ELSEVIER

Mortality Patterns among Workers in a US Pharmaceutical Production Plant

GARY M. MARSH, PHD, ADA O. YOUK, PHD, NURTAN A. ESMEN, PHD, AND JEANINE M. BUCHANICH, MPH

PURPOSE: To examine mortality among workers in a pharmaceutical production plant and to address community concerns about 1980 to 1990 increases in local county cancer mortality rates.
METHODS: Subjects were 1999 workers with some full-time employment during the period between 1970 and 1996. We identified deaths through the year 2000 and reconstructed exposures to nine chemical agents with available exposure measurements. Data analyses included standardized mortality ratios (SMRs) and time trends in local cancer mortality rates.
RESULTS: We observed deficits in deaths from all causes combined, all cancers combined, and most cause of death categories examined. Male workers with potential plant exposure had excesses in deaths from all lymphatic-hematopoietic tissue cancers (LHTC), in particular non-Hodgkin's lymphoma (NHL), and respiratory system cancers (RSC) that were larger among long-term workers, but the pattern of findings suggested the excesses were probably not related to occupational factors at the plant. The increase in local county cancer mortality rates was simply the upward cycle of a periodic trend that peaked in 1990 and returned to 1980 levels in 2000.
CONCLUSIONS: With the possible exceptions of LHTC, in particular NHL, and RSC, this study provided no evidence of elevated total or cause-specific cohort mortality risks. It does not appear that plant factors played a role in the 1980 to 1990 increases in local county cancer mortality rates.
Ann Epidemiol 2005;15:112–122.

KEY WORDS: Pharmaceutical Production, Cohort Study, Mortality, Lymphatic and Hematopoietic Tissue Cancers, Non-Hodgkin's Lymphoma, Respiratory System Cancer.

INTRODUCTION

In the early 1990s, residents of a rural US county discovered that their cancer mortality rates had increased markedly between 1980 and 1990. This generated community concerns that the increases may be linked to local environmental or occupational factors, including the possibility of potential environmental exposures from a large pharmaceutical production plant that began operations in the county in 1970. A variety of human and animal health products are made at the site, including antibiotics. Workers are involved with myriad chemical and biological substances, although most are not known to be associated with adverse human health effects. While some concerns existed about exposures to certain solvents and chlorine compounds, these agents have been routinely monitored to assure compliance with regulatory levels.

The community concerns prompted company management to support a historical cohort mortality study of its workforce to determine whether plant exposures may have played a role in the increased countywide cancer mortality rates. In 1995, the company commissioned us to design and conduct the study. We have since traced the cohort for deaths through 1996, 1998, and 2000. We report here results of the 2000 follow-up and an updated time trend analysis of local county cancer mortality rates.

METHODS

Historical Exposure Assessment

Given the investigation's exploratory nature, no *a priori* hypotheses were formulated about specific exposure–response relationships. Instead, we developed individual worker-level, multi-exposure profiles for all plant exposure agents with available air monitoring data (acetone, aceto-nitrile, di-methyl formamide, ethyl acetate, ethylene di-chloride, isopropyl alcohol, methlyene chloride, tri-chloroethane, and toluene) (1, 2). We found none of the exposures excessive by 1997 exposure guidelines (Threshold Limit Values [TLV 7]). The largest maximum average exposure was estimated for aceto-nitrile, which was only about 70% of the TLV. None of these agents has a known

From the Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA (G.M.M., A.O.Y., J.M.B.); and Department of Occupational and Environmental Health, School of Public Health, University of Illinois at Chicago, Chicago, IL (N.A.E.).
Address correspondence to: Gary M. Marsh, Ph.D., Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261. Tel.: (412) 624-3032; Fax: (412) 624-9969. E-mail: gmarsh@pitt.edu
Received January 5, 2003; accepted May 28, 2004.

360 Park Avenue South, New York, NY 10010
1047-2797/05/$–see front matter
doi:10.1016/j.annepidem.2004.05.010

Selected Abbreviations and Acronyms

CI = confidence interval
ICD = International Classification of Diseases
LHTC = lymphatic-hematopoietic tissue cancer
M = minimally exposed
MPDS = mortality and population data system
NHL = Non-Hodgkin's lymphoma
NOS = not otherwise specified
OCMAP = Occupational Cohort Mortality Analysis Program
PPE = personal protection equipment
RSC = respiratory system cancer
SMR = standardized mortality ratio
TLV = threshold limit value

carcinogenic effect, and only two, methylene chloride and ethylene dichloride, are confirmed animal carcinogens with unknown relevance to humans. Among the plant agents with no air monitoring data was benzene, a known human carcinogen. However, benzene use was very brief, lasting less than 2 years between 1970 and 1972. In 1972 all benzene use was replaced by toluene. Considering that the maximum toluene exposure measurement was less than 20% of the TLV, benzene exposure was considered to be insignificant.

Both quantitative and qualitative job- and department-specific exposure estimates were possible for acetone, dimethyl formamide, methylene chloride, and toluene. For the remaining agents, exposures were limited to qualitative (duration of exposure) estimates. To minimize uncertainties in exposure reconstruction, only personal sampling data were used. By convention, if exposure to a particular agent was below detection level for 75% of the samples taken, or if exposures were less than 5 to 10 percent of the current TLV exposure guideline, then the exposure was deemed minimal (M). Exposure estimation was based on 3488 generally multi-compound, personal samples of sufficiently long duration to be considered to represent a time-weighted average estimate of exposure. These samples spanned about 12 years (1979–1991) and there was no time trend in the indicated exposure levels. This was verified by cross validation. We also compared the measurements to a professional practice guideline as an independent check on the assumption of constant exposure level. Since the exposures were sufficiently low, control measures and extensive exposure reduction effort would not be expected. In fact, only occasional personal protective equipment use was noted. In conjunction with the low exposures, it was decided not to correct for personal protection equipment (PPE) use extensively.

Although the throughput, product, and by-product list of chemicals that were used in production quantities contained more than 50 chemicals, only 16 chemicals had some exposure measurements and out of this number only nine had enough measurements that could be used in exposure reconstruction. At least in one of the buildings, all exposure measurements were moderately to severely left censored; but exposures to methylene chloride (5–67%), acetonitrile (14–74%), and acetone (18–50%) could be estimated with some confidence. The exposure to "product dust" was measured in one of the buildings, but the results were 98% left censored and a meaningful exposure assessment was not possible. The exposure distribution was assumed to be best represented by lognormal distribution and the distribution parameters were calculated by regression and or maximum likelihood estimators as appropriate when the censoring level was less than 70%. Characteristics of the sampling data used in the exposure estimation are provided in the Appendix.

Using exposure estimates linked to individual work histories, we constructed three summary exposure indices for individual workers: duration of exposure, average intensity of exposure, and cumulative exposure. For the duration of exposure measure, we assigned the value M = 0.1 to minimally exposed jobs; for the average intensity and cumulative exposure measures we assigned the value M = 0. All exposure measures were computed through 1996, the last date for which complete work histories were available for all subjects. Table 1 shows the number of workers exposed and the corresponding mean and median estimated exposure values for each of the nine agents studied. Because the job-specific exposure levels to two pairs of agents were highly correlated (aceto-nitrile/ethylene dichloride and ethyl acetate/tri-chloroethane), we considered these in the analysis as two "joint" agents rather than four individual agents.

Study Population

The study cohort included all workers with some full-time employment history at the plant from start-up in May 1970 through the end of 1996. The study population was enumerated from various computerized employee databases and by manual review of hard copy personnel records. We verified the completeness of the cohort by cross-checking names among the various data sources. Because the cohort includes administrative and support staff with no potential for chemical exposures in plant production areas, we dichotomized the cohort into those with and without potential plant exposure. The latter group comprised subjects whose work history contained only jobs with a *measured* exposure value of zero for each of the nine characterized chemical agents. While some workers in the no potential plant exposure group may have had brief or intermittent exposures to some characterized agents, or to other substances in the ambient plant environment, these exposures would have been exceedingly low and would have had negligible impact on mortality risks. Likewise, some workers in the potential plant exposure group may have had brief, intermittent exposures to other substances.

The cohort includes 1999 subjects, including 1346 with potential plant exposure (Table 2). White males comprise

TABLE 1. Estimated worker exposures to nine chemical agents, male workers, 1970–1996

Chemical agent	Workers exposed	Summary statistic	Exposure metric[a,b]		
			Duration of exposure (years)	Cumulative exposure (ppm-years)	Average intensity of exposure (ppm)
Quantitatively-estimated exposure agents (M = 0)					
Acetone	193	Median	0	0	0
		Mean	0.34	20.83	8.14
Di-methyl formamide	533	Median	0	0	0
		Mean	2.41	6.58	1.00
Methylene chloride	468	Median	0	0	0
		Mean	1.57	26.40	5.45
Toluene	368	Median	0	0	0
		Mean	0.78	7.42	1.74
Qualitatively-estimated exposure agents (M = 0.1)					
Aceto-nitrile	802	Median	0.07		
		Mean	0.44		
Ethyl acetate	861	Median	0.15		
		Mean	0.47		
Ethylene di-chloride	805	Median	0.07		
		Mean	0.44		
Isopropyl alcohol	849	Median	0.14		
		Mean	0.48		
Tri-chlorethane	861	Median	0.15		
		Mean	0.47		

[a]Based on individual work histories, computed from date of first exposure to last exposure, death, or end of 1996.
[b]M denotes value used for minimally exposed jobs.

about three-fourths of this group. More than 80% of the potentially exposed group worked 5 or more years and for 55.6% of the cohort, 20 or more years had elapsed since first employment.

Vital Status Tracing and Cause of Death Ascertainment

We used our standard protocol (3, 4) to trace study members for deaths through 2000. Underlying cause of death codes were obtained from the National Death Index Plus system or from death certificates obtained from state health departments. Death certificates were coded to the underlying cause of death by a nosologist using the *International Classification of Diseases* (ICD) rules in effect at time of death. Table 2 shows that 112 or 5.6% of the total cohort was identified as deceased and cause of death was obtained for 110 or 98.2%.

Statistical Analysis

We examined mortality among the cohort from plant start-up in May 1970 through 2000. Person-years were jointly classified by race, sex, age, and time period using the modified life table procedure of the Occupational Cohort Mortality Analysis Program (OCMAP-Plus) (5). Expected numbers of deaths were computed using as standard populations the total US and the local seven-county regional area from which this workforce was largely drawn. Mortality rates were obtained from the Mortality and Population Data System (MPDS) maintained at the University of Pittsburgh (6). Mortality excesses and deficits were expressed as standardized mortality ratios (SMRs) along with their 95% confidence intervals (CI) (7). Certain subgroup analyses were limited to male workers, as only 13 deaths (4 cancers) occurred among female workers (data not shown). To account for geographical variability, SMR analyses focused primarily on the local comparisons. No formal adjustments were made for the many statistical comparisons performed.

RESULTS

Total and Cause-specific Mortality among the Total Cohort

We observed a total of 112 deaths, yielding statistically significant ($p < .01$) 33% and 36% deficits in total mortality compared with the US and local county populations, respectively (Table 3). Overall mortality deficits were also observed for the cause of death categories: all malignant neoplasms, diabetes, cerebrovascular disease, all heart disease, nonmalignant respiratory disease, cirrhosis of liver,

TABLE 2. Selected characteristics of the study cohort by potential plant exposure[a]

	No potential plant exposure		Potential plant exposure		Total cohort	
Characteristic	No.	%	No.	%	No.	%
Persons at risk (1970–1996)	653	100.0	1346	100.0	1999	100.0
Person-years (1970–2000)	11,285	100.0	26,718	100.0	38,003	100.0
Race-gender						
White-male	368	56.3	980	72.8	1348	67.4
Nonwhite-male	31	4.8	87	6.5	118	5.9
White-female	223	34.1	246	18.3	469	23.5
Nonwhite-female	31	4.8	33	2.4	64	3.2
Year of birth						
< 1940	92	14.1	213	15.8	305	15.2
1940–49	123	18.8	442	32.9	565	28.3
1950–59	231	35.4	493	36.6	724	36.2
1960 +	207	31.7	198	14.7	405	20.3
Age at hire						
< 20	23	3.5	66	4.9	89	4.5
20–39	557	85.3	1101	81.8	1658	82.9
40 +	73	11.2	179	13.3	252	12.6
Year of hire						
1970–1979	242	37.1	729	54.2	971	48.6
1980–1989	183	28.0	322	23.9	505	25.3
1990–1996	228	34.9	295	21.9	523	26.1
Vital status (12/31/00)						
Alive	630	96.5	1257	93.4	1887	94.4
Deceased	23	3.5	89	6.6	112	5.6
With death certificate	23	(100.0)	87	(97.8)	110	(98.2)
Without death certificate	0	(0.0)	2	(2.2)	2	(1.8)
Employment type						
Full-time employees only	628	96.2	1290	95.8	1918	95.9
Mixed employment[b]	25	3.8	56	4.2	81	4.1
Duration of employment						
< 1 year	53	8.1	71	5.3	124	6.2
1–4	154	23.6	115	8.5	269	13.5
5–9	195	29.9	383	28.5	578	28.9
10–19	157	24.0	467	34.7	624	31.2
20 +	94	14.4	310	23.0	404	20.2
Time since first employment						
< 10 years	160	24.5	185	13.7	345	17.2
10–19	230	35.2	413	30.7	643	32.2
20 +	263	40.3	748	55.6	1011	50.6

[a]Persons with potential plant exposure had some non-zero exposure to at least one of the nine characterized chemical agents.
[b]Includes workers with both full-time and summer/co-op work experience.

nephritis and nephrosis, and all external causes of death. Some of these deficits are statistically significant. SMRs for all cancer mortality were slightly lower based on the local rates, reflecting the higher general population rates for cancer overall in the regional area. The higher overall regional cancer rates are due largely to respiratory system cancer (RSC), which includes 15 of 37 total cancer deaths. All 15 RSC deaths were due to cancer of the bronchus, trachea, or lung. RSC SMRs reduce from 104 to 85 when going from US to local county rates.

We observed nine deaths from lymphatic and hematopoietic tissue cancer (LHTC) resulting in not statistically significant, near 2-fold excesses based on both comparison populations. All cases were white males. Four of these cases were coded as "malignant lymphoma-NOS" (non-Hodgkin's lymphoma [NHL]) (ICD9: 202.8, ICD10: C859), one as "Hodgkin's Disease – unspecified" (ICD9: 201.9), two as "acute myeloid leukemia" (ICD10: C920), one as "acute lymphoblastic leukemia-NOS" (ICD10: C910) and one as "multiple myeloma" (ICD9: 203.0). The four NHL deaths resulted in not statistically significant 2.13-fold and 1.96-fold excesses based on the US and local county rates, respectively. Similar excesses were observed for the other LHTC subcategories examined. Several mortality excesses and deficits were observed for the other cancer sites examined, although most of these are based on only one or two observed deaths and are not statistically significant.

TABLE 3. Observed (Obs) deaths and SMRs for selected causes of death: Total study cohort, US, and local county comparisons, 1970–2000

Cause of Death (9th Revision ICD Codes)	Obs	US		Local County	
		SMR	95% CI	SMR	95% CI
All Causes of Death (001–999)	112	67**	56–81	64**	53–77
All Cancer (140–208)	37	87	62–120	80	56–110
Digestive Organs and Peritoneum (150–159)	5	52	17–121	50	16–117
Esophagus (150)	2	157	19–568	169	20–611
Large Intestine (153)	1	64	8–230	48	6–173
Pancreas (157)	1	50	1–280	53	1–296
Respiratory System (160–165)	15	104	58–171	85	48–141
Bronchus, Trachea, Lung (162)	15	108	61–179	89	50–146
Breast (174, 175)	1	61	1–342	60	2–337
Other Female Genital (183–184)	1	255	6–1420	195	5–1087
Prostate (Males Only) (185)	2	136	17–493	185	22–668
Kidney (189.0, 189.1, 189.2)	1	86	2–480	70	2–392
Central Nervous System (191, 192)	1	59	2–326	65	2–361
Thyroid (193, 194)	1	644	16–3591	714	18–3977
Lymphatic-Hematopoietic Tissue (200–208)	9	198	91–376	186	85–354
Hodgkin's Disease (201)	1	299	8–1668	279	7–1556
Non-Hodgkin's Lymphoma (200,202.0,202.1,202.8,202.9)	4	213	58–545	196	53–501
Leukemia and Aleukemia (204–208)	3	179	37–524	184	38–538
All Other Lymphopoietic Tissue (202.2,202.3,202.4,202.5,202.6,203)	1	152	4–848	139	4–501
Diabetes (250)	1	28	1–155	25	1–140
Cerebrovascular Disease (430–438)	3	54	11–156	43	9–125
All Heart Disease (390–398,402,404,410–429)	26	59**	39–86	50**	33–74
Ischemic Heart Disease (410–414)	18	58*	34–92	45**	27–71
Nonmalignant Respiratory Disease (460–519)	4	48	13–122	40	11–102
Bronchitis, Emphysema, Asthma (490–493)	2	98	12–354	75	9–272
Cirrhosis of Liver (571)	1	18	1–101	26	1–146
Nephritis and Nephrosis (580–589)	1	94	2–526	79	2–440
All External Causes of Death (E800–999)	24	79	51–118	80	57–119
Accidents (E800–949)	19	111	67–173	106	64–166
Motor Vehicle Accidents (E810–825)	14	154	84–259	138	75–231
Suicides (E950–959)	5	65	21–152	57	19–134
Unknown Causes (in All Causes category only)	2				

*p < .05.
**p < .01.

Total and Cause-specific Mortality by Potential Plant Exposure

For cause of death categories with at least five observed deaths (full detail shown for LHTC and NHL only), Table 4 compares local rate-based SMRs for workers with and without potential plant exposure. SMRs for all causes and all cancers are higher among workers with potential plant exposure but remain well below 100. Eleven of the 15 RSC deaths and seven of the nine LHTC deaths were among workers with potential plant exposure, with respective SMRs that were identical (RSC SMRs of 85) and slightly higher (LHTC SMRs of 206 vs. 186) than among the total cohort. All four deaths due to NHL were among workers with potential plant exposure resulting in a not statistically significant SMR of 279 (vs. 196 for total cohort). Two of the LHTC deaths were observed among workers with no potential plant exposure yielding a not statistically significant SMR of 142.

Study-factor-specific SMRs for Male Workers with Potential Plant Exposure

For all causes of death combined, Table 5 shows deficits in deaths at each level of each study factor considered and many are statistically significant. The increase in SMRs across levels of time since first employment and decrease across levels of year of hire probably reflect the gradual diminution in the "healthy worker effect" as the cohort ages. For all cancers combined, we observed deficits in deaths for most levels of each study factor. SMRs increase with increasing levels of duration of employment and the time since first employment, reaching small, not statistically significant 11 to 16 percent excesses in the highest categories (20 + years). Most of the cancer deaths in the highest duration of employment and time since first employment categories were due to RSC or LHTC.

We observed moderate, not statistically significant 24 to 58 percent excesses in RSC mortality among workers in

TABLE 4. Observed (Obs) deaths and SMRs for selected causes of death: Total study cohort, local county comparisons, 1970–2000, by potential plant exposure[a]

	No Potential Plant Exposure			Potential Plant Exposure		
Cause of Death	Obs	SMR	95% CI	Obs	SMR	95% CI
All Causes of Death	23	46*	29–68	89	71**	57–87
All Cancer	10	71	34–131	27	82	54–119
Digestive Organs and Peritoneum	1	35	1–197	4	57	16–145
Respiratory System	4	78	21–200	11	85	42–152
Bronchus, Trachea, Lung	4	81	22–208	11	88	44–158
Lymphatic-Hematopoietic Tissue	2	142	17–514	7	206	83–426
Hodgkin's Disease	0	–	0–3417	1	357	9–1990
Non-Hodgkin's Lymphoma	0	–	0–606	4	279	76–714
Leukemia and Aleukemia	1	207	5–1154	2	172	21–622
All Other Lymphopoietic Tissue	1	482	12–2688	0	–	0–718
All Heart Disease	5	34**	11–79	21	56**	34–85
Ischemic Heart Disease	5	44	14–102	13	44**	24–76
All External Causes of Death	5	63	20–146	19	86	52–135
Accidents	3	64	13–186	16	122	70–199
Motor Vehicle Accidents	2	74	9–265	12	163	84–285
Suicides	2	87	11–314	3	47	10–138
Unknown Causes (In All Causes only)	0			2		

[a]Persons with potential plant exposure had some non-zero exposure to at least one of the nine characterized chemical agents.
*$p < .05$.
**$p < .01$.

three time-correlated subcategories: hired over the age of 40 years (SMR, 124), employed for 20 or more years (SMR, 158) or followed for 20 or more years (SMR, 125). For LHTC, we observed a not statistically significant 2.27-fold overall excess in deaths (7 deaths, SMR, 227; 95% CI, 91–468). Large, statistically significant, 2.69–4.66-fold excesses in deaths were observed for many time-correlated subcategories examined including: age at hire 40 + years (4 deaths, SMR, 386; 95% CI, 105–988), time period 1990 to 2000 (7 deaths, SMR, 269; 95% CI, 108–554), year of hire 1970 to 1979 (7 deaths, SMR, 331; 95% CI, 133–682), duration of employment 10 to 19 years (5 deaths, SMR, 386; 95% CI, 126–902), and time since first employment 20+ years (6 deaths, SMR, 466; 95% CI, 171–1014). A similar pattern of SMRs was observed for NHL, although most corresponding, factor-specific SMRs were considerably higher than those for LHTC combined.

SMRs in Relation to Occupational Exposure for All Male Workers

For each agent, we constructed an unexposed category and one or two non-zero exposure categories, with the non-zero categories formed to most evenly distribute the number of total cancer deaths (to best balance the precision of the category-specific SMRs). Workers with no potential plant exposure are included in the baseline categories to increase the precision of those risk estimates. For quantitatively-estimated exposure agents, Table 6 shows that most deaths from all cancers combined were observed among workers in the unexposed categories. For all exposure agents, category-specific SMRs were generally less than 100. Some slight to moderate, not statistically significant excesses in deaths were observed for three agents but these did not occur in the highest exposure categories.

For RSC, the analysis of quantitatively-estimated agents was largely uninformative, as we observed only one death in the non-zero exposure categories. For qualitatively-estimated agents, some excesses in deaths were observed in the exposed categories, but these were small (3–13%) and not statistically significant. For all exposure agents, SMRs for LHTC and NHL were generally elevated in both unexposed and exposed categories, but none was statistically significant. SMRs increased with increasing level of cumulative exposure to di-methyl formamide and to increasing duration of exposure to di-methyl formamide, methylene chloride, and ethyl-acetate/tri-chloroethane. While the small number of deaths limited the assessment of trends, the findings for NHL were generally similar to those for LHTC combined, and in addition, SMRs increased with increasing duration of exposure to aceto-nitrile/ethylene di-chloride and isopropyl alcohol.

Local County Cancer Mortality Rate Trend Analysis

To address community concerns about marked 1980 to 1990 increases in local county cancer mortality rates, we conducted an updated mortality trend analysis for this county and several other areas. Figure 1 shows age-adjusted male and

TABLE 5. Observed deaths and SMRs for selected causes of death and study factors: Male workers with potential plant exposure[a], local county comparisons, 1970–2000

	All Causes		All Cancer		Respiratory System Cancer		Lymphatic Hematopoietic Tissue Cancer		Non-Hodgkin's Lymphoma	
Study Factor	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Total Subgroup	82	70** (56–87)	26	86 (56–126)	11	88 (44–158)	7	227 (91–468)	4	307 (84–786)
Age at Hire										
< 30	24	71 (45–105)	5	83 (27–193)	2	108 (13–390)	2	231 (28–834)	1	259 (7–1441)
30–39	19	46** (28–71)	6	53 (20–116)	2	44 (5–159)	1	83 (2–464)	0	– (0–742)
40 +	39	95 (68–130)	15	121 (68–200)	7	124 (50–256)	4	386* (105–988)	3	671* (138–1961)
Time Period										
1970–1979	10	90 (43–166)	1	55 (1–307)	0	– (0–604)	0	– (0–1677)	0	– (0–4535)
1980–1989	15	50** (28–82)	7	97 (39–199)	3	97 (20–284)	0	– (0–481)	0	– (0–1043)
1990–2000	57	76* (57–98)	18	87 (52–138)	8	96 (41–189)	7	331* (133–682)	4	447* (122–1143)
Year of Hire										
1970–1979	76	78* (61–97)	25	96 (62–141)	10	93 (44–171)	7	269* (108–554)	4	365 (99–935)
1980–1989	5	39* (13–91)	1	38 (1–211)	1	104 (3–579)	0	– (0–1061)	0	– (0–2378)
1990–1996	1	18* (1–99)	0	– (0–390)	0	– (0–1252)	0	– (0–2396)	0	– (0–4630)
Duration of Employment										
< 10	24	55** (35–82)	4	45 (12–116)	3	92 (19–269)	0	– (0–350)	0	– (0–820)
10–19	41	87 (62–118)	13	100 (53–170)	3	53 (11–156)	5	386* (126–902)	4	698** (190–1786)
20 +	17	66 (39–106)	9	116 (53–220)	5	158 (51–369)	2	265 (32–956)	0	– (0–1199)
Time Since First Employment										
< 10	14	46** (25–78)	1	19 (1–107)	0	– (0–203)	0	– (0–521)	0	– (0–1209)
10–19	30	72 (49–103)	10	91 (44–168)	4	87 (24–222)	1	90 (2–503)	1	199 (5–1107)
20 +	38	85 (60–116)	15	111 (62–183)	7	125 (50–257)	6	466** (171–1014)	3	574* (118–1679)

[a]Persons with potential plant exposure had some non-zero measured exposure to at least one of the nine characterized chemical agents.
*$p < .05$.
**$p < .01$.

female death rates during the 1950 to 2000 period for all cancer sites combined by geographic area. Each of the 5-year average male or female annual rates (6-year for 1995–2000) comprise about 100 to 120, 1,250 to 1,500, 15,000 to 30,000, and 550,000 to 1,400,000 deaths for the county, county group, state, and US, respectively. For both sexes, all cancer death rates for these areas were similar across the 51-year time period, with smaller geographic areas displaying more random variation than the larger areas. For the surrounding county, the smallest area, the dramatic 1980 to 1990 increase was simply the upward cycle of a widely fluctuating periodic pattern that peaked near 1990 and returned to 1980 levels around 2000. A similar periodic pattern was observed for all LHTC, with even larger random fluctuations due to the much smaller numbers of observed deaths (about 10–15 deaths for each of the time periods compared with 100–120, 1,500–3,500, and 55,000–150,000 for the county group, state, and US, respectively [data not shown]).

DISCUSSION

Our findings of overall deficits in mortality for most of the cause of death categories examined are consistent with those found in other occupational groups, including chemical workers (8) and pharmaceutical production workers (9–15). These favorable mortality patterns are probably influenced in part by the "healthy worker effect," the relative absence of deleterious employment-related health risks, the positive health effects of continuing employment and better health care access. Our analyses of all workers with potential plant exposure and our agent-specific, exposure–response analysis of male workers revealed little evidence that total cancer mortality is related to any of the nine agents examined in this study. This finding was not surprising given that none of these agents is considered a suspected or known human carcinogen.

While not elevated overall, not statistically significant, 58% and 25% excesses in deaths from RSC (lung cancer) were observed among male workers with potential plant exposure employed more than 20 years or followed 20 or more years since first employment, respectively. Although these excesses occurred in the categories appropriate for a possible occupational association, the moderate magnitude of the excesses does not allow us to rule out uncontrolled positive confounding by tobacco smoking as an explanation for at least some of these excesses.

TABLE 6. Observed deaths and SMRs for selected cancer site categories by exposures to chemical agents studied: All male workers, local county comparisons, 1970–2000

		All Malignant Neoplasms		Respiratory System Cancer		Lymphatic/Hemato-poietic Tissue Cancer		Non-Hodgkin's Lymphoma	
Agent	Exposure Metric[a,b,c]	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Acetone	DOE (M = 0.1)								
	Not exposed	7	64 (26–132)	4	90 (24–230)	2	170 (21–615)	0	– (0–732)
	> 0–0.59	11	92 (46–165)	3	62 (13–182)	3	240 (50–702)	2	374 (45–1352)
	0.60 +	15	89 (50–140)	8	115 (50–226)	4	231 (63–592)	2	267 (32–965)
	Cum & AIE[d] (M = 0)								
	Not exposed	31	86 (59–122)	14	94 (52–158)	8	216 (93–424)	4	251 (68–644)
	Exposed	2	52 (6–188)	1	71 (2–394)	1	226 (6–1261)	0	– (0–1890)
Di-Methyl	DOE (M = 0.1)								
Formamide	Not exposed	7	68 (27–140)	4	94 (26–240)	2	184 (22–666)	0	– (0–792)
	> 0–1.34	13	93 (49–158)	7	121 (49–249)	3	212 (44–619)	1	166 (4–923)
	1.35 +	13	84 (45–144)	4	65 (18–165)	4	242 (66–620)	3	418 (86–1223)
	Cum (M = 0)								
	Not exposed	26	88 (58–129)	14	113 (62–190)	6	201 (74–438)	3	237 (49–692)
	> 0–5.497	3	80 (17–234)	1	68 (2–382)	1	243 (6–1354)	0	– (0–2110)
	5.498 +	4	62 (17–158)	0	– (0–153)	2	263 (32–950)	1	290 (7–1616)
	AIE[c] (M = 0)								
	Not exposed	26	88 (58–129)	14	113 (62–190)	6	201 (74–438)	3	237 (49–692)
	> 0–2.13	3	88 (18–257)	0	– (0–279)	1	257 (6–1434)	1	587 (15–3271)
	2.14 +	4	59 (16–150)	1	39 (1–219)	2	255 (31–922)	0	– (0–1056)
Methylene	DOE (M = 0.1)								
Chloride	Not exposed	7	66 (27–137)	4	92 (25–235)	2	179 (22–648)	0	– (0–772)
	> 0–1.34	13	90 (48–154)	7	118 (47–243)	3	202 (42–589)	1	157 (4–874)
	1.35 +	13	88 (47–151)	4	67 (18–172)	4	258 (70–660)	3	447 (92–1307)
	Cum (M = 0)								
	Not exposed	26	86 (56–126)	14	111 (61–186)	6	195 (71–424)	3	229 (47–668)
	> 0–39.68	4	111 (30–284)	1	74 (2–413)	2	489 (59–1765)	0	– (0–2083)
	39.69 +	3	51 (10–148)	0	– (0–163)	1	151 (4–841)	1	337 (8–1876)
	AIE[c] (M = 0)								
	Not exposed	26	86 (56–126)	14	111 (61–186)	6	195 (71–424)	3	229 (47–668)
	> 0–18.93	3	65 (14–191)	1	58 (1–323)	1	181 (4–1007)	0	– (0–1526)
	18.94 +	4	81 (22–208)	0	– (0–195)	2	386 (47–1393)	1	431 (11–2399)
Toluene	DOE (M = 0.1)								
	Not exposed	13	79 (42–136)	5	75 (24–174)	4	231 (63–592)	1	134 (3–747)
	> 0–0.44	8	99 (43–195)	4	123 (34–315)	1	122 (3–680)	1	292 (7–1625)
	0.45 +	12	78 (41—137)	6	96 (35–208)	4	249 (68–638)	2	287 (35–1035)
	Cum & AIE[d] (M = 0)								
	Not exposed	31	86 (59–123)	14	94 (52–158)	8	218 (94–429)	4	254 (69–651)
	Exposed	2	51 (6–185)	1	71 (2–397)	1	210 (5–1169)	0	– (0–1723)
Aceto-nitrile/	DOE (M = 0.1)								
Ethylene	Not exposed	13	78 (41—133)	5	73 (24–171)	4	224 (61–574)	1	130 (3–722)
Di-Chloride	> 0–0.44	8	81 (35—160)	4	103 (28–264)	1	97 (2–542)	1	231 (6–1288)
	0.45 +	12	91 (47—159)	6	108 (40–236)	4	298 (81–763)	2	343 (42–1240)
Ethyl-Acetate/	DOE (M = 0.1)								
Tri-chloroethane	Not exposed	8	57 (25—112)	5	88 (28–205)	2	132 (16–477)	0	– (0–565)
	> 0–0.33	11	119 (60–213)	3	81 (17–236)	2	207 (25–747)	1	245 (6–1364)
	0.34 +	14	85 (46—142)	7	103 (41–211)	5	299 (97–698)	3	414 (85–1209)
Isopropyl Alcohol	DOE (M = 0.1)								
	Not exposed	13	78 (41–133)	5	73 (24–170)	4	226 (62–580)	1	131 (3–732)
	> 0–0.44	8	89 (38–174)	4	113 (31–288)	1	105 (3–584)	1	248 (6–1383)
	0.45 +	12	86 (44–150)	6	103 (38–224)	4	279 (76–714)	2	321 (39–1160)

[a]M denotes value used for minimally exposed jobs.
[b]Notation used for exposure metrics.
DOE - duration of exposure in years units.
Cum - cumulative exposure in ppm-years units.
AIE - average intensity of exposure in ppm units.
[c]Baseline categories include workers with no potential plant exposure.
[d]AIE (M = 0) computed as Cum (M = 0)/DOE (M = 0).

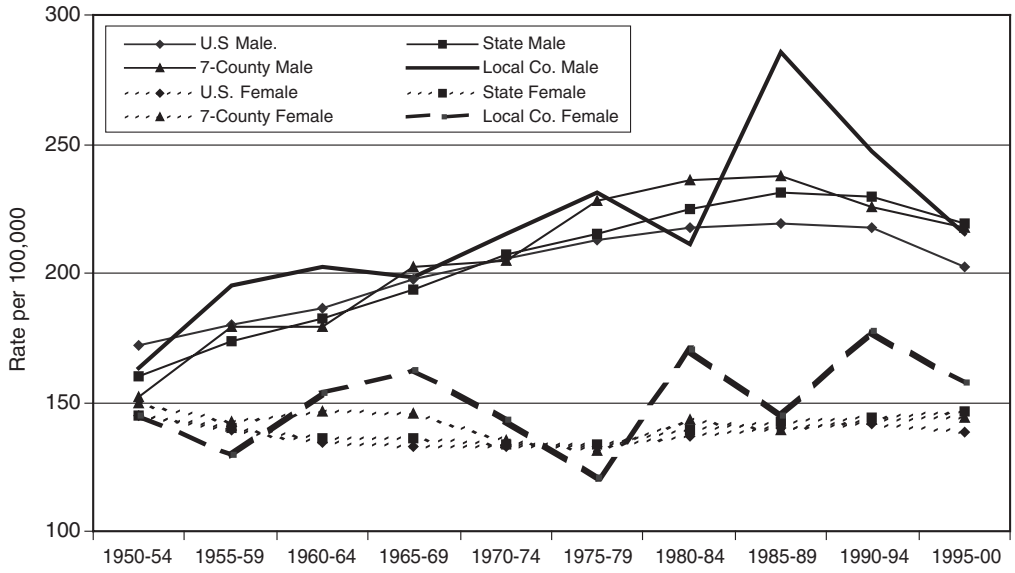

FIGURE 1. Age-adjusted male and female death rates for all cancer, 1950–2000, by geographic area.

Our findings for LHTC, and in particular NHL, revealed some patterns consistent with a possible occupational association: 1) among male workers with potential plant exposure, a 2.27- and 3.07-fold overall excess in LHTC and NHL deaths, respectively; 2) large (3.31–6.98-fold range), statistically significant excesses in the time-correlated subcategories, year of hire 1970 to 1979, time period 1990 to 2000, duration of employment 10 to 19 years, and time since first employment 20 or more years; and 3) some limited evidence of an increasing mortality risk with increasing exposure to di-methyl formamide, methylene chloride, and the joint agent ethyl acetate/tri-chloroethane (for NHL, also some evidence of trend for aceto-nitrile/ethylene di-chloride and isopropyl alcohol). Co-linearity with or acting as a surrogate for some pharmaceutical products by these compounds could neither be evaluated nor dismissed due to lack of exposure data on the products.

Evidence against a possible occupational association for LHTC include the observation of a 42% excess among workers with no potential plant exposure, although this was based on only two deaths. Also four of the seven deaths among workers with potential plant exposure, including three of the four NHLs, occurred among workers hired at this facility at age 40 or older yielding statistically significant, 3.86- and 6.71-fold excess risks, respectively. These workers had ample opportunity to receive potentially hazardous occupational or non-occupational exposures before employment at the study plant. A review of the nine LHTC cases shows that three cases, including one NHL and one with no potential plant exposure, had previously worked at a different site owned by the same company (data not shown). An analysis of work histories and job titles within the study plant and available information on jobs held in other companies before work at the study plant revealed no clear pattern of work history suggesting a common etiologic exposure that was not characterized in our exposure assessment. Two of the cases, including one NHL, had worked for other companies as chemical operators and three cases, including one NHL and one with no potential plant exposure, had military experience with chemical warfare agents or munitions.

Our findings for LHTC also lack outcome specificity. While four of the seven cases with potential plant exposure died of NHL, other types of LHTCs were observed within this category, decreasing the likelihood that the overall excess was related to a common etiologic agent inside or outside the plant. The environmental risk factors associated with LHTC malignancies vary by type of malignancy. Leukemia is most commonly associated with exposures to ionizing radiation or solvents, particularly benzene. Persons at increased risk of NHL include those with primary or acquired immunodeficiency diseases and immunosuppressed patients. There is some evidence implicating phenoxy-herbicide exposures, although this evidence is not conclusive (16, 17). Aside from the brief period of low benzene exposures in the early 1970s, no other known risk factors for LHTC were identified at the study plant.

The results of the cohort study must be interpreted with consideration given to the exploratory, hypothesis generating nature of the statistical analyses. Interpretation is further limited by difficulties inherent in all health studies of pharmaceutical production workers, particularly, the lack of

exposure specificity stemming from the large number and variety of pharmaceutical compounds and intermediate products involved in the manufacturing processes. This diversity of processes and products also greatly limits the ability to compare findings of potential health effects across the relatively few health studies reported. Only five mortality studies of pharmaceutical production workers have previously been published in English language journals (9–13).

Other interpretational difficulties include: 1) the large number of statistical comparisons made (and the likelihood that some comparisons will be deemed statistically significant by chance factors alone); 2) the small number of deaths observed for most of the cause-of-death-specific categories examined, resulting in low precision in estimating mortality risks via SMRs, and low statistical power to detect important mortality excesses for rare diseases; and 3) our inability to control for certain potential confounding factors such as cigarette smoking history or exposures received outside the study plant.

This study also has many strengths: 1) a cohort enumeration verified to be complete and accurate; 2) a near-perfect trace for deaths; 3) a high proportion of workers employed for 5 or more years and followed for 20 or more years; 4) historical exposure profiles for nine agents developed for individual workers based on personal air monitoring data; 5) the use of US and local county area standard populations; and 6) for many cause of death categories examined, good statistical power to detect 1.5-fold or greater mortality excesses (for example, using the total cohort, external comparisons and a one-sided 5% significance level, a 90% + statistical power to detect a 1.5-fold or greater mortality excess in all cancers combined).

CONCLUSIONS

With the possible exception of LHTC, in particular NHL, and RSC, this study provided no evidence of elevated total or cause-specific mortality risks among the cohort. It does not appear that plant factors played a role in the 1980 to 1990 increases in local county cancer mortality rates. Continued follow-up of this cohort with nested case–control studies of respiratory system cancer and all lymphatic and hematopoietic tissue cancers may help to elucidate the reasons for the elevated mortality risks.

We acknowledge the outstanding work of the project staff at the University of Pittsburgh (Kathy McGinnis, Charles Alcorn, Bryan Foltz, Linda Kobus, Stephen Sefcik, and Toni Spatolisano). The research proposal was approved by the Institutional Review Board (IRB) of the University of Pittsburgh.

APPENDIX

Characteristics of sampling data used in exposure assessment

Compound	Parameter	Building A	B	C	D	E	F
Acetone	Median	17.0	24.0	–	8.2	–	–
	Mean	37.5	61.8	–	8.2	–	–
	Geo. Std. Dev.	2.29	2.48	–	53.7	–	–
	No. samples	309	262	–	3.59	–	–
	% Censoring	21.4	18.3	–	297	6.5	–
Acetonitrile	Median	–	X	–	49.2	28.1	–
	Mean	–	X	–	–	3.09	–
	Geo. Std. Dev.	–	X	–	–	290	–
	No. samples	–	225	–	–	13.8	–
	% Censoring	–	77.6	–	–	–	–
Dimethylformamide	Median	0.64	0.4	X	2.45	–	0.90
	Mean	2.3	1.8	X	4.40	–	1.64
	Geo. Std. Dev.	2.87	3.14	X	2.04	–	2.06
	No. samples	109	64	55	757	–	93
	% Censoring	46.8	48.4	83.6	12.3	–	30
Ethyl acetate	Median	4.8	0.3	–	–	–	–
	Mean	17.5	1.49	–	–	–	–
	Geo. Std. Dev.	2.89	3.25	–	–	–	–
	No. samples	546	98	–	–	–	–
	% Censoring	48.8	56.1	–	–	–	–

Continued

AEP Vol. 15, No. 2
February 2005: 112–122

APPENDIX. Continued

Compound	Parameter	Building A	B	C	D	E	F
Ethylene dichloride	Median	–	X	–	–	–	–
	Mean	–	X	–	–	–	–
	Geo. Std. Dev.	–	X	–	–	–	–
	No. samples	–	364	–	–	–	–
	% Censoring	–	75.8	–	–	–	–
Hexane	Median	–	X	–	–	–	–
	Mean	–	X	–	–	–	–
	Geo. Std. Dev.	–	X	–	–	–	–
	No. samples	–	450	–	–	–	–
	% Censoring	–	74.9	–	–	–	–
Isopropyl alcohol	Median	–	–	–	1.3	–	–
	Mean	–	–	–	18.4	–	–
	Geo. Std. Dev.	–	–	–	4.56	–	–
	No. samples	–	–	–	647	–	–
	% Censoring	–	–	–	65.2	–	–
Methylene chloride	Median	7.0	0.13	2.10	4.4	8.3	X
	Mean	19.4	0.85	4.0	15.1	12.3	X
	Geo. Std. Dev.	2.56	3.59	2.11	2.81	1.79	X
	No. samples	388	253	70	405	78	9
	% Censoring	5.9	16.6	24.3	8.4	6.4	88.9
Trichloroethane	Median	0.16	0.24	–	–	–	–
	Mean	2.3	1.13	–	–	–	–
	Geo. Std. Dev.	4.56	3.19	–	–	–	–
	No. samples	587	587	–	–	–	–
	% Censoring	62.0	32.3	–	–	–	–
Toluene	Median	–	X	–	1.75	–	–
	Mean	–	X	–	9.5	–	–
	Geo. Std. Dev.	–	X	–	3.36	–	–
	No. samples	–	400	–	697	–	–
	% Censoring	–	75.2	–	32.8	–	–

–, insufficient data for analysis.
X, data too severely censored for meaningful analysis.

REFERENCES

1. Esmen NA. Retrospective industrial hygiene surveys. Am Ind Hyg Assoc J. 1979;40:58–65.
2. Marsh GM. A strategy for merging and analyzing work history data in industry-wide occupational epidemiology studies. Am Ind Hyg Assoc J. 1987;48:414–419.
3. Schall LC, Marsh GM, Henderson VL. A two-stage protocol for verifying vital status in large historical cohort studies. J Occup Environ Med. 1997;39:1097–1102.
4. Schall LC, Buchanich JM, Marsh GM, Bittner G. Utilizing multiple vital status tracing services optimizes mortality follow-up in large cohort studies. Ann Epidemiol. 2001;11:292–296.
5. Marsh GM, Youk AO, Stone RA, Sefcik SS, Alcorn CA. OCMAP-PLUS: A new occupational cohort mortality program for multifactor work history and exposure based analysis. J Occup Environ Med. 1998;40:351–362.
6. Marsh GM, Ehland J, Sefcik SS. Mortality and Population Data System (MPDS). University of Pittsburgh, Department of Biostatistics, Technical Report. Pittsburgh: University of Pittsburgh; 2003.
7. Breslow NE, Day NE. The Design and Analysis of Cohort Studies. Statistical Methods in Cancer Research. v. 2. Lyon: Oxford University Press; 1987.
8. Greenberg RS, Mandel JH, Pastides H, Britton NL, Rudenko L, Starr TB. A meta-analysis of cohort studies describing mortality and cancer incidence among chemical workers in the United States and Western Europe. Epidemiology. 2001;12:727–740.
9. Thomas TL, Decoufle P. Mortality among workers employed in the pharmaceutical industry: A preliminary investigation. J Occup Med. 1979; 21:619–623.
10. Harrington JM, Goldblatt P. Census-based mortality study of pharmaceutical industry workers. Br J Ind Med. 1986;43:206–211.
11. Baker CC, Russell RA, Roder DM, Esterman AJ. A nine-year retrospective mortality study of workers in a British pharmaceutical company. J Soc Occup Med. 1986;36:95–98.
12. Edling C, Friis L, Mikoczy Z, Hagmar L, Lindfors P. Cancer incidence among pharmaceutical workers. Scand J Work Environ Health. 1995;21:116–123.
13. Dolan D, Youk AO, Marsh GM, Buchanich JM. A 50-year retrospective mortality study of workers in a pharmaceutical production plant. J Occup Environ Med. 2004;46:161–166.
14. Harrington JM. Cancer and the health industry. J Soc Occup Med. 1983;33:114–118.
15. Teichman RF, Fallon LF, Brandt-Rauf PW. Health effects of workers in the pharmaceutical industry: A review. J Soc Occup Med. 1988;38:55–57.
16. Linet MS, Cartwright RA. The leukemias. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer Epidemiology and Prevention. 2nd ed. New York: Oxford University Press; 1996:841–892.
17. Scherr PA, Mueller NE. Non-Hodgkin's lymphomas. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer Epidemiology and Prevention. 2nd ed. New York: Oxford University Press; 1996:920–945.