E. Beane Freeman, PhD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, Bethesda, MD 20892 (e-mail: freemala@mail.nih.gov).

See "Funding" and "Notes" following "References."

DOI: 10.1093/jnci/djp416

Published by Oxford University Press 2009.

Advance Access publication on November 20, 2009.

evidence showing excess numbers of patients with or deaths from nasopharyngeal cancer among exposed groups (16,17). The evidence on occupational exposure to formaldehyde and leukemia was considered strong, but it was not sufficient to establish causality.

To follow-up leads from mortality surveys, we investigated the relationships of lifetime work histories, work practices, and predicted formaldehyde exposure levels in the funeral industry to risk for leukemia, other lymphohematopoietic malignancies, and brain cancer. Nasopharyngeal cancer was also of interest but, as expected, few deaths from this rare disease were identified.

CONTEXT AND CAVEATS

Prior knowledge

More deaths than expected among anatomists, pathologists, and funeral industry workers have been attributed to lymphohematopoietic malignancies, in particular myeloid leukemia, and brain cancer. Individuals in these fields may have worked with formaldehyde.

Study design

In a case–control study in a cohort of deceased funeral industry workers, those who died from lymphohematopoietic malignancies and brain tumors were compared with control subjects. Lifetime work practices and exposures to formaldehyde were obtained by interviews with next of kin and coworkers.

Contribution

The number of years of embalming practice and related formaldehyde exposures in the funeral industry was associated with statistically significantly increased mortality from myeloid leukemia. No associations were observed with other lymphohematopoietic malignancies. Associations with brain cancer were unclear.

Implications

Further studies are warranted to investigate the risk of leukemia in relation to specific embalming practices and exposures and to investigate this risk in other groups of professionals who are exposed to formaldehyde and have an increased risk of leukemia (ie, anatomists and pathologists).

Limitations

Exposures to formaldehyde were obtained from interviews with next of kin and coworkers. There were relatively few deaths from myeloid leukemia among case subjects. There was a considerable amount of missing data that required imputation for analyses.

From the Editors

Participants, Materials, and Methods

Identification of Case and Control Subjects

In previous mortality surveys in the US funeral industry, inactive or deceased funeral directors and embalmers were identified from registries of the National Funeral Directors' Association (NFDA), as well as licensing boards and state funeral directors' associations (n = 6651) (3), the New York State Bureau of Funeral Direction (n = 1678) (4), and the Division of Funeral Directors and Embalmers in the California State Department of Health (n = 5665) (5). We used subjects in these studies and determined their vital status and, if deceased, cause of death by searching state vital statistics offices. We obtained death certificates for 6808 embalmers and funeral directors who died between January 1, 1960, and January 1, 1986. Death certificates were coded for underlying and contributing causes of death according to the rules in effect at the time of death and assigned codes according to the *International Classification of Diseases, Eighth Revision* (*ICD-8*).

In this study, we included all deaths with an underlying or contributory cause identified as lymphohematopoietic malignancies (n = 168; *ICD-8* 200–209; 85% assigned as underlying cause of death), brain tumor (n = 48; *ICD-8* 191, 192, 225, or 238.1; 92% underlying cause of death), and nasopharyngeal cancer (n = 4; *ICD-8* 147; 100% underlying cause of death). In three case subjects, more than one disease of interest occurred among the underlying and contributing causes of death; for the analysis, these were coded to the underlying cause of death. For lymphohematopoietic malignancies, risks were assessed for malignancies of lymphoid (n = 99; *ICD-8* 200–204) or nonlymphoid (n = 48; *ICD-8* 205, 206, 208, or 209) origin and, as a separate rubric, myeloid leukemia (n = 34; *ICD-8* 205). Because there were only four deaths from nasopharyngeal cancer, these subjects were only briefly described.

Control subjects (n = 265) were randomly selected from individuals in the funeral industry whose deaths were attributed to other causes, excluding cancers of the buccal cavity and pharynx (*ICD-8* 140–149), of the respiratory system (*ICD-8* 160–163 or 231), and of the eye, brain, or other parts of the nervous system (*ICD-8* 238). Control subjects were stratified to be similar to the case subjects with respect to data source (NFDA, New York State Bureau of Funeral Direction, and California State Department of Health), sex, and dates of birth and death (5-year intervals).

Interviews

Interviews were carried out with next of kin and coworkers by interviewers who were blinded with regard to the cause of death of the study subject and who used a structured questionnaire to obtain information on the funeral home and work practices of the study subjects and on demographic characteristics and tobacco use, with at least one next-of-kin interview per subject and multiple coworker interviews per subject to cover the working life of the study subject in the funeral industry. Next of kin typically do not know details about the workplace, but the funeral industry is unusual in that many funeral homes are family operated and the next of kin often works and lives with the embalmer in the funeral home. In addition, we asked detailed workplace questions of only those next of kin who had worked in the funeral home with the study subject. The work history component of the questionnaire covered items such as whether the subject had embalmed, the number of intact and autopsied embalmings done by decade for each job held at least 5 years, and the effectiveness of the ventilation system (no fan, poor, moderate, or excellent) and its date of installation. Work practices, including embalming duration for intact and autopsied corpses (<1, 1–2, >2 to 3, or >3 hours) and the frequency of spills (>1 per week, a few times per month, a few times per year, or never), were queried as an average over a subject's lifetime. During 1990–1992, we interviewed at least one next of kin for 220 (96%) of the 228 eligible case subjects and for 265 (94%) of 282 eligible control subjects. We conducted 1221 interviews,

averaging 1.5 next-of-kin interviews and 1.1 coworker interviews per case subject and 1.4 next-of-kin and 1.1 coworker interviews per control subject. The study was approved by the National Cancer Institute's institutional review board, and all interviewed subjects provided informed consent.

Exposure Assessment

We linked the questionnaire responses to measurement data from an exposure-assessment experiment carried out at the Cincinnati College of Mortuary Sciences, as described previously (18). We assigned formaldehyde exposure levels during embalming to case and control subjects by use of a predictive model that was based on the exposure-assessment data, considering the effect of ventilation rate, concentration of the formaldehyde solution, whether an intact or autopsied corpse was embalmed, and measured covariates (19). After the final model was selected, its validity for estimating retrospective formaldehyde levels was evaluated on the basis of measurements from independent embalmings. The model overestimated the measured formaldehyde intensities by an average of 35% with a precision (variation of predicted values around the average bias) of 0.53 parts per million (ppm). The estimated accuracy was similar to the expected variability of repeated measurements of identical embalmings. We modified the approach of Hornung et al. (19) to consider the geometric mean by refitting the model as $\exp(1.976 - 0.092x_1 - 0.488x_2 - 0.894x_3 + 0.4592/2)$, where x_1 is the number of air changes per hour, x_2 is equal to 1 for an intact corpse and 0 for an autopsied corpse, and x_3 is equal to 1 if no spill and to 0 if a spill occurred, and 0.4592/2, which was used to estimate the arithmetic mean, is one half of the variance. The model explained 74% of the variability. Further, we calculated peak exposure level as the maximum of moving averages of any series of measurements covering 15 minutes (90 measurements, with one measurement every 10 seconds), with peak levels estimated according to the formula $\exp(2.354 - 0.0708x_1 + 0.0913x_2 - 0.344x_3 + 0.5312/2)$, with x_1, x_2, and x_3 as above. The model for peaks explained 44% of the variance. The peak model could not be validated because independent real-time measurements were not available for the validation embalmings.

For time periods with multiple interview reports, the average covariate value across reports was used, with interview responses for categorical variables converted to the midpoint of the range. Whenever any one respondent reported embalming for a given year, we assumed the study subject indeed embalmed in that year. If data were missing for a year, information available for other years for the same job was used; if those data were not available, the mean for the same 10-year age group and decade of work among control subjects who ever embalmed was imputed.

For each subject, job- and year-specific formaldehyde exposure estimates were derived with conversions in the predictive model as follows. Fan effectiveness was converted to 1.1, 5.5, and 13.3 air changes per hour to correspond to the responses of poor ventilation or no fan, moderate ventilation, and excellent ventilation, respectively. Duration was converted to 0.75, 1.5, 2.5, and 3.5 hours for less than 1, 1–2, more than 2 to 3, and more than 3 hours, respectively. Spill frequency was converted to 96, 36, 8, and 0 times per year to correspond to more than one spill per week, a few times per month, a few times per year, and never, respectively.

Using the predictive model, we calculated the estimated formaldehyde intensity during embalmings for each combination of characteristics (intact or autopsied corpse, spills, and ventilation) under which embalmings were performed during a given year. After multiplying each intensity estimate by the number and typical duration of each type of embalming, the products were added to yield the cumulative formaldehyde exposure for each year. Nonfuneral home and nonembalming jobs were assigned an intensity estimate of zero. Lifetime cumulative formaldehyde exposure was calculated by summing yearly estimates over the entire job history. Average formaldehyde intensity while embalming was calculated by dividing cumulative exposure by the number of hours of embalming. The 8-hour time-weighted average formaldehyde intensity was calculated by dividing cumulative exposure by the number of years of embalming and by 1950 hours/year (ie, the assumed number of hours worked per year). Lifetime peak formaldehyde exposure was predicted as the maximum 15-minute average intensity ever experienced over all embalmings over all years. We also calculated the lifetime number of embalmings that were associated with predicted peaks exceeding a certain level.

Completeness and Quality of Data

Reported work histories covered 18 534.5 (97%) of the 19 104 person-years between the start of the first and the end of the last reported job. Virtually all reported jobs (99.7% of person-years) were characterized by study respondents as being in a funeral home or not, and, for all jobs in funeral homes, it was reported whether the job included embalming. Reports were frequently unavailable for number of embalmings (2466 [32%] of 7806.5 person-years in embalming jobs for control subjects and 2364.5 [32%] of 7424 person-years for case subjects) and the number of autopsied embalmings (3524.5 [45%] of 7806.5 person-years for control subjects and 3272.5 [44%] of 7424 person-years for case subjects). Frequency of spills and duration of embalming an intact or an autopsied corpse were queried over a subject's lifetime. For those three variables, the proportions of control and case subjects for which none of their respondents reported a value were 43%, 43%, 45%, and 37%, 37%, 40%, respectively. A single value for those variables was available for 17%, 17%, and 17% of control subjects and 11%, 11%, and 13% of case subjects. Thus, although the duration of working in jobs with embalming could be calculated for all subjects, information was frequently missing on at least one of several characteristics used in the calculation of cumulative and average intensity of formaldehyde exposure (4143 [53%] of 7806.5 person-years with embalming for control subjects and 3701 [50%] of 7424 person-years for case subjects) and peak formaldehyde exposure (4014 [51%] of 7806.5 person-years for control subjects and 3578 [48%] of 7424 person-years for case subjects), although the exposure metric for the corresponding person-years may still have been based primarily on observed data. Of all person-time with multiple reports for a particular variable, 14% was discordant for whether embalmings were performed, with no differences between control subjects and case subjects. With discordance for continuous variables defined as a difference of more than 20% from the calculated mean across reports, 2219 (42%) of 5338

person-years with multiple reports were discordant for the number of any embalmings among control subjects, compared with 2848 (44%) of 6506 person-years among case subjects. Corresponding numbers for the number of autopsied embalmings were 1599 (37%) of 4315 person-years for control subjects and 2166 (42%) of 5177 person-years for case subjects, and those for the level of ventilation were 1918 (42%) of 4541 person-years for control subjects and 1951 (34%) of 5706 person-years for case subjects. Where more than one respondent reported frequency of spills or duration of embalming an intact or autopsied corpse, disagreement by more than one category was 5%–10%.

Statistical Analysis

Odds ratios (ORs) were calculated for categories of exposure metrics, with a 2-year lag that was based on unconditional logistic regression adjusted for calendar year of birth (1905 or before, 1906–1914, 1915–1923, or after 1923), age at death (≤56, 57–66, 67–74, or >74 years), sex, data source (NFDA, New York State Bureau of Funeral Direction, or California State Department of Health), and smoking status (ever or never). Continuous exposure metrics described above were grouped for analysis in four categories: nonexposed and by approximate tertiles of exposed control subjects. Tests of trend for categorical variables were based on the estimated slope of the original continuous variable (Wald test). All statistical tests were two-sided at a 5% statistical significance level. We evaluated various lag intervals from 2 to 15 years and found that odds ratios and goodness of fit did not differ substantially. Where we observed associations, we performed nonparametric modeling with generalized additive models (20) to appraise the underlying functional form of the exposure–response relationship. The patterns were adequately described by the category-specific odds ratios and so no results are shown. A sensitivity analysis was performed for each exposure metric by excluding subjects with 30% or more of their work history missing and therefore whose exposure level could not be calculated from reported data without any of the required variables missing.

Results

Demographic characteristics, source of data, employment in funeral homes, and overall history of embalming were generally similar between deceased case subjects and deceased control subjects (Table 1). Years of birth ranged from 1876 to 1959 and years of death ranged from 1960 to 1986. The study population (n = 485) was predominantly male (n = 244 [92%] of control subjects and n = 209 [95%] of case subjects) and white (n = 235 [89%] of control subjects and n = 198 [90%] of case subjects), and a history of tobacco use was common (n = 207 [78%] of control subjects and n = 176 [80%] of case subjects). Approximately 75% (n = 356) of the 485 study subjects were identified through the NFDA, and most subjects (n = 196 [74%] of control subjects and n = 175 [80%] of case subjects) had attended a school of mortuary science. Most subjects began to work in a funeral home before 1950 when they were aged 28 years or younger, and many had worked in funeral homes beyond age 65 years.

Among the 265 control subjects, interview respondents reported that 55 (21%) did not perform embalmings during their employment in the funeral industry. Compared with those who embalmed, these 55 control subjects were more frequently women (16 [29%] nonembalmers vs n = 5 [2%] embalmers), were older at death (mean age at death, 68.1 vs 63.3 years, respectively), were less frequently smokers (n = 32 [58%] vs n = 175 [83%], respectively), had less often attended mortuary science school (n = 13 [24%] vs n = 183 [87%], respectively), had started working in a funeral home later (mean age, 37.2 vs 25.2 years, respectively), and were older when they last worked in a funeral home (mean age, 63.5 vs 57.2 years, respectively). Among the 220 case subjects, 32 never embalmed, including six (13%) of 48 with brain tumors, 18 (18%) of 99 with lymphohematopoietic malignancies of lymphoid origin, four (8%) of 48 with lymphohematopoietic malignancies of nonlymphoid origin, and one (3%) of 34 with myeloid leukemia. We refer to these subjects who never embalmed as nonexposed. Characteristics of embalming practice and formaldehyde exposure among those who embalmed are shown by study group in Table 2.

Lymphohematopoietic Malignancies of Nonlymphoid Origin

Having ever embalmed was not associated with risk for all lymphohematopoietic malignancies (OR = 1.4, 95% CI = 0.8 to 2.6), but it was associated with a borderline statistically significantly increased risk for lymphohematopoietic malignancies of nonlymphoid origin (OR = 3.0, 95% CI = 1.0 to 9.5, P = .059) (Table 3). Increasing years of embalming practice, compared with having never embalmed, were associated with statistically significantly increasing risks for lymphohematopoietic malignancies of nonlymphoid origin (P for trend = .046; eg, among those who embalmed for more than 20 years, OR = 3.5, 95% CI = 1.1 to 10.9, P = .034, data not shown). As other metrics of formaldehyde exposure increased, risk associated with lymphohematopoietic malignancies of nonlymphoid origin also tended to increase, although not always monotonically, with statistically significant increased risk being associated with the highest levels of exposure for cumulative formaldehyde exposure, 8-hour time-weighted average intensity, and peak exposure. Risk was not associated with increasing number of embalmings during which peaks in the highest category of peak intensity occurred (ie, exceeding 9.3 ppm; data not shown).

In a sensitivity analysis for the association of number of embalmings with lymphohematopoietic malignancies of nonlymphoid origin, we excluded subjects with missing data for 30% or more of their work history, and then compared the results for the highest category of number of embalmings with 27 exposed case subjects after exclusions with the full subject series of 44 exposed case subjects. The risks associated with the number of embalmings tended to be elevated in the sensitivity analysis (OR = 2.3, 95% CI = 0.7 to 7.9, vs OR = 3.9, 95% CI = 1.2 to 12.8; Table 3), although there were fewer exposed subjects in the analysis. For modeled formaldehyde exposure estimates, sensitivity analyses excluding subjects with 30% or more of their work history missing (so that the metric could be computed without imputation) were based on only 16 exposed case subjects. In the sensitivity analysis, risks associated with cumulative formaldehyde exposure tended to be elevated (OR = 2.2, 95% CI = 0.6 to 8.5 vs the full subject series of 44 exposed case patients, OR = 4.0, 95% CI = 1.2 to 13.2) as did those associated with average formaldehyde intensity while embalming

Table 1. Characteristics of the study population by case group*

Characteristic	Control subjects, No. (%)	LHPM			Myeloid leukemia, No. (%)	Brain tumors, No. (%)	Nasopharyngeal cancer, No. (%)
		All†, No. (%)	Lymphoid origin, No. (%)	Nonlymphoid origin, No. (%)			
Total	265 (100)	168 (100)	99 (100)	48 (100)	34 (100)	48 (100)	4 (100)
Year of birth							
1905 or before	65 (25)	43 (26)	24 (24)	13 (27)	9 (26)	8 (17)	1 (25)
After 1905–1913	68 (26)	42 (25)	23 (23)	18 (38)	10 (29)	12 (25)	1 (25)
After 1913–1923	66 (25)	51 (30)	33 (33)	9 (19)	8 (24)	11 (23)	1 (25)
After 1923	66 (25)	32 (19)	19 (19)	8 (17)	7 (21)	17 (35)	1 (25)
Year of death							
1976 or before	66 (25)	46 (27)	26 (26)	15 (31)	12 (35)	15 (31)	0 (0)
After 1976–1979	67 (25)	28 (17)	18 (18)	8 (17)	7 (21)	10 (21)	2 (50)
After 1979–1983	66 (25)	47 (28)	28 (28)	12 (25)	7 (21)	13 (27)	2 (50)
After 1983	66 (25)	47 (28)	27 (27)	13 (27)	8 (24)	10 (21)	0 (0)
Age at death							
≤56 y	66 (25)	28 (17)	15 (15)	9 (19)	8 (24)	18 (38)	1 (25)
>56 to 66 y	66 (25)	48 (29)	36 (36)	7 (15)	5 (15)	14 (29)	1 (25)
>66 to 74 y	67 (25)	50 (30)	25 (25)	19 (40)	14 (41)	10 (21)	1 (25)
>74 y	66 (25)	42 (25)	23 (23)	13 (27)	7 (21)	6 (13)	1 (25)
Mean age, y (SD)	64.3 (14.5)	66.4 (13.1)	66.2 (12.4)	66.7 (14.6)	65.1 (14.6)	60.6 (12.5)	64.6 (12.7)
Sex							
Male	244 (92)	161 (96)	93 (94)	47 (98)	33 (97)	44 (92)	4 (100)
Female	21 (8)	7 (4)	6 (6)	1 (2)	1 (3)	4 (8)	0 (0)
Race							
White	235 (89)	150 (89)	85 (86)	47 (98)	34 (100)	45 (94)	3 (75)
Black	29 (11)	17 (10)	13 (13)	1 (2)	0 (0)	3 (6)	1 (25)
American Indian	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Smoking							
Ever	207 (78)	137 (82)	79 (80)	41 (85)	30 (88)	35 (73)	4 (100)
Never	58 (22)	31 (18)	20 (20)	7 (15)	4 (12)	13 (27)	0 (0)
Data source							
NFDA	189 (71)	130 (77)	75 (76)	37 (77)	24 (71)	33 (69)	4 (100)
New York‡	40 (15)	22 (13)	16 (16)	5 (10)	4 (12)	9 (19)	0 (0)
California§	36 (14)	16 (10)	8 (8)	6 (13)	6 (18)	6 (13)	0 (0)
Attendance of mortuary science school							
Yes	196 (74)	134 (80)	76 (77)	41 (85)	29 (85)	39 (81)	2 (50)
No	49 (18)	26 (15)	19 (19)	5 (10)	3 (9)	5 (10)	2 (50)
Unknown	20 (8)	8 (5)	4 (4)	2 (4)	2 (6)	4 (8)	0 (0)
Time worked in funeral home							
≤16 y	67 (25)	30 (18)	17 (17)	7 (15)	5 (15)	10 (21)	0 (0)
>16 to 30 y	70 (26)	35 (21)	23 (23)	10 (21)	8 (24)	14 (29)	3 (75)
>30 to 41 y	67 (25)	58 (35)	35 (35)	16 (33)	11 (32)	17 (35)	1 (25)
>41 y	61 (23)	45 (27)	24 (24)	15 (31)	10 (29)	7 (15)	0 (0)
Mean, y (SD)	29.1 (15.5)	32.2 (14.6)	31.7 (14.5)	33.9 (14.4)	33.1 (13.4)	28.2 (13.7)	31.3 (6.7)
Calendar year first worked in funeral home‖							
1932 or before	71 (27)	54 (32)	25 (25)	23 (48)	15 (44)	8 (17)	1 (25)
After 1932–1942	60 (23)	52 (31)	33 (33)	14 (29)	11 (32)	13 (27)	0 (0)
After 1942–1952	68 (26)	31 (19)	22 (22)	3 (6)	3 (9)	17 (35)	3 (75)
After 1952	63 (24)	30 (18)	19 (19)	8 (17)	5 (15)	10 (21)	0 (0)
Age first worked in funeral home‖							
≤20 y	65 (25)	39 (23)	15 (15)	18 (38)	12 (35)	16 (33)	0 (0)
>20 to 23 y	66 (25)	37 (22)	19 (19)	14 (29)	12 (35)	10 (21)	1 (25)
>23 to 31 y	66 (25)	57 (34)	41 (41)	9 (19)	6 (18)	12 (25)	2 (50)
>31 y	65 (25)	34 (20)	24 (24)	7 (15)	4 (12)	10 (21)	1 (25)
Mean, y (SD)	27.6 (10.3)	26.7 (8.9)	28.0 (9.1)	24.2 (7.4)	23.3 (5.5)	26.8 (11.7)	28.1 (6.4)

(Table continues)

Table 1 (continued).

Characteristic	Control subjects, No. (%)	LHPM All†, No. (%)	LHPM Lymphoid origin, No. (%)	LHPM Nonlymphoid origin, No. (%)	Myeloid leukemia, No. (%)	Brain tumors, No. (%)	Nasopharyngeal cancer, No. (%)
Age last worked in funeral home‖							
≤51 y	65 (25)	29 (17)	15 (15)	10 (21)	9 (26)	14 (29)	1 (25)
>51 to 61 y	66 (25)	46 (28)	28 (28)	11 (23)	8 (24)	15 (31)	1 (25)
>61 to 68 y	66 (25)	46 (28)	25 (25)	15 (31)	11 (32)	10 (21)	2 (50)
>68 y	65 (25)	46 (28)	31 (31)	12 (25)	6 (18)	9 (19)	0 (0)
Mean, y (SD)	58.4 (14.7)	61.0 (13.1)	61.7 (13.0)	60.0 (14.1)	57.7 (13.7)	56.8 (13.7)	59.0 (8.6)

* LHPM = lymphohematopoietic malignancies; NFDA = National Funeral Directors' Association.

† In addition to LHPM of lymphoid and nonlymphoid origin, this category includes 21 case subjects who died from other types of leukemia (*ICD-8* 207).

‡ New York State Bureau of Funeral Direction.

§ Division of Funeral Directors and Embalmers in the California State Department of Health.

‖ Three control subjects and one death from other or unspecified leukemia had never worked in a funeral home.

(OR = 1.7, 95% CI = 0.4 to 6.9 vs OR = 2.9, 95% CI = 0.8 to 9.7) and for 8-hour time-weighted average formaldehyde intensity (OR = 2.0, 95% CI = 0.4 to 8.9 vs OR = 3.4, 95% CI = 1.0 to 11.8). The risk associated with peak formaldehyde exposure was more strongly attenuated (OR = 1.2, 95% CI = 0.3 to 5.3 vs OR = 3.8, 95% CI = 1.1 to 12.7).

Embalming was most strongly and statistically significantly associated with risk for myeloid leukemia (OR = 11.2, 95% CI = 1.3 to 95.6, P = .027). Statistically significant trends were observed with number of years of embalming (P = .020) and peak formaldehyde exposure (P = .036) (Table 3), although there was no evidence that risks increased with the number of embalmings involving peaks in the highest category of peak intensity (ie, exceeding 9.3 ppm; data not shown). When we compared the 27 case subjects who embalmed 20 or more years with the seven case subjects who embalmed for a shorter period, a statistically significant association between embalming and risk for myeloid leukemia was observed (OR = 4.1, 95% CI = 1.6 to 10.7, P = .004; data not shown). The overall pattern was similar when women were excluded from the analysis or when subjects with more than 30% of their work history unavailable for the metric of interest were excluded, although numbers of subjects were substantially reduced (13–19 vs 33 exposed case subjects, depending on the metric; data not shown). When myeloid leukemia was excluded from the analysis of lymphohematopoietic malignancies of nonlymphoid origin, embalming was not associated with risk for the remaining diseases (ie, monocytic leukemia, polycythemia vera, or myelofibrosis, including 11 exposed case subjects and three nonexposed case subjects; OR = 0.8, 95% CI = 0.2 to 3.3; data not shown).

Because there was only one case subject with myeloid leukemia in the reference group of nonembalmers, we also evaluated risks for this condition by considering subjects who performed fewer than 500 lifetime embalmings (to include five case subjects) as the reference group. With this larger referent, increased risk for myeloid leukemia was associated with high-level exposures of more than 34 years of employment in embalming (OR = 3.9, 95% CI = 1.2 to 12.5, P = .024), more than 3068 embalmings (OR = 3.0, 95% CI = 1.0 to 9.2, P = .057), and more than 9253 ppm-hours of cumulative formaldehyde exposure (OR = 3.1, 95% CI = 1.0 to 9.6, P = .047) (all subjects in these high-level exposure groups had carried out more than 500 embalmings) (Table 4). These represent more conservative but probably more reliable risk estimates for high-level exposure than those shown in Table 3.

Among the 34 deaths from myeloid leukemia, 20 were acute, 12 were chronic, and four (including the one death in the nonexposed group) were unspecified. When the extended reference group of fewer than 500 embalmings (including three case subjects with acute myeloid leukemia in the referent) was used to assess association with acute myeloid leukemia, the strengths of associations between these factors and risk for acute myeloid leukemia were similar to those for all myeloid leukemias combined (Table 4).

Lymphohematopoietic Malignancies of Lymphoid Origin

We found no association between embalming practice or estimated formaldehyde exposure level and risk of lymphohematopoietic malignancies of lymphoid origin (odds ratios in the highest exposure categories ranged from 0.6 to 1.2) (Table 3). Data and goodness of fit were very similar when subjects with more than 30% of their work history details incomplete for the metric of interest were excluded. When ever embalming was compared with never embalming, no associations were observed for non-Hodgkin lymphoma (OR = 0.9, 95% CI = 0.4 to 2.1), multiple myeloma (OR = 1.4, 95% CI = 0.4 to 5.6), and all lymphoma including chronic lymphocytic leukemia (OR = 1.0, 95% CI = 0.5 to 1.9) nor for any of the exposure metrics. Detailed analyses were not feasible for Hodgkin disease, because there were only eight case subjects. However, there was no evidence of an association with ever vs never embalming (OR = 0.5, 95% CI = 0.1 to 2.6) and we observed low average exposure levels among case subjects compared with control subjects for all exposure metrics.

Brain Tumors

Embalming was not statistically significantly associated with risk for brain tumors (OR = 1.9, 95% CI = 0.7 to 5.3), and there was little evidence of increasing risks with increasing number of years in jobs with embalming or with other metrics of exposure (Table 3). Associations were somewhat attenuated when subjects with more than 30% of their work history details incomplete for the metric of

Table 2. Characteristics of embalming practices and formaldehyde exposure among subjects who embalmed by case group*

Characteristic	Control subjects (n = 210; 79%)†	All LHPM‡ (n = 144; 86%)†	LHPM of lymphoid origin (n = 81; 82%)†	LHPM of nonlymphoid origin (n = 44; 92%)†	Myeloid leukemia (n = 33; 97%)†	Brain tumors (n = 42; 88%)†	Nasopharyngeal cancer (n = 2; 50%)†
Questionnaire-based metrics							
Years of working in jobs with embalming § (SD)	26.9 (15.3)	30.4 (14.3)	29.6 (13.8)	31.3 (15.0)	29.7 (14.7)	26.2 (12.9)	29.8 (11.7)
No. of embalmings (SD)	2772 (2650)	2915 (2045)	2778 (1941)	3144 (2128)	2836 (1939)	2388 (2184)	3043 (1051)
Questionnaire- and model-based exposure metrics							
Cumulative formaldehyde exposure, ppm-h ‖ (SD)	8508 (9003)	8986 (7376)	8425 (7384)	10 199 (7966)	9300 (7563)	7814 (9620)	10 164 (5575)
Average formaldehyde intensity while embalming, ppm (SD)	1.7 (0.7)	1.7 (0.6)	1.6 (0.6)	1.8 (0.6)	1.7 (.6)	1.8 (.8)	1.5 (1.0)
TWA8 formaldehyde intensity, ppm (SD)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.1 (0.1)	0.2 (0.2)
Peak formaldehyde exposure, ppm (SD)	8.6 (2.2)	8.4 (2.0)	8.1 (1.8)	8.7 (2.0)	8.6 (2.0)	8.5 (1.8)	10.5 (2.5)

* Data shown are the mean (SD). LHPM = lymphohematopoietic malignancies; TWA8 = 8-hour time-weighted average; ppm = parts per million.

† For each case or control group, data in parentheses are the number of subjects who ever embalmed and percentage of those who ever embalmed of all subjects in that group.

‡ In addition to LHPM of lymphoid and nonlymphoid origin, this category includes 21 case subjects who died from other types of leukemia (*ICD-8* 207).

§ For subjects who ever embalmed. Table 1 shows mean duration in jobs with embalming among all subjects.

‖ If 1950 working hours/year is assumed, then 1 ppm-y corresponds to 1950 ppm-h (ie, 8000, 9000, and 10 000 ppm-h correspond to 4.1, 4.6, and 5.1 ppm-y, respectively).

interest were excluded. Patterns that were similar to those for all brain tumors were observed for the subgroup of malignant brain tumors, which excluded the two subjects with benign tumors (*ICD-8* 225) and the eight subjects who died from brain tumors of unspecified origin (*ICD-8* 238.1).

Nasopharyngeal Cancer

Four case subjects died from nasopharyngeal cancer, but only two had embalmed (OR for ever embalming = 0.1, 95% CI = 0.01 to 1.2). Average exposure levels of the two exposed case subjects with nasopharyngeal cancer were, however, equal to or higher than the corresponding levels among exposed control subjects for most exposure metrics.

Discussion

This study was the first epidemiological investigation, to our knowledge, to relate cancer risk to duration of employment, work practices, and estimated formaldehyde exposure levels in the funeral industry. We observed an association between embalming and death from myeloid leukemia, with the greatest risk among those who practiced embalming for more than 20 years. Deaths from myeloid leukemia were also related to greater estimated formaldehyde exposure, which was based on exposure models. The association was specific to myeloid leukemia, with no evidence for an association with deaths from other lymphohematopoietic malignancies. Other studies have also found a greater than expected number of deaths from lymphohematopoietic malignancies in the funeral industry (3–5,8,11), with the most consistent pattern being observed with cell-type groupings that include myeloid leukemia [(3–5) and as reviewed by Zhang et al. (21)]. Reports (6,9,10) of mortality among pathologists and anatomists also indicated that these groups may have a higher number of deaths from lymphohematopoietic malignancies than expected, but studies among these professional groups also had not considered risks in relation to specific work practices (6,7,9,10,12). Two recent assessments (14,15) of formaldehyde and cancer risk in industrial workers also noted a potential relationship between formaldehyde and death from myeloid leukemia, although this relationship was not observed in another industrial study (22). In our study, the findings for brain cancer are inconclusive, which is consistent with the literature on this topic. A meta-analysis (2) found a statistically significant 50% excess of brain cancer deaths in studies among funeral industry professionals, pathologists, and anatomists; however, none of the large industrial cohort studies in the formaldehyde industry observed such an association (14,22,23).

The biological mechanism of formaldehyde as a leukemogen has not been elucidated. Leukemia develops in pluripotent stem and progenitor cells in the bone marrow (21). Formaldehyde reacts rapidly on contact with upper respiratory tract mucosa, and increased blood levels of formaldehyde have not been reported after the respiratory system has been exposed to formaldehyde (24). Respiratory exposure to formaldehyde is related, however, to lymphocyte genotoxicity and damage to other peripheral blood cells (17), potentially including circulating pluripotent cells in the blood vessels of the highly vascularized tissue of the nasal and olfactory mucosa (21).

Table 3. Associations of embalming, compared with no embalming, and risk for all lymphohematopoietic malignancies (LHPM) (*ICD-8* 200–209; n = 168), LHPM of lymphoid (*International Classification of Diseases, Eighth Revision* [*ICD-8*] 200-204, n = 99) and nonlymphoid origin (*ICD-8* 205, 206, 208 and 209; n = 48), myeloid leukemia (*ICD-8* 205; n = 34), and brain tumors (malignant: *ICD-8* 191 and 192; n = 38; benign: *ICD-8* 225; n = 2; unspecified: *ICD-8* 238.1; n = 8), adjusted for date of birth, age at death, sex, data source, and smoking*

		LHPM									
		All		Lymphoid origin		Nonlymphoid origin		Myeloid leukemia		Brain tumors	
Characteristic	No. of control subjects	No. of case subjects	OR (95% CI)	No. of case subjects	OR (95% CI)	No. of case subjects	OR (95% CI)	No. of case subjects	OR (95% CI)	No. of case subjects	OR (95% CI)
Embalming											
Never	55	24	1.0 (Ref.)	18	1.0 (Ref.)	4	1.0 (Ref.)	1	1.0 (Ref.)	6	1.0 (Ref.)
Ever	210	144	1.4 (0.8 to 2.6)	81	1.1 (0.5 to 2.1)	44	3.0 (1.0 to 9.5)	33	11.2 (1.3 to 95.6)	42	1.9 (0.7 to 5.3)
Questionnaire-based metrics											
Duration of working in jobs with embalming, y											
0	55	24	1.0 (Ref.)	18	1.0 (Ref.)	4	1.0 (Ref.)	1	1.0 (Ref.)	6	1.0 (Ref.)
>0 to 20	71	28	0.8 (0.4 to 1.8)	16	0.7 (0.3 to 1.6)	7	1.4 (0.3 to 6.0)	6	5.0 (0.5 to 51.6)	13	1.5 (0.5 to 5.0)
>20 to 34	69	50	1.5 (0.8 to 2.8)	32	1.2 (0.6 to 2.6)	16	2.1 (0.9 to 11.0)	13	12.9 (1.4 to 117.1)	18	2.4 (0.8 to 7.6)
>34	70	66	1.8 (1.0 to 3.4)	33	1.2 (0.6 to 2.5)	21	3.7 (1.1 to 12.2)	14	13.6 (1.6 to 119.7)	11	1.9 (0.6 to 6.1)
P for trend†			.058 (.131)		.449 (.360)		.046 (.348)		.020 (.588)		.189 (.394)
No. of embalmings											
0	55	24	1.0 (Ref.)	18	1.0 (Ref.)	4	1.0 (Ref.)	1	1.0 (Ref.)	6	1.0 (Ref.)
>0 to 1422	70	29	0.9 (0.6 to 1.8)	17	0.7 (0.3 to 1.6)	8	1.8 (0.5 to 6.9)	7	7.6 (0.8 to 73.5)	17	2.2 (0.7 to 6.6)
>1422 to 3068	70	62	1.9 (1.0 to 3.6)	37	1.5 (0.7 to 3.0)	15	3.0 (0.9 to 10.5)	12	12.7 (1.4 to 116.7)	14	1.9 (0.6 to 6.1)
>3068	70	53	1.5 (0.8 to 2.9)	27	1.0 (0.5 to 2.2)	21	3.9 (1.2 to 12.8)	14	12.7 (1.4 to 112.8)	11	1.5 (0.5 to 5.0)
P for trend†			.477 (.844)		–.963 (–.865)		.247 (.662)		.314 (–.891)		–.960 (–.586)
Questionnaire- and model-based exposure metrics											
Cumulative formaldehyde exposure, ppm-h‡											
0	55	24	1.0 (Ref.)	18	1.0 (Ref.)	4	1.0 (Ref.)	1	1.0 (Ref.)	6	1.0 (Ref.)
>0 to 4058	70	40	1.3 (0.6 to 2.5)	23	0.9 (0.4 to 2.0)	10	2.4 (0.6 to 8.9)	9	10.2 (1.1 to 95.6)	15	1.9 (0.6 to 6.1)
>4058 to 9253	70	49	1.4 (0.8 to 2.8)	33	1.3 (0.6 to 2.8)	12	2.3 (0.7 to 8.2)	10	9.4 (1.0 to 85.7)	17	2.3 (0.7 to 7.2)
>9253	70	55	1.6 (0.8 to 3.0)	25	1.0 (0.4 to 2.0)	22	4.0 (1.2 to 13.2)	14	13.2 (1.5 to 115.4)	10	1.4 (0.4 to 4.7)
P for trend†			.422 (.753)		–.965 (–.912)		.140 (.523)		.192 (.966)		.682 (–.880)

(Table continues)

Table 3 (continued).

Characteristic	No. of control subjects	LHPM						Myeloid leukemia		Brain tumors	
		All		Lymphoid origin		Nonlymphoid origin					
		No. of case subjects	OR (95% CI)	No. of case subjects	OR (95% CI)	No. of case subjects	OR (95% CI)	No. of case subjects	OR (95% CI)	No. of case subjects	OR (95% CI)
Average formaldehyde intensity while embalming, ppm											
0	55	24	1.0 (Ref.)	18	1.0 (Ref.)	4	1.0 (Ref.)	1	1.0 (Ref.)	6	1.0 (Ref.)
>0 to 1.4	70	53	1.6 (0.9 to 3.2)	34	1.4 (0.6 to 2.9)	14	3.0 (0.8 to 10.5)	10	11.1 (1.2 to 106.3)	14	1.7 (0.5 to 5.4)
>1.4 to 1.9	70	47	1.4 (0.7 to 2.7)	26	1.0 (0.5 to 2.2)	15	3.3 (0.9 to 11.6)	13	14.8 (1.6 to 136.9)	11	1.4 (0.4 to 4.7)
>1.9	70	44	1.3 (0.7 to 2.5)	21	0.9 (0.4 to 1.9)	15	2.9 (0.8 to 9.7)	10	9.5 (1.1 to 86.0)	17	2.3 (0.8 to 6.7)
P for trend†			.591 (–.443)		–.598 (–.287)		.096 (–.997)		.058 (–.722)		.163 (.588)
TWA8 formaldehyde intensity, ppm											
0	55	24	1.0 (Ref.)	18	1.0 (Ref.)	4	1.0 (Ref.)	1	1.0 (Ref.)	6	1.0 (Ref.)
>0 to 0.10	70	47	1.3 (0.7 to 2.6)	32	1.2 (0.6 to 2.6)	9	1.8 (0.5 to 6.5)	8	8.4 (0.8 to 79.3)	20	2.7 (0.9 to 8.1)
>0.10 to 0.18	70	52	1.6 (0.8 to 3.1)	25	1.0 (0.5 to 2.1)	20	4.2 (1.2 to 14.3)	13	13.6 (1.5 to 125.8)	12	1.6 (0.5 to 5.2)
>0.18	70	45	1.4 (0.7 to 2.8)	24	1.0 (0.5 to 2.1)	15	3.4 (1.0 to 11.8)	12	12.0 (1.3 to 107.4)	10	1.2 (0.4 to 4.1)
P for trend†			.635 (–.855)		–.766 (–.605)		.256 (.951)		.396 (–.642)		–.567 (–.177)
Peak formaldehyde exposure, ppm											
0	55	24	1.0 (Ref.)	18	1.0 (Ref.)	4	1.0 (Ref.)	1	1.0 (Ref.)	6	1.0 (Ref.)
>0 to 7.0	67	48	1.6 (0.8 to 3.2)	29	1.2 (0.6 to 2.7)	14	3.4 (1.0 to 12.1)	12	15.2 (1.6 to 141.6)	12	1.5 (0.5 to 5.0)
>7.0 to 9.3	72	55	1.6 (0.9 to 3.1)	37	1.5 (0.7 to 3.2)	12	2.2 (0.6 to 7.7)	9	8.0 (0.9 to 74.0)	18	2.3 (0.8 to 7.2)
>9.3	71	41	1.2 (0.6 to 2.3)	15	0.6 (0.2 to 1.3)	18	3.8 (1.1 to 12.7)	12	13.0 (1.4 to 116.9)	12	1.7 (0.5 to 5.3)
P for trend†			.555 (–.302)		–.523 (–.111)		.089 (–.944)		.036 (–.778)		.271 (.936)

* CI = confidence interval; OR = odds ratio; ppm, parts per million; Ref. = referent; minus sign (−) = a negative trend; TWA8 = 8-hour time-weighted average.

† *P* for trend (Wald test) among exposed only in parentheses. All statistical tests were two-sided.

‡ If 1950 working hours/year is assumed, then 1 ppm-y corresponds to 1950 ppm-h (ie, category cut points in ppm-y are 2.1 and 4.7).

Table 4. Associations of embalming, compared with performing fewer than 500 embalmings, and risk for lymphohematopoietic malignancies (LHPMs) of nonlymphoid origin (*International Classification of Diseases, Eighth Revision* [*ICD-8*] 205, 206, 208, and 209; n = 48), myeloid leukemia (*ICD-8* 205; n = 34), and acute myeloid leukemia (*ICD-8* 205.0; n = 20), adjusted for date of birth, age at death, sex, data source, and smoking*

		LHPM of nonlymphoid origin		Myeloid leukemia		Acute myeloid leukemia	
Characteristic	**No. of control subjects**	**No. of case subjects**	**OR† (95% CI)**	**No. of case subjects**	**OR† (95% CI)**	**No. of case subjects**	**OR† (95% CI)**
<500 embalmings	83	9	1.0 (Ref.)	5	1.0 (Ref.)	3	1.0 (Ref.)
			>500 embalmings, questionnaire-based metrics				
Duration of working in jobs with embalming, y							
≤20	47	2	0.3 (0.1 to 1.7)	2	0.5 (0.1 to 2.9)	1	0.4 (0.04 to 4.9)
>20–34	67	16	2.0 (0.8 to 5.0)	13	3.2 (1.0 to 10.1)	8	2.9 (0.7 to 12.2)
>34	68	21	2.6 (1.0 to 6.4)	14	3.9 (1.2 to 12.5)	8	3.1 (0.7 to 13.7)
P for trend‡			.046 (.348)		.020 (.588)		.063 (.612)
No. of embalmings							
≥500 to 1422	42	3	0.6 (0.2 to 2.6)	3	1.2 (0.3–5.5)	0	0 (0–1.8)
>1422 to 3068	70	15	1.8 (0.7 to 4.6)	12	2.9 (0.9 to 9.1)	8	2.9 (0.7 to 12.0)
>3068	70	21	2.3 (1.0 to 5.7)	14	3.0 (1.0 to 9.2)	9	2.9 (0.7 to 11.6)
P for trend‡			.247 (.662)		.314 (–.891)		.492 (0.698)
			Questionnaire- and model-based exposure metrics				
Cumulative formaldehyde exposure, ppm-h§							
≤4058	43	5	1.1 (0.3 to 3.8)	5	2.1 (0.5 to 8.1)	2	1.3 (0.2 to 9.4)
>4058 to 9253	69	12	1.4 (0.5 to 3.7)	10	2.2 (0.7 to 7.1)	6	1.9 (0.4 to 8.2)
>9253	70	22	2.4 (1.0 to 5.8)	14	3.1 (1.0 to 9.6)	9	3.2 (0.8 to 13.1)
P for trend‡			.14 (.523)		.192 (.966)		.284 (.940)
Average formaldehyde intensity while embalming, ppm							
≤1.4	63	13	1.7 (0.7 to 4.5)	10	2.6 (0.8 to 8.7)	6	2.5 (0.6 to 10.9)
>1.4 to 1.9	59	12	1.7 (0.7 to 4.6)	10	2.8 (0.8 to 9.1)	5	2.0 (0.4 to 9.4)
>1.9	60	14	1.8 (0.7 to 4.7)	9	2.3 (0.7 to 7.5)	6	2.3 (0.5 to 10.3)
P for trend‡			.096 (–.997)		.058 (–.722)		.068 (.869)
TWA8 formaldehyde intensity, ppm							
≤0.10	56	9	1.3 (0.5 to 3.6)	8	2.4 (0.7 to 8.2)	3	1.4 (0.3 to 7.8)
>0.10 to .18	61	16	2.1 (0.8 to 5.3)	10	2.6 (0.8 to 8.7)	7	2.6 (0.6 to 11.4)
>0.18	65	14	1.9 (0.7 to 4.8)	11	2.6 (0.8 to 8.3)	7	2.6 (0.6 to 11.3)
P for trend‡			.256 (.951)		.396 (–.642)		.441 (–.672)
Peak formaldehyde exposure, ppm							
≤7.0	54	10	1.6 (0.6 to 4.5)	9	2.9 (0.9 to 9.8)	4	1.8 (0.4 to 9.3)
>7.0 to 9.3	66	12	1.4 (0.5 to 3.7)	9	2.0 (0.6 to 6.6)	5	2.1 (0.5 to 9.2)
>9.3	62	17	2.3 (0.9 to 5.6)	11	2.9 (0.9 to 9.5)	7	2.9 (0.7 to 12.5)
P for trend‡			.089 (–.944)		.036 (–.778)		.035 (.636)

* CI = confidence interval; OR = odds ratio; ppm, parts per million; Ref. = referent; minus sign (–) = a negative trend; TWA8 = 8-hour time-weighted average.

† The comparison group was subjects who performed fewer than 500 embalmings, irrespective of the values of the exposure metrics. All statistical tests were two-sided.

‡ *P* trend (Wald test) among exposed only (ie, subjects who embalmed) in parentheses. Trend tests for LHPM of nonlymphoid origin and myeloid leukemia are the same as those presented in Table 3.

§ If 1950 working hours per year is assumed, then 1 ppm-y corresponds to 1950 ppm-h (ie, category cut points in ppm-y are 2.1 and 4.7).

The associations with death from myeloid leukemia that we observed in our study were unlikely to have been the result of confounding exposures. Our analysis in one relatively homogeneous industry allowed us to compare causes of death of subjects who differed by exposure but were similar with respect to most other important factors. Embalming fluids and other embalming products contain numerous agents in addition to formaldehyde, including isopropanol, ethylene glycol, methanol, phenol, and glutaraldehyde; however, none of these have established leukemogenic properties. In contrast, ionizing radiation, exposure to benzene, and cigarette smoking have been related to risk for myeloid leukemia (25). Although exposure to ionizing radiation may occur during the embalming of corpses containing radioactive isotopes (26), the frequency of such embalmings and the resulting levels of radiation exposure are not likely to be sufficiently great to explain the observed association. Benzene is not used in embalming practice, and two surveys found that benzene could not be detected (18) or was present in only trace amounts (ie, <0.1 ppm) (27).

Finally, smoking was not related to embalming practice or formaldehyde exposure in our study. We adjusted our analyses for tobacco use (ever or never), and almost identical results were found after adjustment for the number of cigarettes per day (data not shown). In addition, the similarity of the findings in this study to those in two industrial cohort studies (14,15) is notable, in that embalmers and industrial workers share high levels of exposure to formaldehyde but have few other workplace exposures in common. We observed relatively similar associations between several exposure metrics and death from myeloid leukemia, including metrics that were not correlated with years of embalming practice or number of embalmings, for example, average formaldehyde intensity while embalming. These independent indicators provide support for the overall association of embalming practice and formaldehyde exposure with increased risk of myeloid leukemia.

Because of the absence of a known mechanism of formaldehyde carcinogenesis, we evaluated several exposure metrics that were derived directly from the questionnaire data (ie, ever embalming, duration of working in jobs with embalming, and number of embalmings) and others that relied on predictions derived from external measurements, and we observed relatively similar associations for myeloid leukemia. In formaldehyde industry–based studies, duration of work in jobs with exposure may not be the best estimate of delivered dose because of the many different jobs and tasks and because of assumptions of constant exposure levels across different jobs over time. In our study, however, the variability in exposure levels was likely to be lower than that in industry-based investigations because we studied only one type of job and therefore the number and type of sources and possible variations are more limited than those in other industries. Thus, duration may better approximate the delivered dose in the funeral industry than in most industry-wide studies. Myeloid leukemia was associated with higher model-derived peak exposure levels of formaldehyde but was not associated with frequency of such exposure, perhaps because of the uncertainty involved in predicting both level and frequency of peak exposures or because of the limited resolution of our peak prediction, with a range of predicted peak formaldehyde concentrations of 3.7–12.3 ppm.

This study has several limitations. Surrogate respondents (ie, next of kin and coworkers) may or may not accurately report exposure-related information, depending on the type of information and type of surrogate (28–33). We addressed this concern by including multiple surrogates (next of kin and coworkers) for each study subject. Indeed, the high concordance rates between multiple respondents for the same subject with respect to the number of years worked in the funeral industry (93%) and the number of these years during which embalming was practiced (86%) increase confidence in the accuracy of these variables. Because we used surrogates for both case and control subjects, exposure misclassification was likely to be nondifferential, so that any resulting bias would be toward the null and thus would tend to underestimate risk. In addition, if any systematic positive bias were to occur, it would be expected to affect all cancer types equally. Therefore, the specificity of the association with myeloid leukemia but not with other leukemias was noteworthy.

Under the assumption that formaldehyde exposure is causally linked with myeloid leukemia death, one might have expected stronger associations for the formaldehyde exposure metrics than for duration of embalming. However, the uncertainty in estimating the lifetime formaldehyde exposure may have attenuated estimated risks, despite the prediction model that explained a large fraction of the variation in measured formaldehyde concentrations during embalmings that were performed at various times and by following various protocols. In this context, trend tests that were based on categories were less influenced by extreme values of exposure metrics than those that were based on continuous values, which was the method that we selected a priori. For example, category-specific associations between exposure and death from myeloid leukemia (eg, 8-hour time-weighted average intensity) were statistically significant if ordinal scores (1, 2, 3, and 4) were used as a continuous variable (P for trend = .021) but not if continuous exposure was used (P for trend = .396) (Table 3) (trend tests that were based on ordinal scores gave P = .012 for number of embalmings and P = .023 for cumulative formaldehyde exposure; data not shown). The observation that associations between formaldehyde exposure metrics and myeloid leukemia were generally similar to those for duration of embalming or number of embalmings supports the possibility that formaldehyde may be involved in the greater than expected number of deaths from myeloid leukemia among embalmers.

A major limitation of our study is the relatively small number of deaths from myeloid leukemia, although the numbers of case subjects with myeloid leukemia were roughly similar in our study (n = 34) and in the largest industrial cohort (n = 48) (15). To address small numbers for myeloid leukemia, we carried out additional analyses that combined never and low-frequency embalmers as a referent group and found results that were similar to those in the main analysis. There were also considerable missing exposure data requiring imputation and, when subjects whose work history was more than 30% incomplete were excluded, the strength of the associations decreased. However, because the missing data did not differ substantially between case and control subjects, we believe this decrease can be attributed to smaller numbers of subjects and to chance. The strongest associations were with ever embalming and number of years of embalming, the variables in which we have the most confidence.

Our study also has some unique strengths compared with other studies of formaldehyde exposure (14,15,22). In industrial cohort studies (15,22), exposure is usually assessed for thousands of different job types, and every subject is assigned the same exposure for a given period and job. These studies often rely on aggregated information for plants and departments to estimate job-specific exposure levels and so measurement data, particularly historical data, are limited. In contrast, we studied only one exposed job type (embalming) and individual exposure levels were estimated by use of study subject–specific information from questionnaires combined with statistical models that were based on high-quality measurement data.

This study adds supporting and complementary data to other epidemiological evidence of an association between formaldehyde exposure and risk of myeloid leukemia. When we compared this study in the funeral industry with the National Cancer Institute cohort study of formaldehyde industries (15), we found that funeral home workers who embalm tended to have longer duration of formaldehyde exposure and

higher cumulative levels of formaldehyde exposure but lower 8-hour time-weighted average intensity. Peak exposure levels of greater than 4 ppm, the lower bound of the highest exposure category in the analysis of the industrial cohort study, appear to be more common among embalmers (ie, 77% of control subjects) than among industrial workers (ie, 25% of workers). Our study assessed work in the funeral industry approximately through the early 1980s and so the work patterns and estimated exposure levels of deceased control subjects may not be entirely representative of current practice in the funeral industry. However, the average estimated formaldehyde intensity while embalming among control subjects (1.7 ppm, SD = 0.7 ppm; Table 2) was generally consistent with levels that were reported previously (17) in limited surveys of funeral homes, which tend to show average exposure levels in the range of 1 ppm.

The absolute impact of exposure to formaldehyde on death from myeloid leukemia in the general population is difficult to assess on the basis of data in this study, which are not population based. However, if formaldehyde exposure is causally related to myeloid leukemia, then from the best linear approximation of the exposure–response relationship in this study, US-wide formaldehyde exposure at an equivalence of a decade of employment in an embalming job would roughly increase the age-adjusted mortality from myeloid leukemia in the United States (ie, 3.4 deaths per 100 000 person-years [34]) by approximately 36% (ie, by 1.2 more deaths from myeloid leukemia per 100 000 person-years). Within the limits of this quantitative exposure assessment, the number of additional deaths from myeloid leukemia associated with an additional average formaldehyde intensity of 1 ppm would be 1.7 per 100 000 person-years. Because of the case–control design of this study and the limitations discussed above, these exposure estimates should be used with caution in quantitative risk estimation.

In summary, this is the first study, to our knowledge, to specifically relate number of years of embalming practice and related formaldehyde exposures in the funeral industry to mortality from myeloid leukemia. No associations were observed with other lymphohematopoietic malignancies, and associations with brain cancer were unclear. Further studies of leukemia risk in relation to specific embalming practices and exposures, as well as similar specific exposure studies in other professional groups that are exposed to formaldehyde and that have an increased risk of leukemia (ie, anatomists and pathologists), should help to clarify our understanding of cancer risks related to formaldehyde. This study adds to the accumulating evidence from studies of industrial workers that increased exposure to formaldehyde is associated with increased risk of myeloid leukemia.

References

1. Occupational Safety & Health Administration. *Occupational Exposure to Formaldehyde. Fact Sheet 95–27.* Washington, DC: US Department of Labor; 1995. http://www.medgasexperts.com/docs/01-01-1995%20-%20Occupational%20Exposure%20to%20Formaldehyde.htm. Accessed October 26, 2009.
2. Blair A, Saracci R, Stewart PA, Hayes RB, Shy C. Epidemiologic evidence on the relationship between formaldehyde exposure and cancer. *Scand J Work Environ Health.* 1990;16(6):381–393.
3. Hayes RB, Blair A, Stewart PA, Herrick RF, Mahar H. Mortality of U.S. embalmers and funeral directors. *Am J Ind Med.* 1990;18(6):641–652.
4. Walrath J, Fraumeni JF Jr. Mortality patterns among embalmers. *Int J Cancer.* 1983;31(4):407–411.
5. Walrath J, Fraumeni JF Jr. Cancer and other causes of death among embalmers. *Cancer Res.* 1984;44(10):4638–4641.
6. Stroup NE, Blair A, Erikson GE. Brain cancer and other causes of death in anatomists. *J Natl Cancer Inst.* 1986;77(6):1217–1224.
7. Harrington JM, Shannon HS. Mortality study of pathologists and medical laboratory technicians. *Br Med J.* 1975;4(5992):329–332.
8. Milham S Jr. *Occupational Mortality in Washington State 1950–1979. Technical Report 83-116.* Cincinnati, OH: National Institute of Occupational Safety and Health; 1983.
9. Hall A, Harrington JM, Aw TC. Mortality study of British pathologists. *Am J Ind Med.* 1991;20(1):83–89.
10. Matanoski GM. *Risk of Pathologists Exposed to Formaldehyde. Technical Report NTIS/PB91-173682.* Springfield, VA: National Technical Information Service; 1991.
11. Levine RJ, Andjelkovich DA, Shaw LK. The mortality of Ontario undertakers and a review of formaldehyde-related mortality studies. *J Occup Med.* 1984;26(10):740–746.
12. Harrington JM, Oakes D. Mortality study of British pathologists 1974–80. *Br J Ind Med.* 1984;41(2):188–191.
13. Bertazzi PA, Pesatori A, Guercilena S, Consonni D, Zocchetti C. Carcinogenic risk for resin producers exposed to formaldehyde: extension of follow-up [in Italian]. *Med Lav.* 1989;80(2):111–122.
14. Pinkerton LE, Hein MJ, Stayner LT. Mortality among a cohort of garment workers exposed to formaldehyde: an update. *Occup Environ Med.* 2004;61(3):193–200.
15. Beane Freeman LE, Blair A, Lubin JH, et al. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: update of the NCI cohort. *J Natl Cancer Inst.* 2009;101(10):751–761.
16. Cogliano V, Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F. Advice on formaldehyde and glycol ethers. *Lancet Oncol.* 2004(9);5:528.
17. International Agency for Research on Cancer. *Formaldehyde, 2-Butoxyethanol and Propylene Glycol Mono-t-Butyl Ether.* Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 88. Lyon, France: World Health Organization; 2006.
18. Stewart PA, Herrick RF, Feigley CE, et al. Study design for assessing exposures of embalmers for a case-control study. Part I. Monitoring results. *Appl Occup Environ Hyg.* 1992;7(8):532–540.
19. Hornung RW, Herrick RF, Stewart PA, et al. An experimental design approach to retrospective exposure assessment. *Am Ind Hyg Assoc J.* 1996;57(3):251–256.
20. Hastie TJ, Tibshirani RJ. *Generalized Additive Models.* New York, NY: Chapman and Hall; 1990.
21. Zhang L, Steinmaus C, Eastmond DA, Xin XK, Smith MT. Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. *Mutat Res.* 2009;681(2–3):150–168.
22. Coggon D, Harris EC, Poole J, Palmer KT. Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. *J Natl Cancer Inst.* 2003;95(21):1608–1615.
23. Hauptmann M, Lubin JH, Hayes RB, Stewart P, Blair A. Mortality from solid cancers among workers in formaldehyde industries. *Am J Epidemiol.* 2004;159(12):1117–1130.
24. Heck H, Casanova M. The implausibility of leukemia induction by formaldehyde: a critical review of the biological evidence on distant-site toxicity. *Regul Toxicol Pharmacol.* 2004;40(2):92–106.
25. Linet MS, Devesa SS, Morgan GJ. The leukemias. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention. Chapter 44.* Third edition. New York, NY: Oxford University Press; 2006:841–871.
26. Laughlin JS, Vacirca SJ, Duplissey JF. Exposure of embalmers and physicians by radioactive cadavers. *Health Phys.* 1968;15(5):451–455.
27. Williams TM, Levine RJ, Blunden PB. Exposure of embalmers to formaldehyde and other chemicals. *Am Ind Hyg Assoc J.* 1984;45(3):172–176.
28. Hansen KS. Validity of occupational exposure and smoking data obtained from surviving spouses and colleagues. *Am J Ind Med.* 1996;30(4):392–397.
29. Lerchen ML, Samet JM. An assessment of the validity of questionnaire responses provided by a surviving spouse. *Am J Epidemiol.* 1986;123(3):481–489.

30. Fryzek JP, Lipworth LL, Garabrant DH, McLaughlin JK. Comparison of surrogate with self-respondents for occupational factors. *J Occup Environ Med.* 2000;42(4):424–429.
31. Brown LM, Dosemeci M, Blair A, Burmeister L. Comparability of data obtained from farmers and surrogate respondents on use of agricultural pesticides. *Am J Epidemiol.* 1991;134(4):348–355.
32. Wang FL, Semchuk KM, Love EJ. Reliability of environmental and occupational exposure data provided by surrogate respondents in a case-control study of Parkinson's disease. *J Clin Epidemiol.* 1994;47(7):797–807.
33. Blair A, Kross B, Stewart PA, et al. Comparability of information on pesticide use obtained from farmers and their proxy respondents. *J Agric Safety Health.* 1995;1(3):165–176.
34. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Mortality—All COD, Aggregated With State, Total U.S. (1969–2005), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2008. Underlying mortality data provided by NCHS (www.cdc.gov/nchs).

Funding

Intramural Research Program of the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

Notes

The funding agency did not have any role in the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the article for publication, and the writing of the article.

We thank Drs Michael Thun, Elizabeth Fontham, and Noah Seixas for their review and helpful comments.

Manuscript received May 19, 2009; revised October 10, 2009; accepted October 13, 2009.