Mortality From Brain Tumor and Other Causes in a Cohort of Petrochemical Workers[1]

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ABSTRACT—To evaluate a suspected excess of deaths due to brain tumor (BT) among petrochemical workers, a retrospective cohort mortality study was conducted among 7,595 men ever employed at a plant in Texas City, Texas, between 1941 and 1977. Among hourly employees, overall mortality was lower than expected from U.S. national rates [standardized mortality ratio (SMR)=79]. However, 19 BT deaths (International Classification of Diseases, seventh revision, codes 193, 223, and 237) among hourly employees were observed as against 9.6 expected (SMR=198), and with extension of the analysis to include BT deaths occurring in 1978 and 1979, 22 deaths were observed versus 10.7 expected (SMR=206). Fifteen years or more after being hired, 19 of these workers died from BT versus 7.2 expected (SMR=263), and the standardized mortality ratios increased with duration of employment to 377 for hourly workers who had worked over 20 years. Although nonoccupational etiologies cannot be dismissed, these data suggest an occupational etiology for certain BT deaths in petrochemical workers.—JNCI 1983; 70:75–81.

Age-adjusted white male incidence rates for brain cancer during 1968–72 varied between 4.9 and 7.6 per 100,000 per year among the cancer registries within the United States (*1*). Comparable age-adjusted rates ranged throughout the world from 0.8 among Indians in Singapore to 10.5 among Jews in Israel (*1*). Within the United States, both incidence and mortality rates for brain cancer have risen steadily during the past three decades (*2, 3*). Among white males in the United States, most of the increase in BT deaths is explained by rising age-specific BT mortality rates above age 55 (text-fig. 1). The causes of this increase are obscure, although changing diagnostic patterns have undoubtedly accounted for a part of the rise. Occupational or other environmental exposures may also have contributed, but in previous studies brain cancer has been associated only rarely with such risk factors (*3*).

In 1978, a suspected excess of deaths due to BT among former employees of a petrochemical plant in Texas City, Texas, was reported to the Occupational Safety and Health Administration. To evaluate the etiology of these cases, we undertook a three-phase epidemiologic investigation. The first phase included case identification and pathologic confirmation (*4*). The second phase, a retrospective cohort mortality study of the plant workforce, is reported herein.[6] The third phase, a case-control study nested within the cohort, will examine possible associations between BT and job categories, chemical exposures, and residence.

BACKGROUND

This diversified petrochemical facility is located 40 miles southeast of Houston, Texas, in Galveston County in the heart of the refinery and petrochemical belt along the Texas Gulf Coast. The facility, occupying 400 acres of coastal lowlands, includes more than 200 structures, most of which are exposed to the outdoor environment.

Production, which began in 1941, was initially limited to an olefins plant, ethylene oxide–glycols unit, ethanol acid unit, isopropanol unit, acetone unit, acetaldehyde unit, and dual anhydride unit, all of which continued in use until at least 1970. Soon after World War II, the plant added units for the production of acetates, ethyleneamines, ethylene dichloride, vinyl chloride, polyvinyl chloride, and vinyl acetate. After 1950, other production units were gradually added, including a butadiene unit, polyethylene unit, diethyl sulfate unit, amines unit, and methyl and butyl cellosolve units. The work force grew from 281 to 1,740 during the 1940's and since then has fluctuated between 2,000 and 2,700. Approximately one-third of the current employees are salaried, and the remainder are hourly.

METHODS

Personnel records for all employees have been kept at the plant since 1941. Under NIOSH guidance, personnel at the plant abstracted name, Social Security number, date of birth, race, sex, and a detailed work history for each of the 8,855 current and former employees as of September 30, 1979. A random sample of 5% of the records was also sent to NIOSH and examined independently to verify cohort completeness and coding accuracy. Persons of undetermined race (n=322) and Hispanics (n=114) were classified as white. Blacks and the few orientals employed at the plant were classified as nonwhite (n=991). Females (n=1,168) were usually employed at the plant in office jobs and were

Abbreviations used: BT=brain tumor(s); CNS=central nervous system; ICD=International Classification of Diseases; NIOSH=National Institute for Occupational Safety and Health; PMR=proportionate mortality ratio; PYAR=person-years at risk; SMR=standardized mortality ratio(s); SSA=Social Security Administration.

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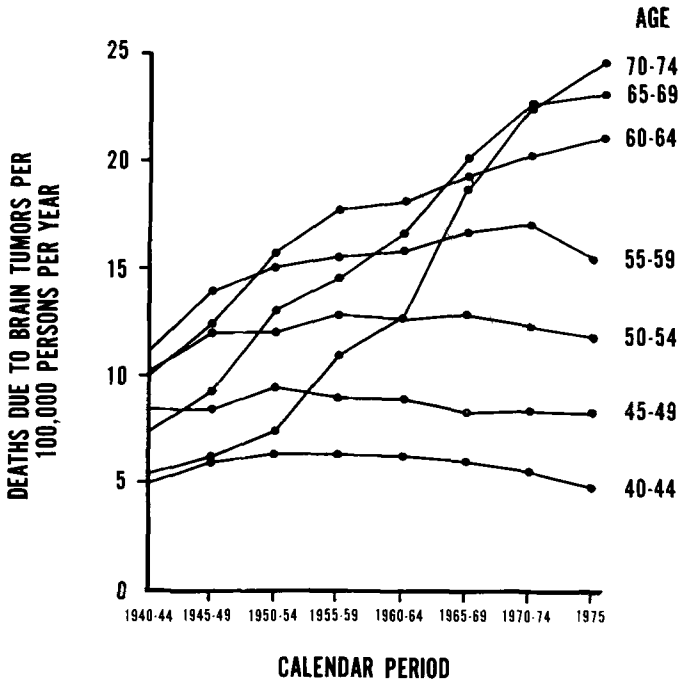
[6] An independent reanalysis of our data is being reported in (*5*).



TEXT-FIGURE 1.—Temporal changes in mortality rates for BT among the white male population in the United States.

consequently excluded from the study. All male employees who began work after the vital status follow-up date December 31, 1977, were also excluded from the study. The final cohort therefore consisted of all 7,595 male employees (6,706 white and 889 nonwhite) who had worked at the plant for at least 1 day between 1941 and 1977. The cohort members were divided into hourly or salaried categories. Those who had worked both as hourly and as salaried employees (n=701) were considered to be hourly for purposes of this study.

Vital status through 1977 was determined for cohort members from various records including those of the company, the SSA, the Internal Revenue Service, and the Texas Bureau of Vital Statistics. The SSA follow-up was the most comprehensive but extended only to December 31, 1977, and thus determined the study end date.

In a supplementary analysis, we tabulated observed and expected deaths through December 31, 1979, for BT only, even though total cohort follow-up for other causes of death was incomplete beyond 1977. The SSA could not determine if persons were alive after December 31, 1977, but it had received notices of a number of death claims through 1979. In addition, deaths among Texas residents were identified for 1978 and 1979 from a computerized match with Texas mortality files maintained by M. D. Anderson Hospital and Tumor Institute. We made extensive additional efforts to achieve what we believe to be a nearly complete ascertainment of deaths due to BT among former plant employees through the end of 1979.

Death certificates obtained from state vital statistics offices or from the company were coded by a nosologist according to the ICD in effect at the time of death. These codes were then grouped into cause-of-death categories that were consistent across ICD revisions and presented in the format of the seventh revision. Persons known to be deceased but for whom no death certificate could be obtained were assumed deceased, cause of death unknown.

A modified life table analysis of the cohort generated PYAR, which were calculated for each cohort member from the date he was first employed at the Texas City plant[7] until the earlier of two events: his death or the study end date. Persons lost to follow-up were considered to be alive through the study end date. Similarly, in the supplementary analysis through 1979, everyone not known to be deceased was considered to be alive through 1979. Three deceased persons whose cause of death and date of death could not be determined were considered to have died on the study end date, cause of death unknown.

PYAR were calculated specific for race and for 5-year categories of age, calendar period, duration of employment at the plant, and time since first employment. Duration of employment was considered to be continuous from the first date until the last date of employment at the plant; any temporary breaks in service were ignored. The observed number of deaths occurring among the cohort by the study end date was compared to the number of deaths expected. We calculated the expected number of deaths by multiplying the appropriate PYAR by the U.S. death rates for males specific for race, 5-year age groups, 5-year calendar periods, and cause. Death rates for 1975 were used for the entire period 1975–77 and for 1975–79 in the supplementary analysis. The results were summed over age-specific and calendar period-specific categories to obtain the total number of expected deaths for each cause.

Observed and expected deaths for all three BT codes malignant (ICD=193), benign (ICD=223), and unspecified as to whether malignant or benign (ICD=237)--are presented both individually and combined into a single category referred to as "BT." This grouping was intended to avoid misinterpretation of the results due to diagnostic misclassifications among these codes. Although corroborative pathologic information was sought for all deaths due to BT, that information was not used to modify death certificate codes, because such modification would have prevented appropriate comparison of the observed deaths with the number of deaths expected from the uncorrected U.S. rates.

We calculated SMR by dividing the observed numbers of deaths by the expected numbers of deaths and multiplying the quotient by 100. SMR were not calculated if both the observed and expected numbers of deaths were less than two. Two-sided 95% confidence intervals for the SMR were calculated assuming a Poisson distribution for the observed deaths. When a confidence interval does not include 100, the SMR is statistically significant at $P<0.05$.

RESULTS

The cohort consisted of 7,595 males employed at the plant any time between 1941 and 1977. The sample verification

[7]For salaried employees, it was necessary to substitute the date first employed by the corporation after 1940 for the date first employed at the study plant because of limitations in record-keeping procedures at the company.

TABLE 1.—*Vital status of cohort of male petrochemical workers as of December 31, 1977*

Vital status	Hourly		Salaried	
	No. of whites (%)	No. of nonwhites (%)	No. of whites (%)	No. of nonwhites (%)
Alive	4,364 (84)	640 (77)	1,380 (93)	52 (98)
Deceased	688 (13)	133 (16)	83 (6)	1 (2)
Death certificate obtained	671	128	80	1
Death certificate outstanding	17	5	3	0
Lost to follow-up	163 (4)	63 (8)	28 (2)	0 (0)
Total	5,215 (100)	836 (100)	1,491 (100)	53 (100)
PYAR	116,461	15,880	27,109	238

procedure indicated that no persons in the plant personnel files had been omitted from the cohort and that key variables were coded with better than 95% accuracy. Seventy percent of the cohort was hired before 1963, thus allowing a minimum of 15 years of follow-up. The mean age at hire for the cohort members was 28. Forty-six percent were hired between 15 and 24 years of age, 38% between 25 and 34 years of age, and the rest over age 34. The cohort was fairly stable; one-half had worked for more than 5 years at this plant, and 31% had worked there for more than 15 years.

Through December 31, 1977, 7,341 (96.7%) of the cohort members were successfully traced. Lost to follow-up were 4% of the white and 8% of the nonwhite hourly employees and 2% of the white salaried employees (table 1). The nonwhite salaried employees were all located, but their mortality experience was not analyzed further inasmuch as there was only one death (due to heart disease) among them. The average year last observed of all persons lost to follow-up was 1952. Because death certificates are missing for less than 4% of the deceased in each subcohort, it was unnecessary to adjust the cause-specific SMR upward to reflect the percentage of missing death certificates.

The 688 deaths observed among white male hourly workers were 80% of the number expected (table 2). Nonwhite hourly and white salaried employees experienced overall SMR of 56 and 61, respectively. Among each of these 3 groups, the SMR for all malignant neoplasms was only slightly higher than the SMR for all causes. Mortality due to vascular lesions of the CNS was much lower than expected among nonwhites. All 3 groups experienced very low risks of death due to nonmalignant respiratory disease.

Analysis of mortality due to neoplasia revealed a marked excess risk for BT among all hourly workers, white and nonwhite. The SMR was 200, based on 19 observed and 9.6 expected deaths (table 3). This excess risk was consistent across the three ICD codes for BT: 193, 223, and 237. Very low SMR were found for cancers of the buccal cavity and pharynx, stomach, rectum, and genital organs. A slightly elevated risk was found for mortality from leukemia (SMR=136).

Few deaths due to all malignant neoplasms (n=17) occurred among salaried workers. These workers experienced no deaths due to BT, although 1.5 were expected. Salaried employees did experience an excess of laryngeal cancer (2 deaths observed vs. 0.3 expected) and a deficit of lung cancer (3 deaths observed vs. 7.7 expected).

Mortality among hourly employees through 1977 was further examined by duration of employment and by time since first employment, the second measure intended as a surrogate for induction latent period (table 4). All observed and expected deaths occurring within 15 years since first employment were ignored in this calculation because occupationally related cancer would most likely be manifest only after an appropriate induction latent period. The observed and expected deaths were divided approximately in half by duration of employment: less than 10 years or greater than 10 years. Excesses of deaths due to pancreatic and kidney cancers occurred only after 10 years' duration of employment, but the SMR for lung cancer and all causes decreased as duration of employment increased. The SMR for BT rose from 172 to 344 with increasing duration of employment. No trends were observed for leukemia mortality when it was

TABLE 2.—*Cause-specific mortality of male petrochemical workers followed through December 31, 1977*

Cause of death	ICD code No.[a]	Hourly[b]								Salaried[b]			
		White				Nonwhite				White			
		Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes		688	859.5	80	74–86	133	235.6	56	47–67	83	136.3	61	49–75
All malignant neoplasms	140–205	131	161.6	81	68–96	29	38.3	76	51–109	17	24.1	71	41–113
Vascular lesions of CNS	330–334	32	45.4	70	48–100	6	22.0	27	10–59	6	6.0	100	37–218
Diseases of circulatory system	400–468	276	360.4	77	68–86	50	79.4	63	47–83	33	50.8	65	45–91
Nonmalignant respiratory disease	470–527	24	41.8	57	37–85	8	12.7	63	27–124	1	5.9	17	1–94
Violent deaths	800–985	130	123.4	105	88–125	22	34.8	63	40–96	18	28.3	64	38–101
Residual deaths		95	126.9	75	61–92	18	48.5	37	22–59	8	21.2	38	16–74

[a] Seventh revision.
[b] Obs=observed deaths; Exp=expected deaths; SMR=100(Obs/Exp); 95% CI=95% confidence interval.

TABLE 3.—*Mortality due to neoplasia among male hourly petrochemical workers followed through December 31, 1977*

Cause of death	ICD code No.[a]	Obs[b]	Exp[c]	SMR[d]	95% CI[e]
All malignant neoplasms	140–205	160	199.9	80	68–93
Buccal cavity and pharynx	140–148	1	7.1	14	1–78
Esophagus	150	5	6.2	81	26–188
Stomach	151	7	11.6	60	24–124
Intestines including colon	152, 153	13	16.0	81	43–139
Rectum	154	3	5.9	51	10–149
Liver and biliary tract	155, 156A	5	5.2	96	31–224
Pancreas	157	9	10.9	83	38–157
Larynx	161	1	3.2	31	1–174
Lung	162–163	50	64.0	78	58–103
Male genital organs	177–179	7	11.7	60	24–123
Kidney	180	6	4.9	122	45–267
Bladder	181	3	4.7	64	13–187
Skin	190–191	4	3.8	105	29–270
Brain	193	13	7.2	181	96–309
Lymphosarcoma and reticulosarcoma	200	4	5.9	68	18–174
Hodgkin's disease	201	1	3.3	30	1–169
Leukemia	204	11	8.1	136	68–243
Other hematopoietic and lymphatic malignancies	202, 203, 205	4	3.0	133	36–341
Benign brain neoplasms	223	2	0.7	286	35–1,032
Unspecified brain neoplasms	237	4	1.7	235	64–603
Total BT	193, 223, 237	19	9.6	198	119–309

[a] Seventh revision.
[b] Observed deaths.
[c] Expected deaths.
[d] SMR=100(Obs/Exp).
[e] 95% confidence interval.

TABLE 4.—*Mortality due to selected causes among male hourly petrochemical workers after 15 years since first employment by duration of employment and followed through December 31, 1977*

Cause of death	Duration of employment					
	<10 yr[a]			≥10 yr[a]		
	Obs	Exp	SMR	Obs	Exp	SMR
All causes	313	373.3	84	292	399.7	73
All malignant neoplasms	61	75.1	81	73	83.1	88
Pancreatic cancer	1	4.2	24	7	4.7	149
Lung cancer	24	25.6	94	22	29.1	76
Kidney cancer	1	1.8	—	5	2.1	238
BT	5	2.9	172	11	3.2	344

[a] Obs=observed deaths; Exp=expected deaths; SMR=100(Obs/Exp).

examined across 5-year intervals of duration of employment and time since first employment.

Supplementary analysis of deaths in the cohort of hourly workers after 1977 indicated that 100 additional deaths had occurred in that group during 1978 and 1979. Death certificates were obtained for 95 of these deaths. During these 2 years, the SMR for all causes among hourly workers was very low (67), reflecting the incomplete follow-up of deaths due to causes other than BT. Three additional deaths due to BT were observed; thus a total of 22 deaths due to BT occurred among hourly workers from 1941 through 1979. Individual data on duration of employment and time from date of first hire until death for each BT death are provided in text-figure 2.

TABLE 5.—*BT mortality among male hourly workers followed through December 31, 1979, by calendar period*

Period of risk	Obs[a]	Exp[b]	SMR[c]	95% CI[d]
1940–49	0	0.4	—	—
1950–59	2	1.9	105	13–380
1960–69	6	3.3	182	67–396
1970–74	9	2.4	375	171–712
1975–79	5	2.8	179	58–417
Total	22	10.7	206	129–311

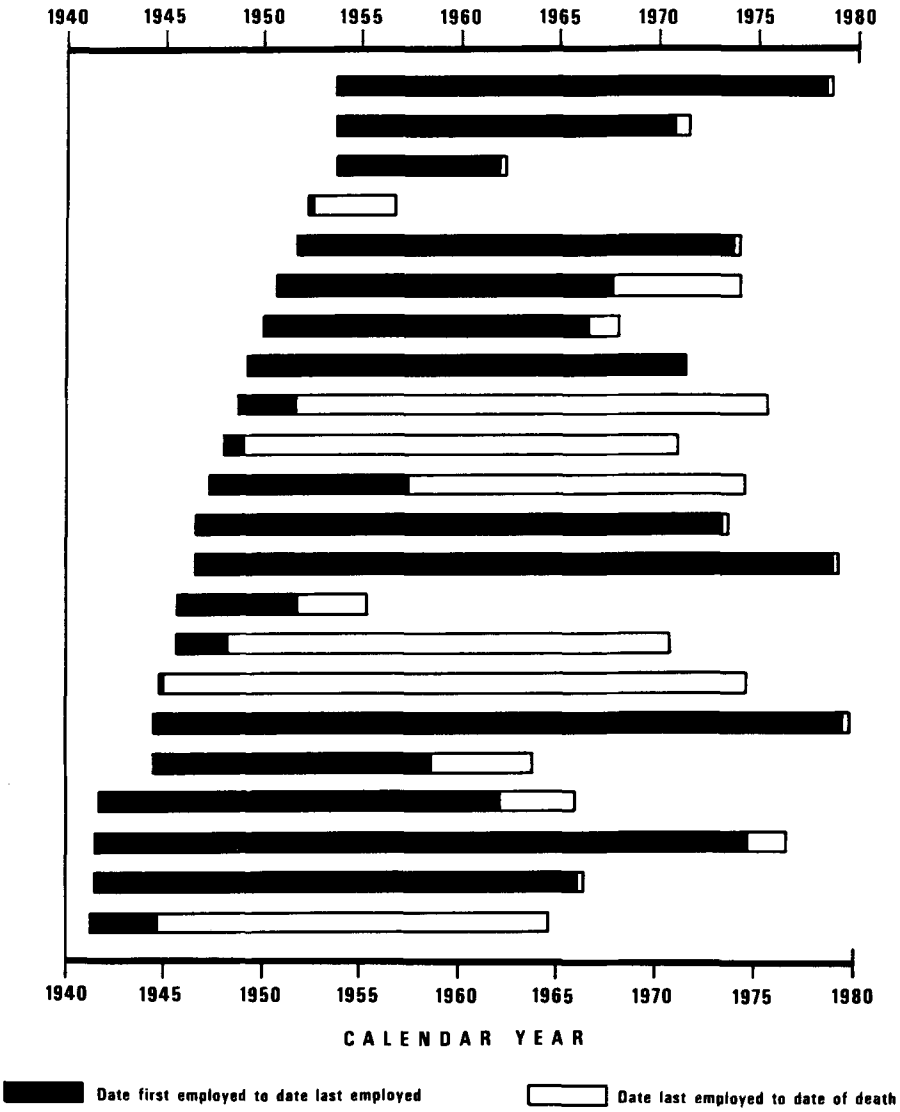
[a] Observed deaths.
[b] Expected deaths.
[c] SMR=100(Obs/Exp).
[d] 95% confidence interval.

From pathologic reports, clinical case records, and reexamination of tissue, we were able to confirm the diagnosis of BT in 19 of the 22 cases whose cause of death was listed as BT on their death certificates. One case had an inadequate biopsy in extremis but was diagnosed as having a glioblastoma multiforme on the basis of a typical clinical picture and rapid progression of the illness. Another case who had worked only 1 year at the plant and who died 23 years after first employment was found to have had a malignant tumor metastatic to the brain from an undetermined primary site. The last case was found to have a congenital anomaly of the cerebellum at autopsy. He died less than 10 years after first employment at the plant. Of the 14 BT that led to death among those men who worked for more than 10 years at the plant, there were 4 meningi-

TABLE 6.—*Mortality due to BT after 15 years since first employment among male hourly petrochemical workers by duration of employment and followed through December 31, 1979*

Duration of employment, yr	Parameter[a]	Years since first employment		
		15–24	≥25	Total
<10	Obs	2	3	5
	Exp	1.77	1.65	3.41
	SMR	—	182	147
	95% CI		38–532	48–342
10–19	Obs	4	1	5
	Exp	1.13	0.27	1.40
	SMR	354	—	357
	95% CI	97–908		116–832
≥20	Obs	4	5	9
	Exp	0.90	1.50	2.39
	SMR	444	333	377
	95% CI	121–1,137	108–779	172–715
Total	Obs	10	9	19
	Exp	3.80	3.42	7.22
	SMR	263	263	263
	95% CI	126–484	120–500	158–411

[a] Obs=observed deaths; Exp=expected deaths; SMR=100(Obs/Exp); 95% CI=95% confidence interval.



TEXT-FIGURE 2.—Duration of employment and time until death of BT cases in a cohort of male hourly petrochemical workers followed through December 31, 1979.

omas, 1 glioma, and 9 glioblastomas (malignant astrocytoma, grades 3 and 4).

Among the hourly male workers, 22 deaths due to BT were observed as against 10.7 expected (table 5). Eighteen of these deaths were observed among whites versus 9.7 expected. The excess risk first became evident in the 1960's and peaked in the early 1970's. When risk of death due to BT was examined by interval since first employment, no excess was seen among the cohort of hourly workers within 15 years since first hire (3 observed deaths vs. 3.5 expected). After 15 years since first employment, the SMR were independent of time since first employment but increased with duration of employment from 147 to 377 (table 6). The excess risk was most evident among men aged 50–70, with 70 being the age at death of the oldest case. After 15 years since first employment, there were 3 observed and 1.86 expected deaths (SMR=161) due to BT below age 50 compared to 16 observed and 5.33 expected deaths (SMR=300) due to BT above age 50. This differentially increased risk by age at risk was not due to confounding from duration of employment.

After 15 years since first employment, the SMR for deaths due to BT increased by age at first employment: 4 observed and 1.80 expected for those hired under age 25 (SMR=222), 9 observed and 3.39 expected for those hired between ages 25 and 34 (SMR=266), and 6 observed and 2.03 expected for those hired after age 35 (SMR=295). This trend, however, was eliminated after stratification by age at risk.

DISCUSSION

The major finding of this retrospective cohort mortality study is a statistically significant excess risk of death due to BT (19 observed and 7.2 expected) among all male hourly employees of a large petrochemical plant after 15 years since first hire. After the passage of that 15-year induction latent period, SMR for death due to BT increased with duration of employment from 147 for workers employed under 10 years, to 357 for those employed 10–19 years, to 377 for those employed over 20 years. These results confirm the excess risk of BT which was suspected 2 years ago upon our initial discovery of several BT cases at this plant (*4*). Thir-

teen of the 14 cases who had worked at the plant for more than 10 years were confirmed pathologically to have had a BT.

Elevated risks of brain cancer have been found among chemists (*6*) and have been associated with employment in the refinery (*7–9*), chemical production (*10*), pharmaceutical (*11*) and rubber (*12–14*) industries, and with occupational exposure to vinyl chloride monomer (*15–18*). In addition, recent data suggest that an excess of deaths due to BT may be emerging among workers exposed to acrylonitrile (*19*); this finding is consistent with the neuro-oncogenicity of this compound in rats (*20*).

Given the complexity of chemical exposures that have existed since 1941 at the plant under study, a specific chemical or other cause for the excess risk of BT observed in the present study has not yet been identified. However, several proven carcinogens are known to have been produced or used at this petrochemical plant (*4*). The likelihood that one of these compounds or some other chemical not yet identified is responsible for the observed excess receives support from the observation of a twofold PMR for deaths due to brain cancer among workers at a petrochemical plant in West Virginia (Marsh G: A preliminary exploratory study of proportional mortality among employees and ex-employees of the Union Carbide Corporation's plant at South Charleston, West Virginia. Union Carbide Corporation, August 22, 1979). That plant, owned by the same company as the plant examined in this study, has used many of the same production processes. To identify a specific chemical carcinogen responsible for the observed excess of BT at this plant, we are conducting a case–control study nested within this cohort; this study will be reported separately.

In evaluating the excess risk of BT at the Texas City plant, one must consider the appropriateness of using BT mortality rates from the entire United States for comparison. Over the last three decades (1950–59, 1960–69, and 1970–78), the annual age-adjusted mortality rate per 100,000 for malignant BT (ICD 193) among white males has risen from 4.0 to 4.6 to 5.0 in the United States and from 2.6 to 5.9 to 7.4 in Galveston County (Riggan WB, Van Bruggen J, Acquavella JF, Beaubier J: U.S. cancer mortality rates and trends, 1950–78, U.S. Environmental Protection Agency). Without age-specific mortality rates, which were unavailable, it was impossible to determine the exact magnitude of change in our SMR that would have resulted if we had used Galveston County rates. However, if Galveston County crude rates had been used instead of U.S. rates for comparison, the number of expected deaths would have increased by approximately 30%. In addition, age-specific BT mortality rates for the United States were not available for the entire period 1975–79. On the basis of the increase in the United States in BT mortality rate over the last two decades, we estimated that the use of 1975 mortality rates for 1975–79 underestimated the total expected deaths due to BT by less than 1%.

The possibility must be considered that BT might be diagnosed more frequently among the employees of this plant than among the general population as a result of the petrochemical workers' better access to medical care. Although numerous occupational cohort studies previously reported in the literature have found no excess of BT, the possible existence of such a bias has been suggested recently by Greenwald et al. (*21*, *22*) and debated by Gann and Rosenman (*23*). The extent of such a bias is, however, difficult to assess from their study.

The observed excesses of pancreatic cancer and of kidney cancer among those employed for more than 10 years and the overall excess mortality due to leukemia are so small that it is difficult to determine whether they represent a real excess risk or a chance occurrence. However, it is intriguing that in Marsh's study of a similar plant in West Virginia there was observed an excess proportionate risk (PMR=274 vs. U.S. values; PMR=386 vs. county values) of death due to kidney cancer based on 12 cases.

The striking deficit of nonmalignant respiratory disease observed in this study is consistent with that reported in previous studies of oil refinery populations (*8–10*, *24*). Strict enforcement of antismoking rules in these facilities to prevent explosions may be partially responsible for this deficit as well as for the observed deficits of lung cancer, bladder cancer, and cardiovascular disease.

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