FAST TRACK ARTICLE

Long-Term Health Experience of Jet Engine Manufacturing Workers: I. Mortality From Central Nervous System Neoplasms

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Objective: *In response to an unusual occurrence of glioblastoma at one jet engine manufacturing facility located in North Haven (NH), Connecticut (CT), we examined mortality rates from central nervous system (CNS) neoplasms at NH and seven other company facilities.* ***Methods:*** *Subjects were 223,894 workers ever employed in one or more of the company's eight CT manufacturing facilities from 1952 to 2001. Vital status was determined through 2004 for 99% of subjects and cause of death for 95% of 68,701 deaths. We computed standardized mortality ratios (SMRs) based on US and CT state rates and modeled internal relative risks (RRs).* ***Results:*** *State comparisons revealed overall deficits in deaths from all CNS neoplasms (606 deaths, SMR = 0.84, confidence interval [CI] = 0.78 to 0.91), including all malignant (462 deaths, SMR = 0.87, CI = 0.79 to 0.95), all benign (23 deaths, SMR = 0.65, CI = 0.41 to 0.98), and all unspecified (121 deaths, SMR = 0.79, CI = 0.65 to 0.94). Not statistically significant excesses in deaths from all malignant brain neoplasms were found among subjects who worked only at NH (49 deaths, SMR = 1.11, CI = 0.82 to 1.47) or partly at NH (24 deaths, SMR = 1.04, CI = 0.67 to 1.55) compared with deficits in non-NH plant groups. In the combined NH plant groups, we found not statistically significant higher risks of malignant brain neoplasms for salaried workers, older hires and the most recent time period, but no association with duration of employment or time since first employment.* ***Conclusions:*** *Total cohort mortality rates for malignant, benign or unspecified CNS neoplasms were not elevated relative to the US and CT general populations. The malignant brain neoplasm excesses in certain subgroups of workers from NH may reflect external occupational factors, nonoccupational factors or workplace factors unique to NH that were not measured in the current study. We will explore reasons for the NH excesses and examine specific types of brain neoplasms (eg, glioblastoma) in our companion cancer incidence, case–control and exposure assessment studies.* (J Occup Environ Med. *2008;50:1099–1116*)

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DOI: 10.1097/JOM.0b013e31818bc30e

Pratt & Whitney (P&W) Aircraft was established in 1925 and became a division of United Aircraft Corporation, the forerunner of United Technologies Corporation, in 1934 (P&W Aircraft, 1966). Since that time P&W has operated up to eight aircraft engine manufacturing, assembly and overhaul and repair plants in Connecticut (CT). The CT plants have operated over various timeframes with the majority open from the 1960s to the 1990s. Sufficient data exist to determine operations performed among the eight facilities in space and time over the course of the study period. The operations may be broadly categorized as new part production, assembly and overhaul and repair. Many of the operations occupied the same facility footprint for the entire life of the operation whereas other operations periodically moved based on the needs of production efficiency or other factors. This distribution of operations over time provides a contrast scheme for future analyses based on a worker's occupational history relative to a particular plant or even a particular process.

In May 2000, the CT Department of Public Health (CTDPH) began an investigation of a perceived increase of brain cancer at the P&W engine manufacturing plant in North Haven (NH), CT. By August 2001, the CTDPH investigation had identified several cases of primary, malignant brain cancer, all of which were confirmed by the CT Tumor Registry Program. All cases occurred among white male

workers, and most of the cases were a common type (glioblastoma). A preliminary comparative cancer incidence analysis conducted by the CTDPH was inconclusive, and the CTDPH recommended that a more comprehensive and rigorous investigation be undertaken by an independent research group.

In August 2001, at the recommendation of the CTDPH and the National Institute for Occupational Safety and Health, two of the authors (G.M. and N.E.) were asked by P&W to evaluate the feasibility of conducting a formal epidemiologic investigation of the suspected brain cancer excess. The feasibility study, which included an evaluation of information assembled by P&W for NH and five other central CT plant sites (East Hartford, Middletown, Rocky Hill, Southington-Aircraft Road and Southington-Newell Street), concluded that sufficient data were available for these plants to warrant a formal epidemiological investigation and recommended that this include two other P&W central CT plants (Cheshire and Manchester Foundry). Only three of these plants (East Hartford, Middletown, and Cheshire) are currently operating. The other plants were closed and the operations contained therein were transferred during the years 1988 to 2002.

In July 2002, we began work on a multipart epidemiology study. The epidemiology and biostatistical component of the study, conducted by the University of Pittsburgh (UPitt), Department of Biostatistics, includes historical cohort mortality and cancer incidence studies, a nested case–control study of malignant and benign neoplasms of the brain and other central nervous system (CNS) cancer sites (termed CNS neoplasms) and a genetics study based on tissue specimens obtained from cases of malignant brain neoplasms. A companion exposure assessment project, conducted independently by the University of Illinois at Chicago (UIC), Division of Environmental and Occupational Health Sciences, is characterizing the historical work practices and exposures that occurred in each P&W study plant. Ultimately, UPitt will link the work history and exposure information to examine the relationship between mortality and incidence from CNS neoplasms and the past working environments of the P&W study plants.

The only well-established association between an environmental or occupational exposure and the occurrence of CNS neoplasms is with exposure to therapeutic doses of ionizing radiation.[1–3] Considering how little is known about the etiology of CNS neoplasms, no specific occupational factors at the NH or other P&W study plants (ie, exposures to specific agents or particular job assignments) have been implicated as risk factors for the perceived brain cancer excess. Thus, we considered this epidemiological investigation as exploratory in nature and did not attempt to test any specific a priori etiologic hypotheses.

We report here the results of our first analysis of CNS neoplasms from the historical cohort mortality study. Our evaluation of total and cause-specific mortality (excluding CNS neoplasms) in this cohort is reported elsewhere.[4] The main objective of the current analysis was to determine definitively whether mortality rates from CNS neoplasms were elevated among the P&W workforce. For selected categories of CNS neoplasms with elevated mortality rates, we also sought to identify possible occupational associations using the currently available data on workplace factors.

Materials and Methods

Study Sites and Subjects

The study cohort includes all persons ever employed for at least 1 day at one or more of the eight study plants from 1952 through 2001, where 1952 is the start-up date of the NH "index" plant. For the three plants that started before 1952 (East Hartford—1930, Manchester Foundry—1943, and Southington Aircraft Road—1943), the earliest cohort entry date is also 1952, thus persons who terminated or died before 1952 were not included. For the remaining plants the earliest cohort entry date is the date of plant start-up (Middletown—1966, Southington Newell Street—1967, Rocky Hill—1967, and Cheshire—1990). From 1957 to 1965 the Middletown site was a government-owned nuclear research laboratory, the CT Advanced Nuclear Engineering Laboratory (CANEL), operated by P&W. P&W acquired the site in 1966 and began jet engine production. Work histories were collected for CANEL employees that continued to hold P&W jobs in 1966. After the acquisition, however, exposures related to CANEL jobs were not characterized because the activities do not truly correspond to those in jet engine manufacturing and work histories for employees who did not transfer to P&W were unavailable. We collected work histories for employees known to have transferred to P&W facilities in West Palm Beach, FL, Berwick, ME, and Columbus, GA to ensure that overall work histories were complete.

Cohort Enumeration

We enumerated the study cohort from multiple sources identified through discussion with company human resources personnel and exhaustive searches of the company's archives and facilities. Study-relevant records were identified on microfilm (n = 100,000), from two company-held human resource databases (n = 80,000), from employee work cards (n = 245,000), and in hard copy personnel files (n = 315,000). Hard copy and work card records were scanned; microfilm was converted to a digitized form. Study variables were then abstracted from the digitized images; data abstraction was verified by cross-checking random samples of files. During the course of our cohort enumeration, we had as many as 266,667 unique potential study participants in the co-

hort but some of these were found not to be eligible because they did not meet the cohort entrance criterion of working one or more days from January 1, 1952 to December 31, 2001 (n = 32,570) or because they never worked at one of the eight CT study facilities (n = 10,203). We have more than three million work history entries for employees in our final cohort.

Independent Validation of Cohort Completeness

We conducted standard internal checks of cohort completeness by examining patterns in work history characteristics relevant to record filing, eg, name, date of hire, and termination. With the help of archivists from the University of CT's Thomas J. Dodd Research Center, a sample of union employees was randomly selected from the archived union records as an external validation of cohort completeness. Records such as union membership and seniority lists were available for four study plants: Middletown, East Hartford, NH, and Southington for the time periods 1967 to 1977, 1975 to 1981, 1964 to 1980, and 1973 to 1979, respectively. A plant and time period-stratified random sample of union employees selected from the lists and cross-checked against the cohort file revealed an acceptable missing rate of only 1.7% (95% confidence interval [CI] = 0.9% to 2.5%).

Vital Status Tracing and Underlying and Contributory Cause of Death Ascertainment

We used our standard two-stage vital status tracing protocol to identify deaths among cohort members[5] with unconfirmed vital status (not known from company-held records to be alive as of the study end date, December 31, 2004). Phase 1 consisted of sending all the names of cohort members not known to be alive to the Social Security Administration. The Social Security Administration identifies living, unknown, and deceased vital status. Subjects with invalid social security numbers and those who were assumed alive at 100 years old were classified as lost to follow-up and person years were stopped at date of termination.

Phase 2 consisted of sending subjects identified as having died before 1979 to the health department of the state of death to obtain a death certificate. Subjects identified as unknown or deceased after 1978 were sent to the National Death Index-Plus to obtain the coded cause of death. Death certificates were coded to the underlying cause of death by a National Center for Health Statistics nosologist using the International Classification of Diseases (ICD) rules in effect at time of death. The Appendix (available online at www.joem.org) provides the special cause of death categories and revision-specific ICD codes used in our detailed evaluation of mortality from CNS neoplasms. Because of the limited amount of information available regarding the etiology of brain cancer and the lack of specific a priori hypotheses in this study, we evaluated mortality from all CNS neoplasms rather than limiting our evaluations to brain cancer to ensure that we did not overlook any important findings. We were unable to identify specific histological types of CNS neoplasms, such as glioblastoma, using ICD codes because these codes do not incorporate histopathological information.

As part of our internal cohort rate analysis, we also made an effort to identify employees for whom CNS neoplasms were a contributory, rather than the underlying, cause of death. We reviewed the National Death Index output, which includes codes for up to 20 contributory conditions, for any mention of a CNS neoplasm code (online Appendix). We also manually scanned all death certificates for any mention of a CNS neoplasm. Every death certificate with mention of CNS was sent to our nosologist who then coded the death certificate for contributory causes of death using the ICD rules in effect at time of death. We added an additional 74 deaths from 1976 to 2004, because of a contributory, rather than underlying, cause of death from CNS neoplasms.

Statistical Methods

External Mortality Comparisons. We examined mortality from CNS neoplasms during the years 1952 to 2004. Because the specificity of the ICD codes for CNS neoplasms increased across the 6th through 10th revisions of the ICD covered by our study, we evaluated four different time-dependent groupings of CNS neoplasms. We also limited our detailed evaluation of CNS neoplasms to the time period 1976 to 2004 to account for the major advancements in diagnostic specificity and sensitivity for brain cancer that began in the mid-1970s with the advent of highly accurate computed tomography scanning, and continued in the 1980s with the introduction of effective nuclear magnetic resonance scanning technology. Parallel to these milestones was the release of the first ICD for specialized oncologic coding (ICD-O) in 1976. Benign CNS neoplasms were not evaluated in detail because of the small number of observed deaths and the diversity of the tumors in this category.

Cohort analyses were performed using a modified life table procedure from the Occupational Cohort Mortality Program (OCMAP-Plus).[6] Person-year counts began at the beginning of the study period or date of hire (whichever occurred later) and continued until date of death or the end of the study period. For workers lost to follow-up, person-year counts stopped at the last date of known vital status, which was employment termination date. Using the proportional allocation module in OCMAP-Plus, person-years and observed deaths for subjects of unknown race were assigned to white or non-white categories in proportion to the factor-specific distributions (ie, age group, time period, sex, and plant group) of study members with known race.

The accuracy of the proportional allocation module procedure has been previously validated by a model-based imputation procedure based on the E-M algorithm.[7] The expectation maximization [EM] algorithm is a statistical tool that can be used for estimating regression coefficients in settings involving incomplete data.[7] In the expectation [E] step, the expectation of the likelihood is computed using the unobserved data as if it were observed. In the maximization [M] step, the maximum likelihood estimates of the regression model parameters are computed by maximizing the expected likelihood found in the E step. The parameters computed in the M step are then used in the next E step. This process is repeated until convergence.

We computed expected numbers of deaths based on both the US and CT state standard population death rates. County-specific rates were not used in this analysis as the contiguous counties surrounding all eight study plants comprised seven of the eight counties in CT. Population-weighted CT state rates were obtained from the Mortality and Population Data System maintained by UPitt.[8] Due to Mortality and Population Data System data limitations (mortality rates for all causes combined and nonmalignant causes limited to 1962 to 2004), expected numbers of deaths for these cause of death categories during the years 1952 to 1961 were based on standard rates for 1962 to 1964. Because the more regional state death rates usually provide more valid external mortality comparisons (as they help to adjust for the social, cultural, and economic factors related to disease) our analysis of general mortality patterns focused primarily on the CT state comparison.

Standardized Mortality Ratios (SMRs) and their 95% CIs were computed for all subjects combined and by the study factors: sex, employment type (short-term [<1 year] vs long-term [1+ years]), age group, time period, age and year of hire, duration of employment (DOE), and time since first employment (TSFE). DOE was considered as a surrogate measure of a subject's overall experience or "exposure" in the working environments of the study sites; TSFE was used to account for the combined induction and latency periods of chronic diseases, which for some diseases, such as cancer, can equal 20 or more years.[9] Using P&W clock number data, we assigned a static, non time-dependent "payroll type" to each study member as hourly, salary or mixed. P&W assigned clock numbers to workers in a systematic fashion at hire or when switching from hourly to salary work. This variable is used as a surrogate measure of socioeconomic status (SES) and, if warranted, to control for potential confounding by SES in some mortality comparisons. Using currently available data, we also created a "plant group" variable to distinguish subjects who had exclusive or partial employment at the "index" NH plant from subjects never employed at NH or whose plant affiliation is currently not known for all jobs (unspecified) (mortality analyses of the P&W cohort are planned that will enable stratification by each of the eight study plants). Statistically significant deviations of the SMRs below and above 1.00 were identified using Poisson probabilities.[10]

Internal Mortality Comparisons for CNS Neoplasms. We used relative risk (RR) regression modeling to investigate the dependence of the internal cohort mortality rates for CNS neoplasms (modeled as time to death) on each of the study factors considered. The analysis was limited to the diagnostically more reliable 1976 to 2004 time period and all study factors were categorized a priori to parallel the descriptive SMR analyses. For each CNS neoplasm category considered, risk sets were explicitly constructed from the cohort data file with age as the primary time dimension, using the RISKSET program module in OCMAP-Plus.[6] Risk sets were matched further on sex and on date of birth (±1 year) to control for cohort effects. Multiplicative RR models of the form $\lambda(t) = \lambda_0(t) \exp\{x(t)\beta\}$ were fit to the internal cohort rates[11,12] and the stratified conditional logistic regression programs in STATA[13] and LogXact[14] were used to estimate β from the explicitly constructed risk sets. No attempt was made to impute race for subjects with unknown race. Study factors were first considered separately to identify patterns of univariate associations with outcome variables and possible sparse data problems. Possible multistudy factor models were then evaluated with a forward stepwise approach to adjust for possible confounders. Effect modification was assessed if warranted by the main effects. We assessed the statistical significance of each main effect (expressed as a global *P* value) with a likelihood ratio statistic and, for relevant factors, also conducted a test for linear trend (expressed as a trend *P* value).

We conducted our internal mortality comparisons of CNS neoplasms using two groupings of cause of death codes: 1) those identified as the underlying cause of death as used in the external mortality analyses and 2) those identified as the underlying or contributory cause of death. The addition of deaths coded as contributory cause(s) helps to identify CNS neoplasms associated with longer-term survival (eg, certain benign CNS neoplasms) and, as such, produces estimates of RRs that are closer to those obtained in cancer incidence studies that ascertain cases via a cancer registry.[15] SMRs and RRs based on small numbers of observed or expected deaths were (and should be) interpreted with appropriate caution due to their relative imprecision (ie, wide CIs). All tests on SMRs and RRs were done at the 0.05 significance level and no formal adjustments were made for multiple comparisons. Results were not stratified by race because of the large number of unknown values.

Results

Characteristics of the Study Cohort

The study cohort includes 223,894 subjects who contributed 7,713,434 person-years of observation during the 1952 to 2004 study period (Table 1). A total of 26,801 subjects (940,820 person-years) worked exclusively at the NH plant and 11,898 subjects (423,515 person-years) spent part of their known work history at this plant. Males comprised 80% of the total cohort and race was unknown for about 60% of all subjects. In all plant groups, the largest percentage of workers was hired between ages 20 and 24 and during the years 1952 to 1969. Short-term workers (<1 year) comprised 36.6% of the total cohort and approximately 2/3 of the cohort worked for less than 5 years; however, a substantial number of workers in each plant group were employed for 5 or more years and followed for mortality for 20 or more years. The only NH group had the largest percentages of hourly workers (91.0%), short-term workers (57.1%), and non-white workers (28.2% of those with known race)—findings consistent with known employment patterns at NH. Table 1 also shows that we identified 68,701 subjects or 30.7% of the cohort as deceased and that cause of death was obtained for 65,272 or 95.0%. Only 2066 subjects, or 0.9% of the cohort, were lost to follow-up. We were able to confirm that 138,087 subjects or 61.6% of the cohort were alive as of the study end date; the remainder (6.8%) were assumed to be alive per our vital status tracing protocol.

External Mortality Comparisons

For the total cohort during the entire 1952 to 2004 study period, Table 2 shows observed deaths and SMRs for CNS neoplasms based on both US and CT state death rates. We observed statistically significant US rate-based deficits in deaths from all CNS neoplasms combined (606 deaths, SMR = 0.85, CI = 0.79 to 0.92), all malignant CNS neoplasms (462 deaths, SMR = 0.83, CI = 0.75 to 0.90), and all benign CNS neoplasms (23 deaths, SMR = 0.56, CI = 0.36 to 0.84). Similar findings were observed based on the CT state comparisons. A total of 121 deaths were observed for all CNS neoplasms of unspecified nature or uncertain or unknown behavior (termed "unspecified"), yielding a not statistically significant 9% excess in deaths based on the US comparison (SMR = 1.09, CI = 0.91 to 1.30) and a statistically significant 21% deficit in deaths based on the state comparison (SMR = 0.79, CI = 0.65 to 0.94).

Observed deaths and state rate-based SMRs for CNS neoplasms during 1952 to 2004 are shown in Table 3 by payroll type and plant group. Hourly workers were associated with about 70% of the observed deaths in all categories except benign CNS neoplasms (52%). With the exception of a not statistically significant 13% excess in benign CNS neoplasms among salaried workers, deficits in deaths were observed in all categories examined and many were statistically significant. By plant group, 109 (18%) and 87 (18%) of deaths from all CNS neoplasms combined and all malignant CNS neoplasms, respectively, occurred among subjects who worked only or partly at NH, compared with 9 or 39% of benign CNS neoplasms. SMRs for all CNS neoplasms, all malignant CNS neoplasms and unspecified CNS neoplasms were below or close to 1.00 in all plant groups; most deficits in the never NH and unspecified plant groups were statistically significant. For all benign CNS neoplasms, 1.34-fold (five deaths, SMR = 1.34, CI = 0.43 to 3.12) and 2.03-fold (four deaths, SMR = 2.03, CI = 0.55 to 5.21), not statistically significant excesses in deaths were observed for the only and partially NH groups, respectively.

Table 4 shows, for the total cohort and the four plant groups, observed deaths and state rate-based SMRs for broad and detailed categories of CNS neoplasms for four overlapping (all end in 2004) time periods (online Appendix). Categories including less than two observed deaths for all subgroups are not shown. During the diagnostically more accurate 1976 to 2004 (B) time period, malignant brain cancer accounted for 381 or 96% of the 398 deaths from all malignant CNS neoplasms combined (Table 4). During the 1979 to 2004 (C) period when the anatomical location of the brain neoplasm was first identifiable from ICD codes, 333 or 92% of the 362 deaths from malignant brain neoplasms were still unspecified as to site. Table 4 shows that during 1976 to 2004, about one-half of the 21 observed deaths from benign CNS neoplasms in the total cohort were located in the cerebral meninges. Other sites included cranial nerves,[2] pituitary gland and craniopharyngeal duct[2] and part unspecified.[4] Deaths from benign CNS neoplasms not shown in Table 4 include one brain and one spinal meninges. During 1976 to 2004, 98 or 91% of the 108 unspecified CNS neoplasms occurred in the brain. SMRs for unspecified CNS neoplasms were mostly less than 1.00 for all plant groups and time periods.

As shown in Table 4, among workers with only NH employment we observed elevated, not statistically significant SMRs for all malignant CNS neoplasms (time periods A–D) and malignant brain neoplasms (time periods B–D), which were higher than those in the other three plant groups that revealed mostly deficits in deaths. The SMRs for malignant brain cancer in the only NH group increased across the time periods, culminating with the largest, not statistically significant SMR in the most recent 1999 to 2004 (D) period (16 deaths, SMR = 1.37, CI = 0.78 to 2.23). With the exception of the partially NH group in the B and C time periods, the other plant groups revealed deficits in malignant brain cancer deaths; the values and pattern of SMRs for the broader cat-

TABLE 1
Distribution of Jet Engine Manufacturing Worker Cohort by Selected Study Factors and Plant Group*

	All Workers		Only North Haven Plant		Partially North Haven Plant		Never North Haven Plant		Unspecified	
Study Factor	***N***	**Percent**	***N***	**Percent**	***N***	**Percent**	***N***	**Percent**	***N***	**Percent**
Persons (1952–2001)	223,894	100.0	26,801	100.0	11,898	100.0	153,130	100.0	32,065	100.0
Person-years (1952–2004)	7,713,434	100.0	940,820	100.0	423,515	100.0	5,124,857	100.0	1,224,242	100.0
Race-sex										
Known race	89,196	39.8	7177	26.8	6005	50.5	65,592	42.8	10,422	32.5
White male	62,673	70.3	4219	58.8	4477	74.6	46,061	70.2	7916	76.0
Non-white male	6849	7.7	1354	18.9	546	9.1	4316	6.6	633	6.1
White female	16,067	18.0	934	13.0	720	12.0	12,868	19.6	1545	14.8
Non-white female	3607	4.0	670	9.3	262	4.4	2347	3.6	328	3.1
Unknown race	134,698	60.2	19,624	73.2	5893	49.5	87,538	57.2	21,643	67.5
Male	109,590	81.4	17,100	87.1	4726	80.2	71,500	81.7	16,264	75.1
Female	25,108	18.6	2524	12.9	1167	19.8	16,038	18.3	5379	24.9
Worker type										
Short-term (<1 yr)	81,938	36.6	15,297	57.1	1257	10.6	60,447	39.5	4937	15.4
Long-term (1+ yr)	141,956	63.4	11,504	42.9	10,641	89.4	92,683	60.5	27,128	84.6
Payroll type										
Salary	64,718	28.9	1786	6.7	4550	38.2	46,118	30.1	12,264	38.2
Hourly	146,693	65.5	24,399	91.0	5812	48.9	99,463	65.0	17,019	53.1
Mixed	12,483	5.6	616	2.3	1536	12.9	7549	4.9	2782	8.7
Vital status (December 31, 2004)										
Alive	153,127	68.4	18,802	70.1	8316	69.9	105,475	68.9	20,534	64.0
Assumed	15,040	9.8	2164	11.5	494	5.9	10,516	10.0	1866	9.1
Confirmed	138,087	90.2	16,638	88.5	7822	94.1	94,959	90.0	18,668	90.9
Dead	68,701	30.7	7868	29.4	3486	29.3	46,092	30.1	11,255	35.1
Cause of death known	65,272	95.0	7594	96.5	3323	95.3	43,662	94.7	10,693	95.0
Cause of death unknown	3429	5.0	274	3.5	163	4.7	2430	5.3	562	5.0
Not traced	2066	0.9	131	0.5	96	0.8	1563	1.0	276	0.9
Working status (December 31, 2001)										
Active	15,913	7.1	565	2.1	2194	18.4	11,635	7.6	1519	4.7
Separated	204,661	91.4	25,932	96.8	9491	79.8	139,424	91.0	29,814	93.0
Died while employed	3320	1.5	304	1.1	213	1.8	2071	1.4	732	2.3
Age at hire										
<20 yr	30,574	13.7	4875	18.2	1357	11.4	19,992	13.0	4350	13.6
20–24	83,560	37.3	10,025	37.4	4572	38.4	57,108	37.3	11,855	37.0
25–29	40,232	18.0	3973	14.8	2480	20.9	27,664	18.1	6155	19.0
30+	69,528	31.0	7928	29.6	3489	29.3	48,366	31.6	9745	30.4
Year of hire										
<1952	27,152	12.1	396	1.5	1433	12.0	18,507	12.1	6816	21.3
1952–1959	58,601	26.2	6597	24.6	4781	40.2	36,173	23.6	11,050	34.4
1960–1969	81,700	36.5	14,429	53.8	2599	21.8	55,083	36.0	9589	29.9
1970+	56,441	25.2	5379	20.1	3085	26.0	43,367	28.3	4610	14.4
Duration of employment (yr)										
<1	81,938	36.6	15,297	57.1	1257	10.6	60,447	39.5	4937	15.4
1–4	61,302	27.4	6308	23.5	3048	25.6	42,564	27.8	9382	29.3
5–19	42,919	19.2	2951	11.0	3622	30.4	27,355	17.8	8991	28.0
20+	37,735	16.8	2245	8.4	3971	33.4	22,764	14.9	8755	27.3
Time since first employment (yr)										
<20	32,610	14.6	2963	11.0	1948	16.4	25,158	16.4	2541	7.9
20–29	33,846	15.1	3591	13.4	1669	14.0	24,974	16.3	3612	11.3
30–39	80,074	35.8	12,403	46.3	2767	23.3	55,056	36.0	9848	30.7
40+	77,364	34.5	7844	29.3	5514	46.3	47,942	31.3	16,064	50.1

*Only North Haven—plant known for all jobs in work history and all plants are North Haven. Partially North Haven—at least one of known plants is North Haven; plant may not be known for all jobs in work history. Never North Haven—plant known for all jobs in work history and none of plants is North Haven. Unspecified—plant not known for all jobs in work history and none of plants is North Haven.

TABLE 2
Jet Engine Manufacturing Worker Cohort Observed Deaths and SMRs for Selected Causes of Death, United States and Connecticut State Comparisons, All Workers, 1952–2004

Cause of Death[a]	Observed	United States		Connecticut	
		SMR	95% CI	SMR	95% CI
All central nervous system (CNS) neoplasms	606	0.85**	0.79–0.92	0.84**	0.78–0.91
Malignant CNS neoplasms	462	0.83**	0.75–0.90	0.87**	0.79–0.95
Benign CNS neoplasms	23	0.56**	0.36–0.84	0.65*	0.41–0.98
Unspecified CNS neoplasms	121	1.09	0.91–1.30	0.79**	0.65–0.94

*$P < 0.05$.
**$P < 0.01$.
[a]See online Appendix for listing of corresponding ICD codes by ICD revision.

TABLE 3
Jet Engine Manufacturing Worker Cohort Observed Deaths and SMRs for Central Nervous System Neoplasms, Connecticut State Comparison, All Workers, 1952–2004, by Payroll Type and Plant Group

Cause of Death[a]	Payroll Type					
	Salary		Hourly		Mixed	
	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
All central nervous system (CNS) neoplasms	152	0.88 (0.75–1.04)	420	0.84** (0.76-.0.92)	34	0.72 (0.50–1.01)
Malignant CNS neoplasms	119	0.92 (0.77–1.11)	319	0.87* (0.78–0.97)	24	0.69 (0.44–1.11)
Benign CNS neoplasms	9	1.13 (0.52–2.15)	12	0.47** (0.24–0.82)	2	0.96 (0.12–3.45)
Unspecified CNS neoplasms	24	0.68 (0.44–1.11)	89	0.82 (0.66–1.01)	8	0.81 (0.35–1.59)

	Plant Group							
	Only North Haven		Partially North Haven		Never North Haven		Unspecified Plant	
	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95 % CI)
All central nervous system (CNS) neoplasms	71	0.93 (0.73–1.18)	38	0.91 (0.64–1.25)	401	0.84** (0.76–0.93)	96	0.76** (0.62–0.93)
Malignant CNS neoplasms	57	1.01 (0.77–1.31)	30	0.97 (0.66–1.39)	306	0.87* (0.77–0.97)	69	0.75* (0.59–0.95)
Benign CNS neoplasms	5	1.34 (0.43–3.12)	4	2.03 (0.55–5.21)	9	0.39** (0.18–0.74)	5	0.76 (0.25–1.78)
Unspecified CNS neoplasms	9	0.56 (0.26–1.07)	4	0.45 (0.12–1.15)	86	0.85 (0.68–1.04)	22	0.81 (0.51–1.22)

*$P < 0.05$.
**$P < 0.01$.
[a]See online Appendix for listing of corresponding ICD codes by ICD revision.

egory "all malignant CNS neoplasms" were similar. Table 4 shows that, in the only and partially NH plant groups, not statistically significant excesses were found for benign CNS neoplasms based on small numbers of deaths (time periods A–C); the never NH and unspecified plant groups showed mainly deficits in the benign CNS categories.

Table 5 shows observed deaths and state rate-based SMRs during 1976 to 2004 for malignant brain neoplasms according to plant group and several selected study factors. For many study factors, SMR patterns for malignant brain neoplasms were consistent between subjects who worked only or partly at the NH plant, eg, excesses in male workers compared with deficits in females; excesses in salaried workers compared with mostly deficits in the hourly or mixed groups; excesses among workers aged 75 to 84 years (only NH plant group, 10 deaths, SMR = 2.18, CI = 1.05 to 4.02, statistically significant) compared with smaller excesses or deficits in younger workers; excesses during the last decade of follow-up (1995 to 2004) compared with mostly deficits in earlier periods (eg, only NH plant group: 1995 to 2004, 28 deaths, SMR = 1.50, CI = 0.99 to 2.16); excesses for workers hired in 1960 or

TABLE 4
Jet Engine Manufacturing Worker Cohort Observed Deaths and SMRs for Selected Central Nervous System Neoplasms, Connecticut State Comparison, All Workers, 1952–2004, by Plant Group and Study Period (A = 1952–2004, B = 1976–2004, C = 1979–2004, D = 1999–2004)

	Cause of Death and (Study Period)[a]	All Workers		Only North Haven		Partially North Haven		Never North Haven		Unspecified Plant	
		Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
All CNS neoplasms	All CNS neoplasms (A)	606	0.84** (0.78–0.91)	71	0.93 (0.73–1.18)	38	0.91 (0.64–1.25)	401	0.84** (0.76–0.93)	96	0.76** (0.62–0.93)
	All CNS neoplasms (B)	527	0.94 (0.86–1.02)	64	1.04 (0.80–1.33)	31	0.97 (0.66–1.38)	349	0.94 (0.85–1.05)	83	0.87 (0.69–1.08)
	All CNS neoplasms (C)	490	0.94 (0.86–1.03)	60	1.05 (0.80–1.35)	28	0.94 (0.63–1.37)	325	0.95 (0.85–1.06)	77	0.87 (0.69–1.09)
	All CNS neoplasms (D)	127	0.89 (0.74–1.06)	19	1.21 (0.73–1.88)	5	0.60 (0.19–1.39)	86	0.92 (0.73–1.13)	17	0.71 (0.41–1.14)
Malignant CNS neoplasms	Malignant CNS neoplasms (A)	462	0.87** (0.79–0.95)	57	1.01 (0.77–1.31)	30	0.97 (0.66–1.39)	306	0.87* (0.77–0.97)	69	0.75* (0.59–0.95)
	Malignant CNS neoplasms (B)	398	0.94 (0.85–1.04)	51	1.10 (0.82–1.44)	25	1.03 (0.67–1.52)	264	0.94 (0.83–1.06)	58	0.81 (0.62–1.05)
	Malignant CNS neoplasms (C)	369	0.94 (0.85–1.04)	49	1.13 (0.84–1.49)	23	1.02 (0.65–1.53)	241	0.93 (0.82–1.05)	56	0.85 (0.64–1.10)
	Malignant CNS neoplasms (D)	96	0.90 (0.73–1.10)	16	1.34 (0.77–2.17)	5	0.79 (0.26–1.85)	65	0.92 (0.71–1.17)	10	0.56 (0.27–1.03)
	Meninges (B)	2	0.41 (0.05–1.46)	0	—	0	—	2	0.61 (0.07–2.21)	0	—
	Spinal cord (B)	2	1.21 (0.15–4.36)	1	—	0	—	1	—	0	—
	Central nervous system, unspecified (B)	10	0.82 (0.39–1.50)	1	—	1	—	7	0.86 (0.34–1.77)	1	—
	Pineal gland (B)	2	3.72 (0.45–13.44)	0	—	0	—	2	5.74 (0.70–20.74)	0	—
	Brain (B)	381	0.95 (0.85–1.05)	49	1.11 (0.82–1.47)	24	1.04 (0.67–1.55)	251	0.94 (0.83–1.07)	57	0.84 (0.64–1.09)
	Brain (C)	362	0.94 (0.85–1.05)	48	1.14 (0.84–1.51)	23	1.05 (0.66–1.57)	235	0.93 (0.81–1.05)	56	0.87 (0.66–1.13)
	Brain (D)	95	0.91 (0.74–1.11)	16	1.37 (0.78–2.23)	5	0.81 (0.26–1.88)	64	0.92 (0.71–1.18)	10	0.57 (0.28–1.05)
	Cerebrum, except lobes and ventricles (C)	10	1.18 (0.56–2.17)	0	—	0	—	9	1.60 (0.73–3.03)	1	—
	Frontal lobe (C)	3	0.60 (0.12–1.76)	1	—	0	—	2	0.60 (0.07–2.18)	0	—
	Temporal lobe (C)	5	1.08 (0.35–2.51)	0	—	0	—	3	0.97 (0.20–2.85)	2	2.58 (0.31–9.30)
	Parietal lobe (C)	3	1.08 (0.22–3.14)	0	—	0	—	2	1.07 (0.13–3.86)	1	—
	Occipital lobe (C)	2	6.36 (0.77–22.97)	0	—	1	—	1	—	0	—
	Cerebellum (C)	2	1.41 (0.17–5.09)	0	—	0	—	2	1.95 (0.24–7.03)	0	—
	Other (overlapping lesions of brain-10th) (C)	3	2.68 (0.55–7.83)	0	—	1	—	2	2.72 (0.33–9.84)	0	—
	Brain, site unspecified (C)	333	0.93 (0.84–1.04)	47	1.20 (0.88–1.59)	21	1.02 (0.63–1.57)	213	0.90 (0.79–1.03)	52	0.87 (0.65–1.14)
Benign CNS neoplasms	Benign CNS neoplasms (A)	23	0.65* (0.41–0.98)	5	1.34 (0.43–3.12)	4	2.03 (0.55–5.21)	9	0.39** (0.18–0.74)	5	0.76 (0.25–1.78)
	Benign CNS neoplasms (B)	21	0.94 (0.58–1.44)	5	2.02 (0.66–4.71)	3	2.44 (0.50–7.14)	8	0.55 (0.24–1.09)	5	1.21 (0.39–2.81)
	Benign CNS neoplasms (C)	19	0.91 (0.55–1.42)	4	1.72 (0.47–4.40)	3	2.57 (0.53–7.51)	8	0.59 (0.26–1.16)	4	1.02 (0.28–2.62)
	Benign CNS neoplasms (D)	4	0.69 (0.19–1.77)	1	—	0	—	2	0.53 (0.06–1.90)	1	—
	Cranial nerves (B)	2	2.04 (0.25–7.36)	0	—	1	—	1	—	0	—
	Cerebral meninges (B)	11	0.76 (0.38–1.37)	3	1.78 (0.37–5.20)	1	—	5	0.54 (0.17–1.25)	2	0.74 (0.09–2.68)
	Part unspecified (B)	4	0.82 (0.22–2.11)	1	—	0	—	2	0.63 (0.08–2.29)	1	—
	Pituitary gland and craniopharyngeal duct (B)	2	1.32 (0.16–4.78)	1	—	1	—	0	—	0	—
CNS neoplasms of unspecified nature or uncertain/ unknown behavior	Unspecified neoplasms (A)	121	0.79** (0.65–0.94)	9	0.56 (0.26–1.07)	4	0.45 (0.12–1.15)	86	0.85 (0.68–1.04)	22	0.81 (0.51–1.22)
	Unspecified neoplasms (B)	108	0.95 (0.78–1.14)	8	0.65 (0.28–1.28)	3	0.46 (0.10–1.35)	77	1.02 (0.80–1.27)	20	1.01 (0.61–1.56)
	Unspecified neoplasms (C)	102	0.98 (0.80–1.19)	7	0.62 (0.25–1.27)	2	0.34 (0.04–1.22)	76	1.11 (0.87–1.39)	17	0.94 (0.55–1.51)
	Unspecified neoplasms (D)	27	0.92 (0.61–1.34)	2	0.62 (0.08–2.23)	0	—	19	0.99 (0.60–1.55)	6	1.17 (0.43–2.56)
	Unspecified brain (B)	98	0.93 (0.76–1.14)	8	0.71 (0.31–1.41)	3	0.50 (0.10–1.46)	69	1.00 (0.77–1.26)	18	0.98 (0.58–1.55)
	Unspecified brain (C)	92	0.97 (0.78–1.19)	7	0.69 (0.28–1.41)	2	0.37 (0.04–1.32)	68	1.09 (0.84–1.38)	15	0.90 (0.50–1.49)
	Unspecified brain (D)	16	0.68 (0.39–1.11)	1	—	0	—	13	0.85 (0.45–1.45)	2	0.49 (0.06–1.78)

*$P < 0.05$.
**$P < 0.01$.
[a]The study periods associated with the selected cancer sites vary according to years identified by the ICD as: A = 1952–2004, B = 1976–2004, C = 1979–2004, D = 1999–2004. See online Appendix for detailed listing of corresponding ICD codes and associated ICD revisions. Cause of death category not shown if all plant groups contain less than two observed deaths.

TABLE 5
Jet Engine Manufacturing Worker Cohort Observed Deaths and SMRs for Malignant Brain Neoplasms, Connecticut State Comparison, All Workers, 1976–2004, by Selected Study Factors and Plant Group

	All Workers		Only North Haven		Partially North Haven		Never North Haven		Unspecified Plant	
Study Factor	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**
All workers	381	0.95 (0.85–1.05)	49	1.11 (0.82–1.47)	24	1.04 (0.67–1.55)	251	0.94 (0.83–1.07)	57	0.84 (0.64–1.09)
Sex										
Male	331	0.97 (0.87–1.08)	45	1.17 (0.85–1.56)	22	1.09 (0.68–1.65)	222	0.98 (0.85–1.11)	42	0.76 (0.55–1.03)
Female	50	0.84 (0.62–1.10)	4	0.72 (0.20–1.85)	2	0.68 (0.08–2.46)	29	0.75 (0.50–1.08)	15	1.18 (0.66–1.95)
Worker type										
Short-term (<1 yr)	145	1.05 (0.88–1.23)	26	1.07 (0.70–1.57)	4	1.48 (0.40–3.79)	109	1.07 (0.88–1.29)	6	0.62 (0.23–1.34)
Long-term (1+ yr)	236	0.90 (0.79–1.02)	23	1.15 (0.73–1.73)	20	0.99 (0.60–1.52)	142	0.87 (0.73–1.03)	51	0.88 (0.66–1.16)
Payroll type										
Salary	99	0.96 (0.78–1.17)	5	1.91 (0.62–4.46)	12	1.36 (0.70–2.37)	55	0.86 (0.65–1.12)	27	0.96 (0.64–1.40)
Hourly	260	0.96 (0.85–1.09)	43	1.08 (0.78–1.45)	10	0.88 (0.42–1.62)	181	0.98 (0.84–1.13)	26	0.78 (0.51–1.14)
Mixed	22	0.81 (0.51–1.23)	1	0.71 (0.02–3.94)	2	0.67 (0.08–2.42)	15	0.91 (0.51–1.51)	4	0.63 (0.17–1.62)
Age group at risk										
<65	221	0.97 (0.84–1.10)	27	0.97 (0.64–1.41)	14	1.13 (0.62–1.89)	152	1.00 (0.85–1.18)	28	0.79 (0.52–1.14)
65–74	109	0.94 (0.77–1.13)	12	1.08 (0.56–1.88)	6	0.81 (0.30–1.76)	73	0.96 (0.75–1.21)	18	0.83 (0.49–1.32)
75–84	46	0.93 (0.68–1.24)	10	2.18* (1.05–4.02)	4	1.46 (0.40–3.73)	23	0.69 (0.44–1.04)	9	0.99 (0.45–1.88)
85+	5	0.60 (0.19–1.39)	0	—	0	—	3	0.54 (0.11–1.58)	2	1.19 (0.14–4.30)
Time period at risk										
1976–1984	78	0.89 (0.71–1.11)	8	0.83 (0.36–1.64)	4	0.82 (0.22–2.09)	53	0.92 (0.69–1.20)	13	0.87 (0.46–1.48)
1985–1994	146	0.99 (0.83–1.16)	13	0.82 (0.44–1.41)	9	1.06 (0.48–2.01)	98	1.00 (0.81–1.22)	26	1.03 (0.68–1.52)
1995–2004	157	0.94 (0.80–1.09)	28	1.50 (0.99–2.16)	11	1.14 (0.57–2.03)	100	0.90 (0.73–1.10)	18	0.65 (0.38–1.02)
Age at hire										
<20 yr	38	1.06 (0.75–1.46)	3	0.58 (0.12–1.69)	2	1.15 (0.14–4.16)	27	1.21 (0.80–1.76)	6	0.92 (0.34–2.00)
20–24	112	0.88 (0.72–1.06)	11	0.81 (0.41–1.45)	9	1.12 (0.51–2.13)	79	0.96 (0.76–1.19)	13	0.56* (0.30–0.96)
25–29	82	0.95 (0.76–1.18)	10	1.36 (0.65–2.49)	6	1.01 (0.37–2.19)	52	0.91 (0.68–1.19)	14	0.90 (0.49–1.50)
30+	149	0.97 (0.82–1.13)	25	1.33 (0.86–1.97)	7	0.93 (0.37–1.92)	93	0.89 (0.71–1.08)	24	1.05 (0.67–1.56)
Year of hire										
<1960	208	0.92 (0.81–1.06)	20	1.11 (0.68–1.71)	16	0.95 (0.54–1.54)	130	0.91 (0.76–1.08)	42	0.91 (0.65–1.22)
1960+	173	0.97 (0.83–1.17)	29	1.10 (0.73–1.58)	8	1.26 (0.55–2.49)	121	0.97 (0.81–1.16)	15	0.68 (0.38–1.13)
Duration of employment (yr)										
<1	145	1.04 (0.88–1.23)	26	1.07 (0.70–1.57)	4	1.46 (0.40–3.73)	109	1.07 (0.88–1.29)	6	0.61 (0.23–1.34)
1–4	85	0.87 (0.69–1.07)	10	1.04 (0.50–1.92)	3	0.53 (0.11–1.55)	59	0.93 (0.71–1.20)	13	0.68 (0.36–1.17)
5–19	79	0.99 (0.79–1.24)	7	1.26 (0.51–2.59)	7	1.01 (0.40–2.07)	46	0.98 (0.71–1.30)	19	0.96 (0.58–1.50)
20+	72	0.86 (0.67–1.08)	6	1.24 (0.46–2.70)	10	1.33 (0.64–2.44)	37	0.71* (0.50–0.98)	19	0.99 (0.60–1.55)
Time since first employment (yr)										
<20	43	0.84 (0.61–1.14)	4	0.57 (0.16–1.47)	2	1.09 (0.13–3.93)	33	0.90 (0.62–1.27)	4	0.73 (0.20–1.87)
20–29	102	0.99 (0.80–1.20)	15	1.09 (0.61–1.81)	2	0.40 (0.05–1.44)	70	1.00 (0.78–1.27)	15	1.00 (0.56–1.65)
30–39	142	1.00 (0.84–1.17)	18	1.09 (0.65–1.72)	16	1.90* (1.09–3.09)	89	0.95 (0.77–1.17)	19	0.78 (0.47–1.22)
40+	94	0.89 (0.72–1.09)	12	1.70 (0.88–2.97)	4	0.51 (0.14–1.30)	59	0.88 (0.67–1.14)	19	0.81 (0.49–1.27)

*$P < 0.05$.
**$P < 0.01$.

later compared with hires earlier than 1960, excesses for subjects employed 20 or more years or followed 30 or more years (partially NH plant group: workers followed 30 to 39 years, 16 deaths, SMR = 1.90, CI = 1.09 to 3.09, statistically significant). Factor-specific SMRs were generally lower for subjects in the never NH and unspecified plant groups and no remarkable patterns in SMRs were evident.

Because of the uncertain nature of the tumors in the unspecified CNS neoplasm category, results for the detailed analyses are not shown. We combined subjects in the only and partially NH groups to form an "ever NH" group due to smaller numbers of observed deaths in these categories. No remarkable patterns or trends in SMRs were apparent across plant groups or by any study factors within the plant groups. Several excesses in deaths occurred sporadically across the study factors examined, but many were based on small numbers of deaths and none was statistically significant.

Internal Mortality Comparisons

Table 6 shows RR regression models relating internal cohort rates for malignant brain neoplasms to selected study factors based on both underlying codes and underlying plus contributory (u+c) cause of death codes. Here, all workers are combined and the plant group variable is used to compare rates by plant group. We did not attempt to impute race in the internal comparisons due to the large number of unknown values (we repeated key internal comparisons assuming all subjects with unknown race were white, ie, white subjects only, and results were not materially different from those based on known whites. This was a reasonable assumption given that only 22 of 381 [5.8%] malignant

TABLE 6

Jet Engine Manufacturing Worker Cohort Observed Deaths and Relative Risks[a] (RR) for Malignant Brain Neoplasms, All Workers, 1976–2004, by Selected Study Factors and Cause of Death Coding Scheme

	Underlying Cause Only (n = 381)				Underlying + Contributory Cause (n = 406)			
Study Factor	**Deaths**	**Noncases[b]**	**RR (95% CI)**	***P****	**Deaths**	**Noncases[b]**	**RR (95% CI)**	***P****
Plant group				0.695				0.560
Never North Haven	251	1,194,012	1.00		271	1,269,335	1.00	
Only North Haven	49	250,249	1.06 (0.78–1.45)		51	263,745	1.03 (0.76–1.39)	
Partially North Haven	24	102,556	1.09 (0.72–1.66)		25	109,770	1.05 (0.69–1.58)	
Unspecified plant	57	289,447	0.87 (0.65–1.16)		59	308,787	0.84 (0.63–1.11)	
Worker type				0.251				0.092
Short-term (<1 yr)	145	752,967	1.00		159	795,548	1.00	
Long-term (1+ yr)	236	1,083,297	0.88 (0.71–1.09)		247	1,156,089	0.84 (0.68–1.03)	
Payroll type				0.580				0.508
Salary	99	408,426	1.00		104	435,207	1.00	
Hourly	260	1,307,479	0.91 (0.72–1.15)		280	1,387,797	0.93 (0.74–1.18)	
Mixed	22	120,359	0.80 (0.50–1.28)		22	128,633	0.77 (0.48–1.22)	
Age at hire				0.633				0.513
<20 yr	38	209,527	1.00		40	219,140	1.00	
20–24	112	762,678	0.77 (0.52–1.14)		116	800,909	0.77 (0.52–1.13)	
25–29	82	412,204	0.85 (0.56–1.30)		91	444,936	0.90 (0.59–1.35)	
30+	149	451,855	0.85 (0.55–1.32)		159	486,652	0.87 (0.57–1.32)	
Year of hire				0.684				0.818
<1960	208	785,605	1.00		224	846,046	1.00	
1960+	173	1,050,659	1.06 (0.82–1.37)		182	1,105,591	1.03 (0.80–1.32)	
Duration of employment (yr)				0.363 (0.312)				0.147 (0.146)
<1	145	752,967	1.00		159	795,548	1.00	
1–4	85	469,737	0.84 (0.64–1.11)		88	499,042	0.80 (0.61–1.03)	
5–19	79	279,013	1.01 (0.76–1.34)		84	297,987	0.98 (0.74–1.28)	
20+	72	334,547	0.82 (0.61–1.10)		75	359,060	0.77 (0.58–1.02)	
Time since first employment (yr)				0.890 (0.470)				0.905 (0.680)
<20	43	236,292	1.00		44	247,188	1.00	
20–29	102	527,533	1.01 (0.66–1.52)		107	565,013	1.03 (0.68–1.54)	
30–39	142	737,172	0.92 (0.59–1.43)		156	778,883	1.03 (0.67–1.58)	
40+	94	335,267	0.86 (0.52–1.43)		99	360,553	0.91 (0.56–1.50)	

*P: global, (trend).

[a]Risk sets were matched on exact age, gender, and date of birth (using a 1 yr caliper).

[b]The number of persons in decedents' risk sets used in calculation of RR.

brain neoplasms were known or estimated as non-white in the SMR analysis [Table 5]). The factors age, time, and sex were matched in the risk sets. Contributory cause of death codes added 25 malignant brain neoplasm deaths to this analysis. For most study factors, results based on the two coding schemes were similar. For malignant brain neoplasms, none of the study factors considered was a statistically significant predictor of mortality risk, and there was no evidence that RRs increased with increasing DOE or TSFE. RRs for the only NH and partially NH plant groups were elevated relative to the baseline never NH plant group (u+c—only NH [51 deaths, RR = 1.03, CI = 0.76 to 1.39], partially NH [25 deaths, RR = 1.05, CI = 0.69 to 1.58]). Long-term workers had lower mortality risks compared with the short-term worker baseline group (u+c—247 deaths, RR = 0.84, CI = 0.68 to 1.03) and hourly and mixed workers had lower risks than the baseline salaried workers (u+c, hourly—280 deaths, RR = 0.93, CI = 0.74 to 1.18; mixed—22 deaths RR = 0.77, CI = 0.48 to 1.22).

Contributory cause of death codes added 19 deaths to the analysis of unspecified brain neoplasms (data not shown). None of the study factors considered was a statistically significant predictor of mortality risk and there was no evidence that RRs increased with increasing DOE or TSFE. Mortality risks were lower among workers in the only and partially NH group compared with the never NH baseline plant group (u+c—only NH [10 deaths, RR = 0.71, CI = 0.37 to 1.38], partially NH [5 deaths, RR = 0.71, CI = 0.29 to 1.75]). RRs for long-term workers were slightly higher than short-term, but not statistically significant (u+c—80 deaths, RR = 1.05, CI = 0.70 to 1.56). RRs were higher among hourly and mixed workers compared with salaried workers, but the excesses were not statistically significant (u+c—hourly [86 deaths, RR = 1.29, CI = 0.81 to 2.06], mixed [7 deaths, RR = 1.06, CI = 0.45 to 2.47]). Additional internal analyses of all workers (results not shown) using 1970 as the cut point for year of hire (corresponding roughly pre-post OSHA eras) produced similar results. Restricting the analysis to workers with five or more years of employment and 20 years or more since first employment produced similar results for plant group, worker type and payroll type and only slight increases in RRs for the

TABLE 7
Jet Engine Manufacturing Worker Cohort Observed Deaths and Relative Risks[a] (RR) for Malignant Brain Neoplasms, Ever North Haven Workers, 1976–2004, by Selected Study Factors and Cause of Death Coding Scheme

	Underlying Cause Only					Underlying + Contributory Cause			
Study Factor	Deaths	SMR (95% CI)	Noncases[b]	RR (95% CI)	*P**	Deaths	Noncases[b]	RR (95% CI)	*P**
Worker type					0.847				0.897
Short-term (<1 yr)	30	1.11 (0.75–1.59)	169,499	1.00		31	178,099	1.00	
Long-term (1+ yr)	43	1.07 (0.77–1.44)	183,306	0.95 (0.59–1.55)		45	195,416	0.97 (0.60–1.56)	
Payroll type					0.175				0.220
Salary	17	1.49 (0.87–2.39)	51,756	1.00		17	55,189	1.00	
Hourly	53	1.04 (0.78–1.35)	280,803	0.61 (0.35–1.06)		56	296,670	0.64 (0.37–1.12)	
Mixed	3	0.68 (0.14–1.99)	20,246	0.43 (0.13–1.48)		3	21,656	0.44 (0.13–1.50)	
Age at hire (yr)					0.602				0.339
<25	25	0.86 (0.56–1.28)	202,618	1.00		25	211,318	1.00	
25–29	16	1.19 (0.68–1.94)	71,124	1.45 (0.71–2.99)		18	77,008	1.69 (0.85–3.38)	
30+	32	1.22 (0.83–1.72)	79,063	1.22 (0.54–2.78)		33	85,189	1.33 (0.59–2.99)	
Year of hire					0.370				0.335
<1960	36	1.03 (0.72–1.42)	135,400	1.00		37	145,384	1.00	
1960+	37	1.13 (0.80–1.56)	217,405	1.30 (0.74–2.27)		39	228,131	1.31 (0.76–2.27)	
Duration of employment (yr)					0.762 (0.697)				0.634 (0.574)
<1	30	1.11 (0.75–1.59)	169,499	1.00		31	178,099	1.00	
1–4	13	0.85 (0.44–1.45)	81,795	0.76 (0.40–1.47)		13	86,732	0.74 (0.38–1.42)	
5–19	14	1.11 (0.61–1.86)	46,806	1.07 (0.55–2.08)		15	50,023	1.12 (0.58–2.13)	
20+	16	1.30 (0.74–2.11)	54,705	1.10 (0.59–2.06)		17	58,661	1.14 (0.62–2.11)	
Time since first employment (yr)					0.820 (0.415)				0.729 (0.363)
<20	6	0.68 (0.25–1.48)	44,172	1.00		6	46,093	1.00	
20–29	17	0.91 (0.53–1.46)	103,885	0.91 (0.33–2.49)		17	111,092	0.91 (0.33–2.50)	
30–39	34	1.36 (0.94–1.91)	149,125	0.86 (0.29–2.52)		36	156,457	0.88 (0.30–2.58)	
40+	16	1.07 (0.61–1.73)	55,623	0.63 (0.19–2.12)		17	59,873	0.61 (0.18–2.02)	

*P: global, (trend).
[a]Risk sets were matched on exact age, gender, and date of birth (using a 1 yr caliper).
[b]The number of persons in decedents' risk sets used in calculation of RR.

25+ age of hire groups and year of hire 1960+.

Table 7 shows RR models based on both cause of death coding schemes for malignant brain neoplasms for workers from the only and partially NH groups combined as "ever NH." Corresponding SMRs based on underlying cause are also shown. Some study factor categories were combined due to small numbers of deaths. For most study factors, results based on the two coding schemes were similar. Internal comparisons revealed that none of the study factors considered was a statistically significant predictor of mortality risk for malignant brain neoplasms and we observed no evidence of an increasing trend in RRs with increasing DOE or TSFE. The not statistically significant excesses among only and partially NH workers during 1976 to 2004 noted in Table 4 are associated mainly with salaried workers (17 deaths, SMR = 1.49, CI = 0.87 to 2.39) and both short-term (30 deaths, SMR = 1.11, CI = 0.75 to 1.59) and long-term (43 deaths, SMR = 1.07, CI = 0.77 to 1.44) workers. Mortality risks were elevated but not statistically significant among workers hired on or after 1960 compared with those hired before 1960 and for workers hired at ages 25 to 29 (u+c—18 deaths, RR = 1.69, CI = 0.85 to 3.38) and 30 or more years old (u+c—33 deaths, RR = 1.33, CI = 0.59 to 2.99). Not statistically significantly elevated RRs were observed for workers with 5 to 19 years of employment (15 deaths, RR = 1.12, CI = 0.58 to 2.13) and 20 or more years of employment (17 deaths, RR = 1.14, CI = 0.62 to 2.11) based on underlying and contributory causes combined.

For unspecified brain neoplasms (results not shown), internal comparisons found only one factor, TSFE, was a statistically significant predictor of mortality risk based on u+c causes (global P value = 0.049) and a marginally statistically significant predictor based on underlying codes only (global P value = 0.065). These main effects were driven by relatively large, but imprecise, 10.39-fold (underlying cause only—4 deaths, CI = 0.70 to 175.8) and 7.04-fold (u+c—5 deaths, CI = 0.60 to 77.9) elevations in RRs for subjects followed 40 or more years from first employment, giving rise to a nearly statistically significant trend in RRs (trend P = 0.053) based on underlying causes (a review of the risk sets involved in these results revealed a highly skewed distribution of latency periods among the non-cases in the risk sets. Of the eleven risk sets, two had no non-cases and seven had very small numbers of non-cases in the 40+ latency category giving rise to large, imprecise estimates). Mortality risks were lower among long-term workers compared with short-term workers (u+c—8 deaths, RR = 0.72, CI = 0.22 to 2.40) and hourly and mixed workers compared with salaried workers (u+c, hourly—11 deaths, RR = 0.85, CI = 0.22 to 4.78). None of the study factors considered was a statistically significant predictor of mortality risk nor was there any evidence of a trend in DOE or TSFE in separate internal analyses of the never NH and unspecified plant groups (results not shown).

Discussion

We found that during the entire 1952 to 2004 study period, the total cohort of P&W employees had fewer than expected deaths from all CNS neoplasms combined based on external comparisons with the general populations of the US and the State of CT. Except for a slight 9% excess in deaths from unspecified CNS neoplasms based on the US comparison, we found the same pattern of statistically significant overall deficits in deaths for the three major subcategories of CNS neoplasms: all malignant, all benign, and unspecified. Further analyses involved external and internal mortality comparisons of more detailed categories of CNS neoplasms during diagnostically more accurate time periods and by several demographic and work history factors. We relied more heavily on the internal comparisons to assess possible workplace associations as these afforded better control for potential selection and confounding biases related to the healthy worker effect and socioeconomic or other differences between the P&W workforce and the general population.

The etiology of CNS neoplasms remains enigmatic and largely unknown. The increase in incidence and mortality rates in recent decades was initially thought by some to suggest the effect of an environmental exposure, but this now appears to be largely an artifact of improved diagnoses.[2,3,16,17] Certain inherited syndromes, such as tuberous sclerosis, can predispose persons to the development of brain tumors, but this factor accounts for less than 5% of cases.[2,3] A number of occupational epidemiology studies have reported elevated brain cancer risks for workers in certain industries. Although some studies have suggested that electrical and electric utility workers may be at a slightly increased risk of brain cancer, these studies have important limitations, such as exposure misclassification and a lack of dose-response relationships.[18] Recent reports have proposed a link between occupational exposure to lead and brain cancer risk,[19,20] but these findings need to be interpreted cautiously because of limitations in the exposure assessment. There is also some evidence that farmers, petrochemical workers and meat cutters have an increased risk of glioma,[21–24] but much of the information is from case–control rather than cohort studies.[2] In addition, a number of specific risk factors have been hypothesized, including organic solvents, lubricating oils, acrylonitrile, vinyl chloride, formaldehyde, polycyclic aromatic hydrocarbons, and *N*-nitroso and phenolic compounds.[1,2] However, none of these suggested associations has been well established. Therapeutic ionizing radiation, such as ionizing radiation used to treat tinea capitis,

has been shown to be strongly associated with brain tumors, especially when the exposure occurs as a child.[1,2,25–27] The effect is most strongly associated with nerve sheath tumors but also with meningiomas and, to a lesser extent, gliomas.[1,3,28–31] Diagnostic radiation techniques, such as dental radiographs, have not shown an association with increased risk of glioma.[1,32]

Unusual occurrences of brain cancer have been investigated in other occupational settings and these may provide some insights into the reasons for the excesses noted in the P&W cohort. For example, epidemiologic studies of petroleum workers, many initiated as a result of a brain cancer cluster in a plant in Texas, have found elevated risk of brain cancer.[23,33–37] One study found statistically significantly elevated risks for hourly employees[37] but was not able to conclusively identify any associations to suspected chemical carcinogens. To date, no specific carcinogen has been implicated in the observed elevated risks. Vinyl chloride has also been studied extensively in occupationally-exposed populations after findings that vinyl chloride exposure induced brain tumors in animals. Nevertheless, although some studies have found elevated risks for brain cancer[38–41] others have found no significantly increased risk in these workers.[42–45]

Another cancer cluster investigation evaluated brain cancer incidence among workers at a petrochemical research facility in Illinois.[46–49] The investigators found a statistically significant excess in brain cancer incidence, which they were able to restrict to white males who had worked in one building. No association with carcinogenic exposures was identified, although they did identify an association between cases and potential exposure to ionizing radiation and *n*-hexane. The authors concluded that the ionizing radiation exposure was of "doubtful biologic significance"[49] and that epidemiologic and toxicologic evidence were inconclusive regarding *n*-hexane as a neurocarcinogen. A mortality study of this same cohort found no elevations in brain cancer deaths with follow-up through 1996 (1 death of 1.8 expected in the research facility).[50] Nevertheless, the authors were aware of three brain cancer deaths that occurred in 1997 and two that occurred in early 1998. Comprehensive identification of deaths was not possible for the entire cohort through 1997 (at the time of the manuscript) but the authors preliminarily estimated that they would find a 2-fold excess through 1997 and potentially higher than that through 1998.[50]

Malignant Brain Neoplasms

In the current study, malignant brain neoplasms comprised 96% of all malignant CNS neoplasms, so mortality patterns for these two categories were similar. Thus, detailed analyses focused on malignant brain neoplasms during the diagnostically more accurate 1976 to 2004 period. This cause of death category includes deaths from glioblastoma, although these cannot be identified with the mortality data used in the current analysis. External mortality comparisons revealed not statistically significant excesses in deaths from malignant brain neoplasms for subjects who worked only or partly at the index NH plant compared with deficits in deaths for subjects in the never NH and unspecified plant groups, where mortality patterns were essentially unremarkable. Within the NH plant groups, the excesses concentrated among salaried workers, workers hired at older ages, older subjects and the recent time periods. We did not observe elevated risks for salaried or older workers or in later time periods in the never NH and unspecified plant groups.

Our observation of a statistically significant 2.18-fold excess among only NH workers at risk between 75 and 84 years of age raises the possibility of age-related diagnostic sensitivity bias, considering the small overall excess (SMR = 1.01 for 1952 to 2004) and lack of association with the usual work-related factors such as DOE and TSFE in the internal cohort analyses. Researchers found increased use of computed tomography scans on the elderly 75 to 84 and 85 or more years of age[51,52] from 1986 to 1994 and this may reflect an effort by physicians to use more aggressive diagnostic testing for neurologic symptoms in the elderly. The larger excesses found among only NH workers in the more recent calendar time periods may not be an indication of a possible workplace association, as there was no evidence of an association with the time-correlated workplace factors such as DOE and TSFE in our internal comparisons. Nevertheless, the observation of a near-statistically significant 50% excess in deaths among only NH workers for all pay types combined during the last decade of the 53-year observation period (1995 to 2004) and the excesses at the highest levels of DOE and TSFE may reflect risks not identifiable with currently available data on workplace factors; more definitive evaluations of potential work-related risks will be conducted in subsequent analyses.

The larger excesses among salaried NH workers may be explained, at least partly, by SES differences between these workers and the general US and CT populations. Some researchers have found a strong positive relationship between SES and risk of brain tumors,[53–55] although the positive relationship may exist for some, but not all, subgroups of the population. Although there is a trend of increasing incidence with increasing social class, the trend appears to hold only for white males.[1] White females show a clear trend only for nerve sheath tumors; trends for gliomas and meningiomas are less evident. Nevertheless, studies of white-collar petrochemical workers have found brain cancer mortality rates at or slightly below those of the general population.[23,37]

The results of our internal cohort rate comparisons based on all workers were generally consistent with the results of the external comparisons. We found that mortality risks from malignant brain neoplasms were higher among workers from the only and partially NH plant groups compared with never NH baseline, among short-term (less than 1 year employment) compared with long-term workers and among salaried workers compared with hourly or mixed workers. We also found no evidence that mortality risks were related to general workplace factors, such as increasing levels of DOE or TSFE. The somewhat smaller mortality risk differential noted for plant group in the internal comparisons (Table 6—underlying cause only) compared with the external comparisons (Table 5) most likely reflect the underlying homogeneity of the internal comparison groups that helps to control for certain selection or confounding biases associated with external comparisons (eg, the healthy worker effect).

Our internal comparisons of combined workers from the only and partially NH plant groups ("ever NH") also found a higher risk of malignant brain neoplasms for salaried workers, but here the difference between hourly and salary workers was larger, possibly reflecting for NH workers a more pronounced differential between hourly and salary workers in SES or other correlated occupational or nonoccupational factors. For the "ever NH" plant group, we also observed higher risks among workers hired at older ages and in the more recent 1960 to 2001 period. Mortality risks were not associated with DOE or TSFE. Although the findings for salaried workers may be explained by SES or other correlated occupational or nonoccupational factors, the findings in the "ever NH" group for older and later hires, in contrast to the absence of an association with DOE or TSFE, suggests the role of other employment or nonoccupational factors. It may also reflect a "diagnostic sensitivity bias" wherein people with access to quality medical care have more thorough medical evaluations and, thus, a greater likelihood of a tumor being identified.[56]

With the currently available data on workplace factors, we cannot evaluate further the questions of why the elevated risks for malignant brain neoplasms are limited to the only and partially NH plant groups, or why the patterns of risk by payroll type, age and time period were limited to the NH workers. For example, compared with the other plant groups, only NH, in particular, had the smallest percentage of salaried workers (6.7%) and the largest excess among salaried workers, although this was measured imprecisely from a small number of deaths (5 deaths, SMR = 1.91, CI = 0.62 to 4.46). These findings may reflect external occupational factors, nonoccupational factors or workplace factors unique to the NH plant that were not measured in the current study. Other explanations for the excesses noted are not possible without the exposure assessment information under development by UIC and the supplemental information being collected in the cancer incidence and case-control studies.

Benign CNS Neoplasms

Less is known about the causes of benign CNS tumors than about malignant tumors, although radiation exposure is thought to be associated.[1,3,57] Some studies have suggested that exposure to exogenous female sex hormones may increase the risk of meningioma, which is twice as common in women than men,[3,58] but we did not see an increased risk among women in this cohort. In contrast to gliomas, previous head injuries have also shown some association with the risk of meningioma.[1,3,57,59,60] Occupational studies have typically focused on gliomas or have not differentiated between types of CNS tumors. Nevertheless, some association has been seen with meningioma among persons exposed to petroleum products.[57] The prevalence of clinically silent meningiomas has been reported to be as high as 2800 of 100,000[61] in a cohort of older women given MRIs. The increase seen in this study could be a result of detection bias given the brain cancer concern among cohort members; this possibility will be investigated further in the case–control study.

In the current study, results for benign CNS neoplasms, which were limited to external comparisons and the study factors plant group, payroll type and calendar time, were difficult to interpret reliably and meaningfully due to the small total number of observed deaths (observed = 23) and diversity of the neoplasms included in this broad category. Only one benign brain neoplasm death was observed among the total study population. Similar to our findings for malignant brain neoplasms we observed elevated, but not statistically significant, mortality risks for benign CNS neoplasms among workers from the only and partially NH plant groups and among salaried workers. As with malignant brain neoplasms, possible SES differences may explain at least part of the excess observed among all salaried workers, but the reasons for the overall excesses that were observed only in NH workers remain unknown.

CNS Neoplasms of Unspecified Nature or Uncertain or Unknown Behavior

Results from this category of CNS neoplasms were also difficult to interpret because of the unspecified nature or uncertain or unknown behavior of the associated tumors. That is, an unknown number of these neoplasms actually belong to the malignant CNS neoplasms (or malignant brain) category or the benign CNS neoplasm category. Nevertheless, we conducted a sensitivity analysis that proportionally allocated unspecified CNS neoplasms as malignant or benign and this did not materially

change the results in any category. With these limitations notwithstanding, we did not find a pattern of overall higher mortality rates from unspecified brain neoplasms by study plant group, among subjects who worked only or partially at NH, and patterns in mortality risks by other factors were generally unremarkable in external and internal analyses of the total cohort. Our isolated finding of a statistically significant association with TSFE in the internal comparisons of the ever NH plant group appeared to be a statistical artifact stemming from a highly skewed distribution of latency periods for non-cases within the corresponding risk sets.

Interpretational Considerations

The interpretation of the observed mortality excesses for malignant brain neoplasms and benign CNS neoplasms at NH is complicated by the fact that the index cases that prompted this study arose in this plant. Nevertheless, the number of index cases (mostly glioblastoma) was small relative to the total number of malignant CNS or brain neoplasms identified in this study, and our systematic and comprehensive case ascertainment and cohort enumeration obviated the ascertainment bias that can arise in extended evaluations driven by index cases.[79,80] Further, the index cases were mainly of a specific histological type, glioblastoma, and because of death coding limitations, an evaluation of the risk from this particular neoplasm is only possible in the companion cancer incidence and nested case-control analyses. It is possible that an environmental exposure-based increased risk for malignant brain neoplasms is relevant only to a specific histological type, or even a specific molecular subgroup within a larger histological type. For example, mechanisms affecting p53 function would be relevant to low grade astrocytomas, a subset of anaplastic astrocytomas, and not the group of glioblastomas that develop de novo.

The results of this cohort mortality study must be interpreted with consideration given to the exploratory, hypothesis generating nature of the statistical analysis. While the overall investigation began in response to an unusual occurrence of glioblastomas at the NH facility, we did not attempt to test any specific a priori hypotheses about the etiology of the brain tumors observed in this study cohort. To minimize false positive results stemming from the multiple statistical comparisons inherent in exploratory analyses, we examined a relatively small number of available study factors and limited the number of corresponding subcategories. Study factors were categorized a priori to the extent possible and re-categorized only to evenly distribute or ensure sufficient numbers of observed deaths used in risk estimate calculations. Despite these precautions, the likelihood remains that some comparisons were deemed statistically significant by chance factors alone.

Although large size and high statistical power are major strengths of this study, many very small excesses or deficits were detected as being statistically significant. Recognizing that very small excesses or deficits derived from observational epidemiology studies may not be meaningful indicators of the presence or absence of mortality risks, we placed little importance on statistical significance in these situations and focused primarily on the magnitude, patterns and consistency of our risk estimates across the subgroups of the study population examined. Despite the large overall size of the study, we observed relatively small numbers of deaths in some categories of the rarer forms of CNS neoplasms examined, such as benign CNS neoplasms, resulting in low precision in estimating mortality risks via SMRs or RRs and low statistical power to detect possibly important mortality excesses.

The current analysis has other important limitations. Because of ongoing efforts to finalize the work histories and exposure assessment component of the investigation, we were limited here to evaluating only basic work history factors, such as plant group, worker type, payroll type, year of hire, age at hire, DOE and TSFE. Refinements made to subjects' work histories in the ongoing exposure assessment component of this investigation should result in a decrease in the number of employees in the unspecified plant group and may involve reclassifying some subjects from one category to another (eg, partially NH to only NH employment). The companion exposure assessment will also allow us to evaluate findings of interest at the detailed job level and with respect to potential exposures to classes of chemical and physical agents instead of the basic work history factors analyzed here. It will also permit us to perform detailed analyses of the remaining seven study plants rather than only NH.

In the current analysis, we were unable to investigate patterns of CNS neoplasms by histological type due to the inherent limitations in death certificate-based data. Nevertheless, we are currently working on the brain cancer incidence component of the study that will allow us to examine those patterns more fully. Brain cancer incidence will be examined from 1976 to 2004, rather than 1952 to 2004, to allow for better overlap with the state cancer registries, most of which did not exist until the late 1970s and beyond, and to take advantage of the improved diagnostic techniques which began approximately in the mid-1970s. Because of this, the CNS neoplasm cases investigated in the mortality study will not correspond exactly to those in the cancer incidence study. Our CNS incidence study will include more cases than the mortality study because some types of tumors, especially benign, are not fatal or are not recorded as a contributory cause of death and some of our cases were diagnosed within the study period but died after 2004. Some state cancer registries did not begin collecting

benign incident cases until 2004, however, because the number of incident cases identified in these states is generally small, it should not materially affect case enumeration. The analysis of CNS deaths by time period was also affected by the fact that we were examining both prevalence and incidence cohorts (ie, employees alive and working before the follow-up periods were included in the analysis); these "healthy survivors" could have biased the results of our analyses slightly toward the null.

Our historical cohort study also has many unique features and methodological strengths. It is among the largest and most comprehensive historical cohort studies ever undertaken in an occupational setting and is the first and only large-scale, comprehensive epidemiological study of workers in the jet engine manufacturing and repair industry. Only a limited number of health studies have been conducted on allied professions or subareas of this industry including cancer incidence studies of pilots and flight attendants,[62–64] several noise and hearing studies for airport personnel,[65–68] toxicological studies on jet fuel, engine exhaust and jet engine lubricating oils,[69–74] and one study looking at respiratory, rheumatic, and neurobehavioral symptoms among jet engine repair workers.[75] Larger cohort studies have been conducted on aircraft maintenance workers[76–78] and aircraft manufacturing workers.[79,80] No excess risk of CNS or brain cancer was found in these investigations, although the exposures in those operations do not correspond closely to those found in the jet engine manufacturing processes studied here.

Our cohort of 223,894 subjects contributed more than 7.7 million person-years of observation, of which about 1.4 million or 18% were among workers employed more than 5 years and followed for 20 or more years from first employment. This led to the observation of 68,701 deaths through 2004, including 18,641 deaths from all cancers combined. The exceedingly large number of person-years enabled us to identify a large number deaths overall ($n = 606$) from the rare disease outcomes of a priori interest in this study (malignant, benign and unspecified CNS neoplasms, including brain neoplasms), and to examine these with good precision in many of the larger cohort subgroups of interest. For example, the a priori statistical power (the a priori statistical power is the probability of obtaining an SMR or RR statistically significantly greater than 1.00 at the 0.05 level [one-sided] assuming no excess risk and estimated numbers of expected deaths) to detect a 2.0-fold or greater overall excess number of deaths among subjects who only worked at the "index" NH plant was 1.00 for all CNS neoplasms, 0.95 for malignant CNS neoplasms, 0.91 for malignant neoplasms of the brain, 0.47 for benign CNS neoplasms and 0.94 for unspecified CNS neoplasms. Other major strengths of the study include: long (up to 53 years) observation periods; nearly complete cohort enumeration; internal and external validation of cohort completeness; excellent rates of vital status ascertainment and cause of death determination; the use of national and state external mortality comparisons and robust statistical modeling of internal cohort rates based on both underlying and contributory cause of death codes.

Conclusions

At the total cohort level, mortality rates for the broad categories of malignant, benign and unspecified CNS neoplasms examined were not elevated relative to the general populations of the US and CT. Our internal cohort rate comparisons of all workers revealed small, not statistically significant elevated mortality risks from malignant brain neoplasms among workers employed only or partly at the index NH plant. In contrast with the other plants, within NH we found elevated, but not statistically significant, risks for malignant brain neoplasms among salaried workers, workers hired at older ages and in the more recent time period, and no evidence of an association with DOE or TSFE. While the NH findings for salaried workers may be explained by SES or other correlated occupational or nonoccupational factors, the findings for older and later hires, in contrast to the absence of an association with DOE or TSFE, suggests the role of other employment or nonoccupational factors. We will be able to further explore these and other possible explanations for the excesses noted with the exposure assessment information under development by UIC and the supplemental information being collected in the companion cancer incidence and case-control studies.

Acknowledgment

The Pratt & Whitney Company (P&W) sponsored this research, but the design, conduct, analysis, and conclusions are those of the authors. We acknowledge the cooperation and assistance of the representatives and consultants of P&W, in particular, Barbara Aiudi, Hugh Johnson, Sharon Asselin, Robert O'Hara, Chris Boccaccio, Jennifer Whitlow, Jane Teta, Matt Falco, Dave Alberghini, and Maureen LeClair and of the P&W union members and their representatives, Debra Belancik, Paul Dickes, Chuck O'Neal, John Tronier, and Rodney Conlogue. We also acknowledge the assistance and support of the Connecticut Department of Public Health, Division of Environmental Epidemiology and Occupational Health, in particular, Mary Lou Fleissner. Our special thanks to our external Scientific Advisory Committee for their thoughtful contributions and guidance and the Communications Facilitation Workgroup for their support. In addition, we acknowledge the data processing and management work done by DataBanque of Pittsburgh, the computer programming work of Charles Alcorn, Michael Lann, and Stephen Sefcik, the data collection management efforts of Annette Krag-Jensen and the death certificate coding performed by June Pearce. The research proposal was approved by the Institutional Review Boards (IRB) of the University of Pittsburgh, the University of Illinois at Chicago and the Connecticut Department of Public Health.

References

1. Preston-Martin S, Mack WJ. Neoplasms of the nervous system. In: Schottenfeld D, Fraumeni JF, eds. *Cancer Epidemiol-*

ogy and Prevention. 2nd ed. New York: Oxford Press University; 1996.
2. Wrensch M, Minn Y, Chew T, et al. Epidemiology of primary brain tumors: current concepts and review of the literature. *Neuro Oncol*. 2002;4:278–299.
3. Fisher JL, Schwartzbaum JA, Wrensch M, et al. Epidemiology of brain tumors. *Neurologic Clin*. 2007;25:867–890.
4. Marsh G, Buchanich J, Youk A, et al. Long-term health experience of jet engine manufacturing workers: II. Total and cause-specific mortality excluding central nervous system neoplasms. *J Occup Environ Med.* 2008;50:1117–1129.
5. Buchanich J, Dolan D, Marsh G, et al. Under ascertainment of deaths using Social Security records: a recommended solution to a little-known problem. *Am J Epidemiol*. 2005;162:193–194.
6. Marsh G, Youk A, Stone R, et al. OCMAP-PLUS, a new program for the comprehensive analysis of occupational cohort data. *J Occup Environ Med*. 1998; 40:351–362.
7. Youk A, Stone R, Marsh G. A method for imputing missing data in longitudinal studies. *Ann Epidemiol*. 2004;14:354–361.
8. Marsh G, Youk A, Sefcik S. *Mortality and Population Data System* (*MPDS*). Pittsburgh, PA: University of Pittsburgh, Department of Biostatistics Technical Report; 2005.
9. Checkoway H, Pearce N, Kriebel D. *Research Methods in Occupational Epidemiology*. Oxford: Oxford University; 2004.
10. Breslow NE, Day NE. *Statistical Methods in Cancer Research. IARC Scientific Publications*. Lyon: Oxford University Press; 1987.
11. Cox D. Regression models and life tables. *J Royal Stat Soc*. 1972;34:187–220.
12. Cox D. Partial likelihood. *Biometrika*. 1975;62:269–276.
13. StataCorp. *Stata Statistical Software: Release 9.0*. College Station, TX: StataCorp; 2004.
14. Cytel S. *LogXact 8: Discrete Regression Software Featuring Exact Methods*. Cambridge, MA: Cytel Software; 2007.
15. Richardson D. Use of multiple cause of death data in cancer mortality analysis. *Am J Ind Med*. 2006;49:683–689.
16. Modan B, Wagener DK, Feldman JJ, et al. Increased mortality from brain tumors: a combined outcome of diagnostic technology and change of attitude toward the elderly. *Am J Epidemiol*. 1992;135: 1349–1357.
17. Davis DL, Ahlbom A, Hoel D, et al. Is brain cancer mortality increasing in industrial countries? *Am J Ind Med*. 1991; 19:421–431.
18. Kheifets LI. Electric and magnetic field exposure and brain cancer: a review. *Bioelectromagnetics*. 2001;5:S120–S131.
19. Cocco P, Dosemeci M, Heineman EF. Brain cancer and occupational exposure to lead. *J Occup Environ Med*. 1998;40: 937–942.
20. van Wijngaarden E, Dosemeci M. Brain cancer mortality and potential occupational exposure to lead: findings from the National Longitudinal Mortality Study, 1979–1989. *Int J Cancer*. 2006;119: 1136–1144.
21. Navas-Acien A, Pollan M, Gustavsson P, et al. Occupation, exposure to chemicals and risk of gliomas and meningiomas in Sweden. *Am J Ind Med*. 2002;42:214–227.
22. De Roos AJ, Stewart PA, Linet MS, et al. Occupation and the risk of adult glioma in the United States. *Cancer Causes Control*. 2003;14:139–150.
23. Waxweiler RJ, Alexander V, Leffingwell SS, et al. Mortality from brain tumor and other causes in a cohort of petrochemical workers. *J Natl Cancer Inst*. 1983;70: 75–81.
24. Khuder SA, Mutgi AB, Schaub EA. Meta-analyses of brain cancer and farming. *Am J Ind Med*. 1998;34:252–260.
25. Rimm IJ, Li FC, Tarbell NJ, et al. Brain tumors after cranial irradiation for childhood acute lymphoblastic leukemia. A 13-year experience from the Dana-Farber Cancer Institute and the Children's Hospital. *Cancer*. 1987;59:1506–1508.
26. Soffer D, Gomori JM, Siegal T, et al. Intracranial meningiomas after high-dose irradiation. *Cancer*. 1989;63:1514–1519.
27. Tsang RW, Lapierre NJ, Simpson WJ, et al. Glioma arising after radiation therapy for pituitary adenoma. A report of four patients and an estimation of risk. *Cancer*. 1993;72:2227–2233.
28. Hodges LC, Smith JL, Garrett A, et al. Prevalence of glioblastoma multiforme in subjects with prior therapeutic radiation. *J Neurosci Nurs*. 1992;24:79–83.
29. DeAngelis LM. Brain tumors. *N Engl J Med.* 2001;344:114–123.
30. Wrensch M, Bondy M, Wiencke J, et al. Environmental risk factors for primary malignant brain tumors: a review. *J Neurooncol*. 1993;17:47–64.
31. Karlsson P, Holmberg E, Lundell M, et al. Intracranial tumors after exposure to ionizing radiation during infancy: a pooled analysis of two Swedish cohorts of 28,008 infants with skin hemangioma. *Radiat Res.* 1998;150:357–364.
32. Ryan P, Lee MW, North B, et al. Amalgam fillings, diagnostic dental X-rays and tumours of the brain and meninges. *Eur J Cancer Part B Oral Oncol*. 1992; 28:91–95.
33. Austin S, Schnatter R. A case-control study of chemical exposures and brain tumors in petrochemical workers. *J Occup Med*. 1983;25:313–320.
34. Leffingwell S, Waxweiler R, Alexander V, et al. Case-control study of gliomas of the brain among workers employed in a Texas City, Texas chemical plant. *Neuroepidemiology*. 1983;2:179–195.
35. Bond G, Cook R, Wight P, et al. A case-control study of brain tumor mortality at a Texas chemical plant. *J Occup Med*. 1983;25:377–386.
36. Wen C, Tsai S, Gibson R. A report on brain tumors from a retrospective cohort study of refinery workers. *Ann N Y Acad Sc*. 1982:130–138.
37. Teta MJ, Ott MG, Schnatter AR. An update of mortality due to brain neoplasms and other causes among employees of a petrochemical facility. *J Occupat Med*. 1991;33:45–51.
38. Monson RR, Peters JM, Johnson MN. Proportional mortality among vinyl chloride workers. *Lancet*. 1974;ii:397–398.
39. Cooper WC. Epidemiologic study of vinyl chloride workers: mortality through December 31, 1972. *Environ Health Perspectives*. 1981;41:101–106.
40. Waxweiler RJ, Stringer W, Wagoner JK, et al. Neoplastic risk among workers exposed to vinyl chloride. *Ann N Y Acad Sci*. 1976;271:40–48.
41. Wong O, Whorton MD, Foliart DE, et al. An industry-wide epidemiologic study of vinyl chloride workers, 1942–1982. *Am J Ind Med*. 1991;20:317–334.
42. Jones RD. Epidemiology of brain tumours in man and their relationship with chemical agents. *Fd Chem Tox*. 1986;24: 99–103.
43. Wu W, Steenland K, Brown D, et al. Cohort and case-control analyses of workers exposed to vinyl chloride: an update. *J Occup Med*. 1989;31:518–523.
44. Hagmar L, Akesson B, Nielsen J, et al. Mortality and cancer morbidity in workers exposed to low levels of vinyl chloride monomer at a polyvinyl chloride processing plant. *Am J Ind Med*. 1990;17: 553–565.
45. Simonato L, L'Abbe KA, Andersen A, et al. A collaborative study of cancer incidence and mortality among vinyl chloride workers. *Scand J Work Environ Health*. 1991;17:159–169.
46. Sathiakumar N, Delzell E, Rodu B, et al. Cancer incidence among employees at a petrochemical research facility. *J Occup Environ Med*. 2001;43:166–174.

47. Delzell E, Beall C, Rodu B, et al. Case-series investigation of intracranial neoplasms at a petrochemical research facility. *Am J Ind Med*. 1999;36:450–458.
48. Beall C, Delzell E, Rodu B, et al. Case-control study of intracranial tumors among employees at a petrochemical research facility. *J Occup Environ Med*. 2001;43:1103–1113.
49. Beall C, Delzell E, Rodu B, et al. Cancer and benign tumor incidence among employees in a polymers research complex. *J Occup Environ Med*. 2001;43:914–924.
50. Rodu B, Delzell E, Beall C, et al. Mortality among employees at a petrochemical research facility. *Am J Ind Med*. 2001;39:29–41.
51. Legler JM, Gloeckler Ries LA, Smith MA, et al. Brain and other central nervous system cancers: recent trends in incidence and mortality. *J Natl Cancer Inst*. 1999;91:1382–1390.
52. Lowry J, Snyder J, Lowry P. Brain tumors in the elderly. *Arch Neurol*. 1998; 55:922–928.
53. Theriault G, Goldberg M, Miller AB. Cancer risks associated with occupational exposure to magnetic fields among electric utility workers in Ontario and Quebec, Canada, and France: 1970–1989. *Am J Epidemiol*. 1994;139:550–572.
54. Grayson JK. Radiation exposure, socioeconomic status, and brain tumor risk in the U.S. Air Force: a nested case-control study. *Am J Epidemiol*. 1996;143:480–486.
55. Demers PA, Vaughan TL, Schommer RR. Occupation, socioeconomic status, and brain tumor mortality: a death certificate-based case-control study. *J Occup Med*. 1991;33:1001–1006.
56. Greenwald P, Friedlander BR, Lawrence CE. Diagnostic sensitivity bias—an epidemiologic explanation for an apparent brain tumor excess. *J Occup Med*. 1981; 23:690–694.
57. Preston-Martin SW, Mack S, Henderson BE. Risk factors for gliomas and meningiomas in males in Los Angeles County. *Cancer Res*. 1989;49:6137–6143.
58. Wigertz A, Lonn S, Mathiesen T, et al. Risk of brain tumors associated with exposure to exogenous female sex hormones. *Am J Epidemiol*. 2006;164:629–636.
59. Preston-Martin S, Henderson BE, Peters JM. Descriptive epidemiology of central nervous system neoplasms in Los Angeles County. *Ann N Y Acad Sci.* 1982;381: 202–208.
60. Inskip P, Mellemkjaer L, Gridley G, et al. Incidence of intracranial tumors following hospitalization for head injuries. *Cancer Causes Control*. 1998;9:109–116.
61. Krampla W, Newrkla S, Pfisterer W, et al. Frequency and risk factors for meningioma in clinically healthy 75-year-old patients. *Cancer*. 2004;100:1208–1212.
62. Band PR, Le ND, Fang R. Cohort study of Air Canada pilots: mortality, cancer incidence, and leukemia risk. *Am J Epidemiol*. 1996;143:137–143.
63. Rafnsson V, Hrafnkelsson J, Tulinius H. Incidence of cancer among commercial airline pilots. *Occup Environ Med*. 2000; 57:175–179.
64. Buja A, Lange JH, Perissinotto E, et al. Cancer incidence among male military and civil pilots and flight attendants: an analysis on published data. *Toxicol Ind Health*. 2005;21:273–282.
65. Becker AB, Warm JS, Dember WN, et al. Effects of jet engine noise and performance feedback on perceived workload in a monitoring task. *Int J Aviat Psychol*. 1995;5:49–62.
66. Frendi A, Dorland WD, Maung T, et al. A jet engine noise measurement and prediction tool. *J Acoustic Soc Am*. 2002; 112:2036–2042.
67. McNeil EL. The effect of jet engine harmonics on conscious and subconscious repetitive recall of music. *Aviat Space Environ Med*. 1988;59:386–387.
68. Warner RL, Bender RA. Thresholds of discomfort for complex stimuli: acoustic and sound-quality predictors. *J Speech Lang Hearing Res*. 2002;45:1016–1026.
69. Tessereaux I. Risk factors of jet fuel combustion products. *Toxicol Lett*. 2004; 149:295–300.
70. van Netten C, Leung V. Comparison of the constituents of two jet engine lubricating oils and their volatile pyrolytic degradation products. *Appl Occup Environ Hyg*. 2000;15:277–283.
71. Kobayashi A, Kikukawa A. Increased formaldehyde in jet engine exhaust and changes to JP-8, lower temperature, and lower humidity irritates eyes and respiratory tract. *Aviat Space Environ Med.* 2000;71:396–399.
72. van Netten C, Leung V. Hydraulic fluids and jet engine oil: pyrolysis and aircraft air quality. *Arch Environ Health*. 2001; 56:181–186.
73. Mackerer CR, Barth ML, Krueger AJ, et al. Comparison of neurotoxic effects and potential risks from oral administration or ingestion of tricresyl phosphate and jet engine oil containing tricresyl phosphate. *J Toxicol Environ Health*. 1999;57:293–328.
74. Miyamoto Y. Eye and respiratory irritants in jet engine exhaust. *Aviat Space Environ Med*. 1986;57:1104–1108.
75. Kilburn KH. Neurobehavioral and respiratory findings in jet engine repair workers: a comparison of exposed and unexposed volunteers. *Environ Res Sect*. 1999;80: 244–252.
76. Spirtas R, Stewart PA, Lee JS. Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. *Br J Ind Med*. 1991;48:515–530.
77. Stewart PA, Lee JS, Marano DE. Retrospective cohort mortality study of workers at an aircraft maintenance facility. II. Exposures and their assessment. *Br J Ind Med*. 1991;48:531–537.
78. Blair A, Hartge P, Stewart PA, et al. Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow-up. *Occup Environ Med*. 1998;55:161–171.
79. Garabrant D, Held J, Langholz B, et al. Mortality of aircraft manufacturing workers in southern California. *Am J Ind Med*. 1988;13:683–693.
80. Boice J, Marano D, Fryzek J, et al. Mortality among aircraft manufacturing workers. *Occup Environ Med*. 1999;56: 581–597.